II. INTRODUCTION 59

Future space crews will face serious health and safety issues such as radiation exposure, prolonged isolation and confinement, and severe physiological deconditioning due to prolonged weightlessness (39, 307). Figure IA illustrates responses of some major physiological systems during microgravity over a 6-mo period, showing the difference of each system in time course and associated risks. Some are adaptive changes towards new set points, promoting physiological function in a weightless environment. For example, microgravity-induced adaptation changes include hypovolemia (33, 35), cardiac atrophy (53, 54, 116, 169, 228, 310, 314, 318), and region-specific vascular remodeling (72, 288, 293, 311, 313, 318). Many adaptations to microgravity stabilize after a period of ~4–6 wk. However, upon return to Earth, these changes may become maladaptive and notably lead to postflight orthostatic intolerance (35, 40, 288, 314) and sensory-neural adaptation (readaptation sickness). On the other hand, bone mineral loss steadily increases (ranging from 0.5 to 1.5% per month) and does not reach a plateau within 6 mo (162, 264). Figure 1B shows that an early hypothesis that redistribution of blood pressures and tissue fluids during microgravity alters macro- and microvascular structure and function (114, 288, 318). Figure 1C compares rat control (CON) arteries to hindlimb suspension (SUS)-induced, region-specific remodeling of rat arteries in fore- and hindlimbs and its prevention by gravitation in a suspension + daily 1-h –Gx (SUS+1G) group over 28 days (311). Figure 1D illustrates reduced bone loss with intermittent artificial gravity in SUS rats (Yang Lian-Jia et al., unpublished data).

In general terms, mechanisms responsible for physiological adaptations to the microgravity of space include 1) loss of hydrostatic (gravitational) pressures within fluid columns of the body such as arterial and venous blood, cerebrospinal fluid, and lymph; 2) loss of body weight and greatly-reduced mechanical loads; 3) decreased sensory inputs; and 4) altered transcapillary and lymphatic transports. Normal daily activity on Earth involves ~16 h of upright posture with activity. The remaining part of the day consists of 8 h of sleep without axial loading. In actual microgravity, external compression of body surface areas is minimal. The greater compression of tissues on Earth due to body weight increases interstitial fluid pressures and probably dehydrates these tissues with weight bearing due to greater interstitial fluid flow into the microcirculation (111). The recently
A

Clinical horizon

zero G set point

1 G set point

Time scale (months) 1 1/2

Point of adaptation

1 G set point

Pre-flight (1G)

Microgravity

Post flight (1G)

B

100

200

70

100

Bird legs

Facial puffiness

Faintness

C

Fore body arteries

(Lumen diameter, μm)

Common carotid artery (~630 μm)

Basilar artery (~270 μm)

Middle cerebral artery (~230 μm)

Hind body arteries

Abdominal artery (~1200 μm)

Anterior tibial artery (~280 μm)

Mesenteric small artery (~200 μm)

CON

SUS

SUS + 1G

D

CON

SUS

SUS + 1G
defined visual impairment intracranial pressure (VIIP) syndrome is evidenced by visual changes in International Space Station (ISS) astronauts (157, 182). VIIP is an example of a maladaptive outcome of microgravity such as bone loss and muscle atrophy that may persist long after return to Earth, perhaps permanently (192). NASA recently redefined this syndrome as Spaceflight-Associated Neuro-ocular Syndrome or SANS.

Over the last 40 yr, visual changes reported anecdotally in astronauts were thought transient and of little operational impact. As mission duration on ISS has lengthened, reports of changes in astronauts’ visual function and ocular structure during spaceflight have increased, and these changes are now defined as the VIIP syndrome (85). The VIIP syndrome manifests itself as decreased near-field visual acuity. Although the microgravity-induced cephalad fluid shift is considered the primary causative factor, other contributors such as poorer cardiovascular health of men compared with women (few, if any, females exhibit VIIP-related disk edema to date), elevated cabin CO2 concentration, high-salt diet, and resistive exercise are implicated as potential secondary contributing factors. Interestingly, right eyes have greater VIIP-related changes than left eyes. However, the etiology and exact pathophysiology of the space VIIP syndrome remain unclear. As prolonged missions to Mars and other deep-space destinations are actively planned, it is increasingly important to understand the pathophysiology of the VIIP syndrome.

The objectives of this review are to 1) synthesize what we have learned to date on microgravity-induced alterations of cerebral and ocular circulations, cerebrospinal fluid (CSF), and aqueous humor (AH) hydrodynamic systems and vision; 2) evaluate the possible role of a mismatch between intraocular pressure (IOP) and intracranial pressure (ICP) and the resulting acclimation of the optic nerve head (ONH) in the pathogenesis of space VIIP syndrome; 3) provide a perspective on future directions; and 4) examine whether artificial gravity is an appropriate countermeasure.

The reader is also referred to a number of recently published reports or review papers (8, 85, 192, 204, 217, 271) and original articles (157, 182, 183) that summarize VIIP case data. With this background, it is important to understand how the evidence gathered to date relates to relevant pathophysiological conditions of humans on Earth.

**II. VIIP SYNDROME AND CURRENT HYPOTHESES**

A comparison of pre- and postflight ocular measures has identified a potential risk of permanent visual changes in long-duration spaceflight. Mader et al. (182) reported that after 6 mo of space flight on ISS, seven astronauts had ophthalmic abnormalities consisting of optic disk edema, posterior globe flattening, choroidal folds, cotton wool spots, retinal nerve fiber layer (RNFL) thickening, and decreased near vision and hyperopic shifts. Also, postflight lumbar puncture opening pressures suggest that CSF pressure may be mildly elevated inflight. But, whether the postflight CSF pressures reflect elevated pressures inflight is not known because preflight lumbar punctures were not performed on these individuals. Some vision changes persist years after prolonged space flights. Whether an increase in severity is associated with mission duration remains unknown. In addition, a postflight survey of ~300 astronauts documented that 29 and 60% of astronauts on short-duration and long-duration missions, respectively, experienced degradation in distant- and near-vision visual acuity (85). Since Mader’s pioneering paper (182), additional cases have been reported. To date, 15 long-duration male astronauts were diagnosed with inflight and postflight visual acuity and ocular anatomical problems (8). Similar findings were previously reported among Russian cosmonauts flown on the Russian MIR Orbital Space Station (8, 196). The Russians studied 16 cosmonauts, 8 of whom had mild to moderate papilloedema on landing. Compared with preflight upright data, inflight blood flow velocity in cerebral straight venous sinus was elevated in 9 of 13 cosmonauts. The spaceflight environment of the MIR Space Station was similar to that for ISS, including chronic exposure to both microgravity and elevated levels of environmental CO2.

In a retrospective study of 27 postflight astronauts by using 3-T MRI, Kramer et al. (157) found various combinations of optic-nerve sheath distension, posterior globe flattening, optic-disk protrusion, increased optic nerve diameter and tortuosity, and moderate to great concavity of the pituitary gland with posterior stalk displacement. They conclude that exposure to prolonged microgravity produces a spectrum of intraorbital and intracranial similarities to idiopathic intracranial hypertension (IIH) and pseudotumor cerebri. However, some authors suggest
that elevated ICP is not the only cause of VIIP, because none of the astronauts with ophthalmic changes presents with chronic headache and other clinical symptoms noted with terrestrial IIH. Moreover, the prominent degree of globe flattening and disk edema are out of proportion to the documented ICP speculated from post-flight lumbar puncture opening pressures (85, 182).

Currently, microgravity-induced head-ward blood and fluid shifts are considered the primary etiological factors causing chronic and mildly elevated intracranial hypertension as compared with variable ICPs on Earth (8, 85, 157, 163, 182, 192, 204, 217), but the exact degree of intracranial fluid shift and the relevant mechanisms remain speculative. Several specific explanations/hypotheses are proposed to explain the underlying pathogenetic mechanisms. For example, it is hypothesized that direct transmission of elevated subarachnoid pressure from the intracranial to the intracoelomic compartment through the perioptic subarachnoid space may lead to optic nerve sheath distension and disk edema (8, 182). An elevated pressure gradient across the lamina cribrosa caused by a chronic, but mildly elevated ICP may contribute to posterior-globe flattening, disk edema, choroid folds, and a hyperopic shift (182–184). More recently, the crucial role of chronic IOP/ICP mismatch (316) and resulting changes in transmameral pressure gradient (28, 204) are proposed for the pathogenesis of VIIP. In addition, other factors may contribute to vision impairment symptoms, e.g., elevated cabin CO₂ concentration, higher incidence in men with poorer cardiovascular health compared with woman, high-salt diet, and restictive exercise (8, 85, 192) as well as genetic predisposition associated with a difference in metabolic pathway (321). However, the exact contributions and their underlying mechanisms need further elucidation.

III. BASIC CONCEPTS

A. Hydrostatics and Distribution of Vascular Transmural Pressures in Normal Gravity Versus Weightlessness

On Earth, pressures at any point within blood vessels have three basic components, namely, the static, hydrostatic, and dynamic pressure components. Among them, the hydrostatic component depends on the force of gravity and is expressed as $\rho gh$, where $\rho$ is blood density, $g$ is the gravitational acceleration constant, and $h$ is the vertical height of the vascular column relative to the hydrostatic indifferent point (HIP) with negative or positive sign above or below the HIP, respectively. The dynamic pressure is generated by the heart and equals blood flow $\times$ resistance. In supine position, the arterial and venous driving pressures are ~100 and 10–15 mmHg, respectively (247). On Earth, the venous hydrostatic indifference point is located below the heart (229). Above this level, intravenous pressures may become slightly negative collapsing the vein, but do not fall as the height of the hydrostatic column above the heart increases. On the other hand, below the venous hydrostatic indifference point, venous pressures become increasingly positive in proportion to $pgh$ below the heart (35, 96, 120, 247, 288) except where venous valves interrupt the hydrostatic column. During microgravity exposure, loss of gravity negates all circulatory hydrostatic pressures between the head and feet and thus shifts blood and other fluids towards the chest and head regions (Figure 2A).

Investigators hypothesize that fluid redistribution initiates cardiovascular adaptation to microgravity (8, 35, 51, 114, 288). However, our review emphasizes the importance of this initial redistribution of transmural pressures along the vasculature of the body as the primary initiating factor. Subsequently, the cephalad fluid shift may be considered a secondary consequence, mainly restricted to extracranial organs, due to the lack of arteriolar autoregulation and the high compliance of the venous system (109, 111, 288, 311, 313, 318).

This concept is also important in elucidating the pathogenesis of VIIP syndrome for the following reasons. First, it is important to ascertain whether the chronic, mildly elevated ICP during microgravity (163) as compared with normal ICP variations with posture and activity on Earth can be largely accounted for by the elevated perfusion pressures in the intra- and extracranial organs and the neck regions due to the removal of gravity. Because hydrostatic pressure components of body fluid columns disappear in space, the redistribution of blood pressures is maintained even though the body fluid and volume redistribution have attained a new equilibrium state with acclimation. Furthermore, a microgravity-induced, cerebral transmural-pressure redistribution is theoretically affected by a simultaneous pressure redistribution within the CSF and venous columns (152, 185, 186, 247, 311). Second, sustained increases in the transmural pressures along cerebral and ocular microvasculature, relative to the upright conditions on Earth, may well alter microvascular structure and function (73, 293, 311, 313). Thus a microvascular adaptation to a chronic elevation of arteriolar pressure during prolonged microgravity may initiate maladaptive mechanisms of VIIP. In addition, at least in the AH outflow system, both the pulsatile flow pattern (135) and outflow resistance adjustments (3) probably involve mechanotransduction and tissue re-modeling processes similar to that in blood vessels. Third, given that redistribution of transmural pressures, rather than blood volume, is the primary causative factor, one may predict that artificial gravity (AG) is a unique countermeasure that can prevent and mitigate the VIIP syndrome by providing daily Earth-like distribution of transmural pressures along cerebral and ocular vasculatures (109, 288, 311–313).
B. Intracranial and Intraocular Fluid Systems: Pressures and Compliance

It is not surprising to find that there is a remarkable similarity between the CSF and AH fluid systems because the central nervous system is evolved from a fluid-filled and fluid-surrounded neural conduit and the eye is an outgrowth of the central nervous system (68, 70). The CSF bathes and buoy the brain, thus providing a conduit for clearing brain metabolic byproducts. The AH and vitreous body constitute a part of the refracting media of the eye, and IOP pressure maintains a degree of rigidity in the eye and preserves corneal curvature. In addition to these mechanical roles, the two fluids are also concerned with nutrition of the tissues which they bathe (68, 70, 101). The similarities in chemical composition between AH and CSF are striking because the neuroepithelia of the brain choroid plexus and the eye ciliary body have a common neuroectodermal origin and share similar anatomy and function (128).

The dynamics of the two fluid systems can be viewed as follows. In the cerebrospinal system, fluctuations in arterial pressure will have small effects per se due to the low distensibility of the arterial muscular coat. However, changes in venous pressure will have more pronounced effects due to the high venous distensibility and thus may be reflected in corresponding short-term changes in ICP. CSF is continuously generated in choroid plexuses and drains from the
ventricles into the subarachnoid space where it passes back into the blood via dural sinuses and arachnoid villi (68, 70). The resistance offered to this egress of fluid contributes to ICP, but blood volume shifts into the brain contribute more to ICP. In the AH fluid system, fluid formation in the posterior chamber is from active secretion of ciliary body epithelium cells. AH fluid leaves the eye via flow from the trabecular meshwork-Schlemm’s canal and uveoscleral pathways, thus emptying into the ocular venous system.

The principal factors that determine ICP and IOP include venous pressures and the rate of secretion and frictional resistance to fluid drainage. The total pressure is expressed as

$$P_o = P_v + F \times R$$

where $P_o$ is ICP or IOP, $P_v$ is the superior sagittal sinus pressure or episcleral venous pressure, $F$ and $R$ are the formation rate and outflow resistance of CSF or AH system, respectively. In the case of ICP, this relationship is known as the Davson equation (69, 70), whereas in the case of IOP, it is known as the Goldmann equation (102). Although the relationship established is acceptable, it is oversimplified and the real picture of each fluid system is far more complex. Thus expanded equations are needed in some cases (9, 14, 29, 30, 38, 69, 70, 101) (FIGURE 2, A–C) and venous and CSF pressures may be lower than depicted due to vessel collapse (229).

Considering healthy, supine individuals on Earth, mean IOP is 16 mmHg, while ICP is considerably less with mean of 12 mmHg as measured by lumbar puncture in the lateral recumbent position (25). This pressure differential helps maintain the shape of the eyeball and appropriate spacing and alignment of its optical contents in normal subjects. This pressure matching closely relates to the unique anatomical and functional characteristics of the connection between the two fluid systems (8, 25, 68, 101, 209, 237) (FIGURE 2D).

A recent pioneering paper by Lawley et al. (163) documents that ICP during short-term weightlessness with parabolic flight is slightly less than ICP in supine posture (supine, 17 ± 2 mmHg vs. microgravity, 13 ± 2 mmHg). Importantly, ICP has large diurnal variations during 16 h of upright posture (sitting, standing, walking activities) and ~8 h of sleeping posture. Supine or sitting posture alone is not an adequate reference point. Therefore, Lawley et al. (163) also conclude that during 24 h in microgravity, brain ICP is slightly above that observed on Earth which may explain the VIIP syndrome in astronauts. We agree with Lawley et al. that ICP is not elevated to pathological levels seen in intracranial hypertensive patients on Earth; but we postulate a chronic and mildly elevated ICP in space may adversely affect eye structure and function during prolonged space flight. With reference to central and peripheral venous pressures, Earth-based models (horizontal posture and head-down tilt analogs) are inadequate for reproducing headward fluid shifts in space (111, 112), so current, ongoing fluid shifts experiments on ISS will aid our understanding of the role of jugular vein dimensions and flow during prolonged microgravity.

The pressure-volume relationship between ICP and intracranial volume of CSF, blood, and brain tissue, expressed as the Monro-Kellie doctrine, is another important concept to understand ICP homeostasis on Earth and during weightlessness (83, 199). The brain is the largest component of the skull, having a mass of 1,400 g. Normally, there is ~150 ml of blood inside the skull, 100 ml of which is venous blood. Because these components are housed in a fairly-rigid cranium having a fairly fixed volume, any volume increase of one component within the cranium is primarily offset by an equal decrease in the volume of another component. The small buffering capacity for increases in intracranial volume is primarily by CSF volume displaced into the spinal canal and to a lesser extent by the volume of venous blood. In the normal brain, small changes in the volume of one of the contents (e.g., venous blood volume during coughing or straining) do not cause a sustained rise in ICP. However, once compensatory mechanisms are exhausted, e.g., due to the presence of a hematoma or edema, ICP will rise dramatically.

The relationship between ICP ($P_{IC}$) and intracranial volume ($V$, equal to the sum of the volume of CSF, blood, and brain tissue) is expressed as a monoexponential function or the elastance curve. When volume of craniospinal space increases, ICP increases exponentially. Consequently, at low pressure, the compliance is larger than in a high-ICP state. Thus the pressure-dependent compliance is expressed as

$$C = 1/(K \cdot P_{IC})$$

where $C$ is intracranial compliance, $K$ is a subject/patient-specific constant that characterizes the elastance of the CSF system, and $P_{IC}$ is ICP (83). Based on this relationship, ICP can be measured noninvasively. The pulsatile nature of blood flow into the brain generates cyclic intracranial volume changes. These volume changes are on the order of 0.1% of the total intracranial volume. Elastance is the derivative of pressure with respect to volume and is related linearly to absolute ICP. Intracranial volume and pressure changes are calculated from phase-contrast MRI imaging measurements of CSF and blood flow (11, 12), or using mathematical modeling, along with active infusion of artificial CSF (83). The pressure-volume relationship is thus expressed as

$$P = P_1 \cdot e^{E_1 \cdot V}$$

where $E_1$ is a constant elastance coefficient (units of volume$^{-1}$), $P_1$ is a pressure coefficient related to the exponential shape of the curve, and $V$ is intracranial volume (CSF + blood + brain tissue) (190).
Intracranial compliance (ICC) is actually the rate of volume change of the overall craniocerebral CSF system, $\Delta V_{\text{total}}/\Delta P$, with respect to ICP, or $P_{\text{IC}}$, which can be approximated by $\text{ICC} = \Delta V_{\text{total}}/\Delta P_{\text{IC}}$. ICC is important because it describes the ability of the compartment to accommodate volume changes. Using an MRI-based method to estimate the craniocerebral compliance, Tain et al. (274) find that spinal canal contributions are consistently greater in healthy subjects, accounting for approximately two-thirds of overall compliance. This is also consistent with anatomic features suggesting that the dura is less confined by bony structures, especially in the lumbar spine where CSF may expand into the nerve-root dural sleeve.

The pressure-volume relationship in the eye is nonlinear. Global volume depends on IOP logarithmically so that global compliance continuously decreases as pressure increases as expressed by $C = \Delta V/\Delta P$ (65, 260). The derivative of the pressure-volume relation with IOP $(dP/dV)$ is a major determinant of ocular rigidity. Dastiridou et al. (65) report that the average ocular rigidity coefficient of eyes is $0.0224 \mu l^{-1}$ (SD 0.0049). Ocular rigidity is related to the biomechanical properties of the whole globe and thus is a clinical parameter characterizing biomechanical properties of ocular coats. The nonlinear relationship between ICP pulse amplitude and ICP level is well known. A significant change in ICP amplitude occurs at high ICP, not in the range of normal ICP or a chronic but slightly elevated ICP level during microgravity (compared with more variable and lower ICP with activity on Earth). Similarly, we suggest that the IOP pulse amplitude may not change significantly with microgravity because there may be no long-term IOP elevation. New technology proposed by Morgan et al. (206) may allow better definition of these relationships.

C. Immediate Adaptation Responses and Acclimation Changes

After the immediate responses to the removal of gravity, cerebral and ocular circulations and intracranial and intracocular pressures acclimate to microgravity in roughly two phases: a dynamic adjustment over hours to days and a subsequent long-term adjustment (288). Approximately two-thirds of space crew members experience some combination of headache, malaise, lethargy, anorexia, nausea, vomiting, and gastric discomfort during the first few hours or days of spaceflight (129, 268, 279). Increased IOP, facial edema, and distension of temporal, forehead, and neck veins are due to loss of hydrostatic pressures and the subsequent cephalad fluid shift (78, 180, 226).

On Earth, transmural pressures redistribute themselves along the vasculature and CSF, thus generating daily axial fluid shifts during upright and recumbent postures. However, during prolonged weightlessness, these diurnal alterations of peripheral circulations disappear. Thus, during long-duration spaceflight, acclimation to sustained microgravity produces vascular remodeling and functional adjustment (125, 222, 288, 311, 313). By analogy, the diurnal variation and circadian rhythm of both IOP and ICP as in a 1-G environment are probably significantly altered or lost entirely in space. Additionally, loss of tissue weight of the intraorbital and intracranial content may well induce significant acclimation changes that remain unexplored (111, 223).

IV. PATHOPHYSIOLOGY

A. Cerebral Circulation

1. Cerebral autoregulation

Although cerebral perfusion pressure is increased in microgravity due to the disappearance of hydrostatic components to blood pressure, the cerebral circulation appears well maintained and cerebral blood flow is stable in long-duration spaceflights aboard orbital stations Salyut-7 and Mir and International Space Station (17, 119, 156). This is because the cerebral resistance arteries exhibit myogenic tone and reactivity to increased transmural pressure (66, 67, 133). Cerebrovascular autoregulation responds within 2–5 s after cerebral perfusion pressure changes to maintain cerebral blood flow in the pressure range between 50 and 150 mmHg (88, 227). Long-term autoregulation during sustained elevated systemic arterial pressure produces structural remodeling in cerebral arteries and arterioles (133). This vasomotor response plays an important role in the autoregulation of cerebral blood flow and the homeostasis of cerebral capillary fluid pressure that is important for tissue fluid balance. Autoregulation also serves a critical and protective role to prevent capillaries from damage (133). In addition to the myogenic regulation, several other mechanisms such as metabolic influences ($\text{PaCO}_2$, $\text{PaO}_2$) and autonomic innervations, may contribute to the tight regulation of cerebral blood flow (32, 227). In the brain, the pial and smaller arterioles imbedded in the tissue are mainly under metabolic control (133).

During manned spaceflight, cerebrovascular responses are investigated by using impedance rheoencephalography (REG) and transcranial Doppler (TCD) sonography (16, 32, 51, 97, 288). Early autoregulatory responses for mean middle cerebral artery blood flow velocity in sitting posture during parabolic flight microgravity (36) and short-term bed rest (142, 288) are well documented. In the Salyut and Mir missions, the autoregulatory mechanism is evaluated by using REG. During short-duration flights, no consistent changes are detected. However, REG responses to LBNP and exercise are altered during and after flights, with the character of the response varying with the duration of flight (51, 288). Using REG, Gazenko et al. (97) found significant
reduction in the cerebral blood flow pulsatility (“pulse blood filling”) to HDT after spaceflight relative to preflight. These differences document an enhanced cerebral vasoconstriction. Furthermore, this response appears more evident following longer flights. These data suggest that chronic adaptation to microgravity may lead to enhanced cerebral vasoconstriction, especially after longer flights (51, 97, 288, 313). In the 16-day Neurolab space shuttle mission, beat-by-beat changes of mean arterial blood pressure and TCD middle cerebral artery blood flow velocity were measured during LBNP in space and HUT on Earth (127, 168). Lowered cerebral blood flow velocity during orthostatic stress was somewhat less during and after microgravity exposure than before flight. Cerebral autoregulation was quantified by the analysis of transfer function between these two signals which suggests that the cerebral autoregulation is preserved, and possibly even improved, by short-duration spaceflight. However, it is also reported that cerebral circulatory adjustments during short-duration spaceflight were associated with postflight orthostatic intolerance (31, 32, 40, 311). Recently, on assessing by an autoregressive moving average model to separate the myogenic component from metabolic influences of PaCO2, it is documented that long-duration exposure to microgravity on ISS is associated with reduced indices of cerebrovascular dynamic autoregulation and CO2 reactivity (320). However, human studies are limited by using noninvasive techniques. For example, cerebral blood flow velocity measured by TCD is only a reflection of, but not absolute, global cerebral blood flow because, to date, no study has involved simultaneous measurement of cerebral arterial dimensions (31, 32, 99, 127, 295). Moreover, errors are linked with small changes in the angle of insonation (32). Nevertheless, combining concurrent measurements of cerebral blood flow velocity of middle and posterior cerebral arteries and cerebral blood flow from extracranial conduit arteries (while PaCO2 is controlled) measures cerebral perfusion during acute changes in posture (99).

The extracranial organs lack efficient autoregulatory mechanisms. In humans, facial puffiness is very prominent during spaceflight and may last throughout exposure to microgravity. Using ultrasound, Kirsch et al. (151) demonstrate that the cutaneous tissue thickness over the forehead and tibia of a cosmonaut is increased and reduced, respectively, during a 9-day spaceflight. Studies of local transcapillary pressures of the head and neck region during bed rest demonstrate that skin blood flow and capillary blood pressure in the head and neck are increased (226, 288). It is suggested that potential factors causing facial edema include increased capillary pressure, reduced capillary blood colloid osmotic pressure, elevated microcirculatory flow, along with sparse distribution of lymphatic vessels and lower intrastitial fluid pressures due to unweighting of tissues (109, 111). In addition, feeling of fullness in the head, sinus and nasal congestion, periorbital and facial edema, and distension of neck vein may lessen after the first few flight days and partially subside until return to Earth (51, 109, 288).

In animal studies, Tanaka et al. (276) show that transient microgravity exposure during parabolic flight elicits significant increases in jugular venous and carotid arterial blood pressures with temporal muscle blood flow of anesthetized rats being kept at 30° HUT position. Moreover, cerebrocortical blood flow increases within 3 s of entry into microgravity and rapidly recovers, indicating different vascular control mechanisms between intra- and extracranial organs. Such findings are reported in humans (224), and the increased jugular vein pressure may be due to the difference between the reference point in microgravity and normal gravity. Shimizu (252) reports that, in anesthetized rabbits and rats, 20° HDT increases blood pressure and flow in the ascending aorta and common carotid artery and decreases the same variables in the abdominal aorta and femoral artery. Also, ~75% of the increased blood flow is distributed to the extracranial regions. Studies with the tail-suspended HDT rat model (SUS) (201, 202) document that SUS for 28 days increases cerebral vascular resistance, decreases blood flow, and induces hypertrophic change and augmented myogenic tone and vasoreactivity in the middle cerebral artery (MCA). In cerebral conduit and resistance arteries, SUS-induced adaptations are consistent with those reported for genetic and nongenetic hypertensive rats (98, 170, 294, 300, 311, 313, 319). For isolated MCAs, it is documented that SUS increases myogenic tone and vasoreactivity (98, 170, 293), reduces endothelium-dependent vasodilatory function (234) and hypertrophy, as characterized by increases in vessel media thickness and cross-sectional area as well as the number of vascular smooth-muscle-cell layers (170, 311). A surprising and important result is that daily 1-h –Gs over 28 days, which simulates intermittent artificial gravity (IAG) countermeasure, prevents the structural remodeling changes, but not augmented myogenic tone and increased vasoreactivity in the MCA (170, 302, 311). These findings suggest that cerebrovascular adaptation is different between the large cerebral artery that contributes importantly to cerebrovascular resistance (84) and the proximal resistance artery. For the basilar artery, both the augmented vasoreactivity and hypertrophy are fully prevented by this IAG countermeasure (270, 311). Furthermore, biomechanical studies reveal that MCAs from 28-day SUS rats exhibit pronounced and active stiffening as well as lower strains with increasing pressure which is prevented by simulated IAG for the most part. MCAs from IAG rats show greater distensibility in their passive state which may reduce the rightward shift of the bottom part of the cerebral autoregulatory curve. In this regard, distensibility represents compliance in a uniaxial stress state (56). However, recent findings with the basilar arteries isolated from space-flown mice are quite different from those from rats exposed to simulated microgravity on Earth (266, 278). It seems that the difference in blood volume distribution between upright
humans and standing quadrupeds is the principal factor that determines this discrepancy (74, 309).

2. Cerebral venous circulation

Three main venous drainage systems converge to drain various regions of the brain (296). The final common venous outlets are the two internal jugular veins. Smaller additional venous drainage is provided by vertebral veins and venous plexuses and orbital veins and venous plexuses. Dural venous sinuses are composed of dura mater lined with endothelium which is unlike normal vessels. Dural venous sinuses also lack tunica media and may be more susceptible to external compression even though they are suspended in meninges (296). Unlike the arterial system, the venous vasculature is greatly influenced by hydrostatic pressures associated with gravity and is only weakly modified via local myogenic and neurohumor factors.

In the 1-G condition, the distribution of pressures in the venous system is determined almost solely by the hydrostatic pressure component except when interrupted by venous collapse above heart level and venous valves below heart level. In upright posture on Earth, intravenous pressures above right atrial level is negative, but probably doesn’t reach as low as $-40 \text{ mmHg}$ at the top of the head as depicted in FIGURE 2A. Also, the measured CSF pressure is $-12.5 \text{ mmHg}$, or $-30\%$ of the predicted value (247). However, recent direct measurements indicate that CSF pressures are only slightly negative during upright posture on Earth (15, 230). At 1G, cerebral venous drainage depends on posture and central venous pressure (CVP) (11, 12, 100). In supine position, venous outflow occurs predominantly through the internal jugular veins which are the major drainage outlets. However, a predominantly nonjugular drainage pattern is found in $\sim 6\%$ of volunteers (75). Whereas in the upright posture, jugular veins are liable to collapse and venous outflow is considerably less pulsatile and occurs predominantly through the vertebral venous plexuses, a marked CVP increase can make these veins completely reopen. In a weightless environment, CSF pressure may be elevated in the head and neck as compared with Earth gravity due to the loss of hydrostatic pressure gradients. Although elevation of venous pressures has not been noted in space, elevated CSF pressure in the head and neck may increase ICP immediately (51). Nevertheless, cerebral flow during spaceflight is stable and close to the preflight level and the jugular vein remains distended throughout the flight. Arbeille and co-workers (17, 119) have examined the cross-sectional areas of both the jugular and femoral veins during 6-mo Mir spaceflights and a bed rest study up to 42 days. During Mir flights, both veins remain enlarged throughout the flight, whereas during simulated microgravity, only the jugular vein is distended while the femoral vein diameter is reduced. This disparity is apparently due to different physical principles involved (111, 288, 311, 313). An echographic study during a 6-mo ISS spaceflight documents increased jugular and portal vein volume and increased femoral vein cross-sectional area and reduced calf vein area. These observations suggest that there is increased venous volumes in cephalic, splanchnic, and pelvic regions during long-duration spaceflight (19).

Any compromise to the cerebral venous outflow may increase cerebral venous pressures and ICPs, because internal jugular veins drain 700 ml/min at rest, and the average adult male intracranial volume is only twice this value (296). More data from the Fluid Shifts experiment presently on ISS will aid our understanding of ICP, IOP, internal jugular vein drainage, and other important parameters during prolonged microgravity. It is also possible that drainage from venules and lymphatic vessel is reduced by edema. Wiener (292) proposed that cerebral venous return in microgravity is more dependent on internal jugular vein drainage and thus might be a contributing factor causing venous hypertension and mildly elevated ICP. In addition, whether valves exist in distal portions of the internal jugular veins in the great majority of persons (115, 167) or different patterns of cerebral venous drainage occur in supine position (75) could have important implications in the pathogenesis of space VIIP. For example, in very tall animals such as the giraffe, venous valves are important to prevent retrograde flow and elevation of ICP during head-down drinking (110). Moreover, in 90% of IIH patients, bilateral transverse sinus stenosis is found (for review, see Ref. 296). In some IIH patients, chronically elevated ICP is probably due to prolonged elevated extracranial resistance to cerebral venous outflow, although cerebral venous drainage is highly variable among individuals (10). In IIH patients, the spinal canal contribution of compliance is significantly smaller than normal controls (274).

B. ICP and CSF Dynamics

1. ICP definition, normal range, and measurement

ICP is the pressure inside the fairly-rigid cranium and thus represents pressure in the brain and intracranial CSF. The ICP value depends on body position and measurement method. Normal ICP ranges from 5 to 15 mmHg with a mean of 12 mmHg when measured by lumbar puncture in the lateral decubitus position (25), but in the sitting position being $-10$ to 0 mmHg at eye level (186).

ICP is lower when standing due to the G-vector change because the head is above the HIP. The HIP of the craniospinal CSF fluid column is located between C-6 and T-5. In sitting position, the level of zero CSF pressure is located at the upper cervical region (186). However, recent findings suggest that ICP changes with posture don’t match those expected by the HIP of the craniospinal CSF fluid column (230, 239). Using a chronically implanted telemetric pressure sensor, Chapman et al. (50) also determined the quanti-
titative relationship between changes in body position and intraventricular fluid pressure in a group of subjects. Alterations in body posture cause predictable changes in ICP and cephalic venous pressure that are similar both qualitatively and quantitatively. As is indicated in *Equation 1*, altered superior sagittal sinus pressure may provide the largest contribution to the immediate and profound changes in ICP due to tilting ([Figure 2A](#)) for which the venous HIP location is more important than the CSF HIP location. Klarica et al. (152) report that altered hydrostatic pressure gradients along the craniospinal CSF fluid column and a subsequent CSF volume shift from the cervical to spinal subarachnoid space contribute to ICP during tilting in anesthetized cats.

Quantitative determination of ICP in space is crucial to understanding the pathogenesis of VIIP syndrome. However, ICP has never been directly measured in humans during spaceflight. Currently, the “gold standard” for ICP measurement is invasive measurement of the pressure in the CSF via direct insertion of the pressure sensor into the brain’s ventricle or less directly via lumbar puncture. The invasive nature of lumbar puncture is probably not feasible in the near future for inflight human studies (21). To date, lumbar punctures have been performed postflight on six crew members who had significant VIIP signs and symptoms (8). However, no preflight lumbar puncture measurements were made, thus limiting the value of these results.

Indirect, noninvasive measures of ICP have been proposed and developed. Several technologies have been employed to estimate ICP, such as ultrasound (282), computed tomography, magnetic resonance imaging, transcranial Doppler sonography, audiometric technique (107), near-infrared spectroscopy, visual-evoked potentials, ophthalmodynamometry, optical coherence tomography (OCT), and confocal scanning laser ophthalmoscopy (CSLO) (246, 256). In addition, ultrasound measurements of the optic nerve sheath diameter ONSD and Doppler flow are promising (240, 246). Several noninvasive techniques for ICP measurement are presently employed in flight on ISS, including technologies based on cerebral cochlear fluid pressure and tympanic membrane displacement, distortion product otoacoustic emissions, pulsatility index and waveform analysis of transcranial Doppler, two-depth ophthalmic artery Doppler, and others (cited in Ref. 23).

NASA and UCSD developed a pulsed phase lock loop (PPLL) device for noninvasive monitoring of ICP waveforms (282). It is demonstrated that the PPLL device has a sufficient sensitivity to detect ICP pulsation changes during body tilt, both in the transcranial (268, 281, 282) and the anterior-posterior skull direction (175). Audiometry that evaluates tympanic membrane displacement is a promising technique to assess ICP indirectly (256, 262). Using a noninvasive Cerebral and Cochlear Fluid Pressure Analyzer (CCFP) that is based on a sigmoidal relationship between membrane displacement and ICP, Murthy et al. (215) reported that 6° head-down tilt was associated with a significant displacement that corresponded to an estimated ICP value of 17 mmHg.

However, many of these noninvasive technologies are still under development and only provide qualitative rather than quantitative ICP data. Therefore, performance of pre-, in-, and postflight lumbar puncture is still being evaluated by NASA. Hence, there are concerns about unique aspects of spaceflight, such as operational considerations and medical constraints, and their limitations for using traditional lumbar puncture as an adjunct or as an alternative to noninvasive ICP measurements (23).

2. CSF dynamics and ICP homeostasis in 1-G environment

The parenchyma of the brain and spinal cord is devoid of lymphatic vessels, but has a free lymphlike fluid, the CSF, which fills the interconnected ventricular cavities within the brain and subarachnoid space around the brain and the spinal cord. CSF is primarily produced by choroid plexuses and circulates from the ventricles into basal cisterns. The choroid plexus, comprised of a rich capillary bed, pia mater, and choroid epithelial cells, produces CSF and generates 500–600 ml of CSF every day (132). Importantly, the total CSF volume in humans is ~150–270 ml, demonstrating the high turnover of this fluid, thus replacing all CSF every 8 h (241). Four choroid plexuses, situated within the lateral, third, and fourth ventricles, generate about two-thirds of the total CSF and the remainder is produced by several extrachoroidal sources (37, 132). Likely sources include ependyma lining the ventricles (233) and the capillary-astrocytes complex in the blood-brain barrier (1, 62).

In choroid plexuses, CSF is formed by passive filtration of fluid across choroidal capillary endothelium, and then by a regulated active secretion by a single-layered epithelium. The choroid plexus has epithelial mechanisms similar to those in the renal tubule, and the fluid is generated at a high rate by transferring a large volume of ions and water. This active process involves pumps, cotransporters and antipor- ers, ion channels, and aquaporins. Flow of CSF is pulsatile and the fluid courses from its origin at the choroid plexus to exit at the foramina of the fourth ventricle out to the basal cisterns, then flows into the spinal and cortical subarachnoid spaces. A circadian variation in human CSF flow through the cerebral aqueduct, with a nightly peak, is demonstrated by MRI (221).

CSF must be reabsorbed at a constant rate to prevent accumulation and increases in ICP. Present data support the importance of both the cranial and spinal arachnoid villi
and lymphatic drainage in the reabsorption of CSF from the subarachnoid space. The arachnoid villi in the superior sagittal sinus are probably the primary source of CSF absorption in humans. Spinal CSF absorption through arachnoid granulations located along the nerve roots is suggested. With the use of radionuclide cisternography, spinal CSF absorption rate in humans is more pronounced in active than in resting state. Approximately 38 and 76% of the CSF absorption in resting and active states, respectively, could be accounted for from the spinal arachnoid villi (81). Arachnoid granulations facilitate CSF outflow by hydrostatic gradient mechanisms (directed from CSF to venous blood) and by lymphatic channels (55). The driving pressure is a 0.6 ratio favoring CSF pressure. An increase in venous pressure of just a few mmHg alters the pressure gradient significantly and inhibits CSF reabsorption. The physiological relationship between the CSF and extracranial lymph compartments is primarily by way of the olfactory nerve perineural space that traverses the cribriform plate and is absorbed by the lymphatics of the submucosa in the olfactory and respiratory epithelium (134). Other cranial nerves may contribute, but little evidence supports a leading role of this pathway for CSF drainage. Similarly, lymphatic vessels nearby spinal nerves absorb CSF from the spinal subarachnoid space. CSF absorption values vary with the specific animal tested with 13–80% of CSF absorption in peripheral lymphatics (153, 232). The lymphatic system develops earlier than that of the cranial arachnoid villi system, but the latter becomes less efficient as a function of age, thus influencing CSF turnover rate (232). A number of hypotheses could explain how CSF may contribute to ICP and, thus, to eye alterations in space. For example, a headward shift of CSF volume with loss of gravity would increase intracranial volume and ICP in a relatively low compliance skull.

In addition to CSF circulation by bulk flow through ventriculo-subarachnoid spaces, there is a local fluid exchange between blood, interstitial fluid (ISF), and CSF. Cerebrospinal fluid is re-circulated by bulk flow from the cortical subarachnoid space into paravascular spaces (or Virchow-Robin spaces) surrounding the penetrating cerebral arteries, and then out of brain via CSF drainage routes (37, 124, 132). The extracellular fluid compartment of the brain can be divided into two components: CSF and parenchymal ISF. The ISF is actively secreted by the capillary endothelial cells, which are linked by tight junctions, constituting the blood-brain barrier (BBB). CSF is secreted by the circumferentially arranged epithelial cells of the choroid plexuses with tight junctions forming the blood-CSF barrier (BCSFB). Concerted transport at these barriers is vital to provide a stable fluid microenvironment for neuronal networks. The BBB is a dynamic system regulated by all cellular elements of the neurovascular unit, composed of endothelial cell monolayer, integral neighboring cells (including pericytes and smooth muscle cells), and astrocytic end feet (2, 218). Both CSF and ISF drain partly or wholly into regional lymph nodes by separate routes from the brain, especially in humans (37, 63, 121, 290, 291). Lymphatic drainage of ISF and solutes is via the paravascular drainage route. ISF drains from the brain along the 100- to 150-nm-wide basement membranes in the walls of capillaries and arteries, then via carotid and vertebral arteries to lymph nodes in the cervical spine. Vessel pulsations may be the driving force for the lymphatic drainage along artery walls. Recently, using in vivo two-photon microscopy, vascular wall pulsatility in penetrating intracortical arteries in mice can be directly visualized, and thus the important role of cerebral arterial pulsation for paravascular CSF-ISF exchange in the brain is further illustrated (124). Furthermore, CSF and ISF are strongly interrelated. CSF flows from the ventricles into the white matter where CSF is probably absorbed into blood or drains with ISF in approximation to blood vessel walls (290, 291). Additionally, parenchymal ISF formed at the capillary-glial complex moves into the Virchow-Robin spaces and ultimately mixes with the CSF in the subarachnoid compartment. Astrocytes, aquaporins, and other membrane transporters are key elements in brain fluid and CSF homeostasis (37). The contribution of parenchymal ISF to total CSF production is between 10 and 30% (134). Continual CSF and parenchymal ISF turnovers maintain an optimal microenvironment for neurons and are vital to brain health, such as facilitating the clearance of interstitial solutes, including amyloid-β (123) and extracellular tau (122) from the brain. Natural sleep or anesthesia is associated with a striking increase in convective exchange of CSF with ISF in mice (299). Thus sleep may provide a restorative function with enhanced removal of accumulating brain waste products. As this brain-wide pathway depends on glial (trans-astrocytic) water flux and provides a lymphatic function in interstitial solute clearance, so it is proposed as the “glymphatic” pathway (122, 123). Human glymphatic pathway function may be evaluated by dynamic contrast enhanced MR perfusion imaging (305).

In brief, recent novel findings indicate that the CSF circulation is much more complex than previously recognized. It comprises a directed bulk flow with pulsatile forward and backward movement throughout the entire brain and a continuous bidirectional fluid exchange at the BBB and the cell membranes at the borders between CSF and ISF spaces (37, 132). The important role of extracranial lymphatic pathways for the drainage of ISF and CSF as immunological pathways of the brain is also apparent (46, 291).

A significant imbalance between CSF formation and drainage may lead to a rapid rise in CSF pressure or ICP. Elevated ICP may reduce cerebral blood flow and oxygenation and alter protein expression in neurons and glia. One hypothesis proposes that atrial natriuretic peptide mediates a ventricular servomechanism to stabilize ICP by reducing CSF formation (131, 132). Several animal studies demonstrate the
important role of CSF production and drainage mechanisms in ICP homeostasis. For example, increases in ICP induce a significant and profound decrease in CSF formation in isolated cerebral ventricles of cats (225). Blocking CSF drainage through the cribriform plate increases ICP and the amplitude of its pulse pressure in anesthetized sheep (200). Additionally, increased ICP is associated with a downregulation of CSF in chronic hydrocephalus patients (261).

3. ICP adaptation in real and simulated microgravity

Redistribution of transmural pressures along the vasculature and CSF fluid system due to the loss of hydrostatic pressure gradients immediately induces a mild and sustained increase in ICP during weightlessness (see Equation 1). Gottoh et al. (103) find that transient microgravity exposure during free fall increases ICP significantly in anesthetized rats kept at the 30° HUT position. In ground-based simulation studies, an immediate ICP rise during HDT is demonstrated in human subjects (215, 268), monkeys (143), cats (154), rabbits (141, 277), and rats (195). Gradual return towards the pre-HDT baseline has been noted in some studies (141, 163, 268, 277). Additionally, Maurel et al. (195) demonstrated the impairment of the circadian pattern of the diurnal ICP profile during HDT in rats. Recent, important findings in humans document that ICP during short-term weightlessness with parabolic flight (163) is slightly less than ICP in supine posture (supine, 17 ± 2 mmHg vs. microgravity, 13 ± 2 mmHg). However, the best reference point for ICP on Earth is ~16 h of upright posture (highly variable during sitting, standing, walking) and ~8 h of sleeping posture. Supine or sitting posture alone is not an adequate reference point. Therefore, it is reasonable to conclude that during 24 h in microgravity, brain ICP is slightly but chronically above the variable ICP levels observed on Earth which may explain the VIP syndrome in astronauts. A chronic and mildly elevated ICP in space may adversely affect eye structure and function during prolonged space flight.

What acclimation changes in the important aspects of CSF dynamics and/or intracranial compliance may contribute to the development of VIP syndrome remains unknown. The postflight MRI data of one long-duration astronaut indicated that the CSF production and peak velocity of flow through the aqueduct approximately doubled during the postflight period. And the lumbar puncture opening pressure of this astronaut measured 57 days postflight was 38.7 cmH2O (Kramer, unpublished data cited in Ref. 8). Thus there may be a new set-point for ICP during spaceflight that leads to increased CSF production upon return to Earth.

Gabrion and co-workers (92, 93) have investigated the histology of choroid plexus from both space-floated and ground-based HDT rats. Disorganization of apical microvilli, accumulation of apical vesicles, and partial loss of cell polarity in the choroid plexus epithelial cells were observed. Studies with HDT rats further showed that several proteins involved in the choroidal production of CSF, including Na+-K+-ATPase, carbonic anhydrase II, and aquaporin 1, were affected in the early phase (194). The cGMP levels in choroid plexus tissues from both space and HDT rats were elevated during the adaptation phase (47). These findings suggest a reduced CSF production during adaptation to microgravity. In addition, in space-floated rat fetuses, the development of choroid plexus seems delayed (187). Little is known whether microgravity exposure induces cerebral edema. Kaplansky et al. (140) reported that 6° HDT for 7 days resulted in perivascular edema in the brain tissue of monkeys. However, Shimoyama and Kawai (141, 253) document that no edematous changes are observed and the tight junctions of the capillary endothelium are intact in the brain tissue from the rabbits subjected to 45° HDT for 8 days. Jennings (129) proposes that in microgravity the cerebral postcapillary venous pressure is elevated, and thus cranial interstitial fluid accumulates. Using MRI to detect tissue water changes within the cranium of human subjects during HDT, Caprihan et al. (45) demonstrate that a tendency for global cerebral edema is not indicated, but the water fraction in the eyes and subarachnoid CSF is reduced (Figures 2A and 3).

C. IOP and AH Dynamics

1. AH dynamics and IOP homeostasis on Earth

As summarized in Equation 1, IOP is determined by episcleral venous pressure and the flow of ocular AH against resistance. Episcleral venous pressure in healthy humans is in the range of 7–14 mmHg with typical values between 9 and 10 mmHg (231). Episcleral venous pressure increases by 3.6 mmHg changing body position from seated to supine. In the healthy eye, the resistance of the conventional AH drainage tissues is ~3–4 mmHg·µl⁻¹·min⁻¹ and AH flow against the resistance generates an average IOP of ~15 mmHg (101). IOP is necessary to inflate the eye and maintain the proper shape and optical properties of the globe. Pooled data from large epidemiologic studies indicate that the mean supine IOP is ~16 mmHg with standard deviation of 3 mmHg (lower by ~1 mmHg in seated posture). However, the frequency distribution of IOP is non-Gaussian with a bias towards greater pressures, especially over the age of 40 yr (61). No distinct threshold exists for a safe/unsafe IOP because some eyes undergo damage at 18 mmHg or less, whereas other eyes tolerate IOP values at 30 mmHg and above. A simple postural change from upright to recumbent elevates IOP by 3–4 mmHg, regardless of the time of the day, because of the increased episcleral venous pressure. Human IOP also varies significantly during the wake-sleep cycle. Twenty-four-hour assessment in glaucoma and sleep studies (213) documents that IOP peaks roughly around 5:00–5:30 in the morning (during sleep
period), and aging has a shifting effect delaying the peak post-awakening (189). A posture-dependent change in episcleral venous pressure per se does not explain the circadian rhythm of IOP with nocturnal elevations because the nocturnal elevation of IOP is detected in healthy young adults in both the sitting and the supine positions (173, 174) (FIGURE 2, B AND C).

The IOP reflects a balance between production and drainage of ocular AH. AH is a transparent and colorless medium between the cornea and the lens and constitutes an important component of the eye’s optical system. Approximately 250 μl of AH are present in the anterior and posterior chamber, and a complete turnover of this fluid occurs approximately hourly (101). Aqueous flow averages 2.9 μl/min in young healthy adults and 2.2 μl/min in octogenarians and has a circadian pattern (cited in Ref. 8). The rate of aqueous humor turnover is estimated at 1.0–1.5% of the anterior chamber volume per minute, which is 2.4 ± 0.6 μl/min (mean ± SD, daytime measurements). AH flow in humans follows a circadian rhythm, being higher in the morning than at night: ~3.0, 2.4, and 1.5 μl/min in the morning, afternoon, and at night, respectively (101). Moreover, many ocular parameters such as IOP, corneal thickness, corneal topography, and anterior chamber biometrics also show diurnal oscillations. These circadian rhythms may be important in the control of ocular growth. Animal studies document that altering ocular circadian rhythms may result in an inability of the eye to regulate its growth to achieve emmetropia. Furthermore, loss of circadian rhythms may illicit a constancy in which the eye defaults into responses of light or dark (219). In a human study, it is found that rhythms in axial length and choroidal thickness are in approximate anti-phase, and IOP and axial length have an in-phase relationship with eyes being longest during the day and choroids thickest during the night (49).

There are two drainage pathways for AH: the trabecular meshwork-Schlemm’s canal and the uveoscleral pathway (29). The majority of drainage (up to 80%) flows out through the trabecular meshwork into the Schlemm’s canal and is subsequently absorbed into the episcleral veins via the collector channels. The trabecular meshwork is a specialized vessel wall, consisting of three portions, namely, the

FIGURE 3. Hypothetical model for an IOP/ICP mismatch and pathogenesis of VIIP syndrome during prolonged spaceflight. Weightlessness induces 1) mildly but chronically elevated ICP due to loss of hydrostatic pressures and tissue weight, 2) initial IOP rise due to episcleral venous pressure elevation and choroidal congestion, and 3) chronic IOP/ICP mismatch between compartments on either side of the lamina cribrosa, leading to an anterior movement of the optic disk with visual impairment. However, additional factors may aggravate the maladaptation of eyes and vision during prolonged weightlessness.
uveal, corneoscleral, and juxtacanalicular meshwork. The trabecular meshwork is a triangular, porous structure in cross section that consists of connective tissue surrounded by endothelium. The Schlemm’s canal is a venous sinus, comprised of endothelial cells surrounded by connective tissue. In humans, 75% of the resistance to AH outflow is localized within the trabecular meshwork with the juxtacanalicular portion being the main site of outflow resistance. Because normal IOP transients (such as occur during the cardiac pulse, blinking, and eye movement) induce deformation of the trabecular meshwork and because the Schlemm’s canal has valves, the aqueous outflow is pulsatile (29, 135, 136). Whereas for long-term homeostasis, mechanotransduction and tissue remodeling through biomechanical coupling of IOP, flow and wall stresses are involved. Regulation of the extracellular matrix composition appears to influence AH outflow resistance. Deposition of glycosaminoglycan and proteins, such as cochlín, in the trabecular meshwork may be responsible for increased outflow resistance at this specific site (101, 275). In the uveoscleral pathway, AH flows through the uveal meshwork at the anterior face of the ciliary body and iris root into the supraciliary and suprachoroidal spaces to either veins in the choroid and sclera or through scleral pores to episcleral tissue and ultimately drains into the lymphatic system. In non-human primates, 40–50% of AH leaves the eye by the uveoscleral route. In humans, most data by indirect calculations suggest a similar fraction, at least in eyes from younger individuals (9). The uveoscleral pathway is relatively independent of IOP and the proportion of AH exiting the eye via this pathway decreases with age. The behavior in response to different pharmacological agents also differs between the two drainage pathways. The rate-limiting step in unconventional pathway is flow through the ciliary muscle. Whereas in the conventional pathway, flow proceeds through the inner wall of Schlemm’s canal (9, 29, 30, 101).

A great deal of interest and study is directed towards elucidating the underlying mechanism responsible for the homeostasis of IOP. Elevated IOP imposes a greater pressure load than normal to the inner surface of the eye wall (76, 257). IOP-related stress is magnified at the ONH and affects the ganglion cell axons and small blood vessels traversing the ONH (41, 87, 179, 245, 259). Bui et al. (41) find that chronic IOP elevation even at a mild level may induce a cumulative retinal dysfunction, producing progressive changes in the ONH and the retina. Intraocular pressure is regulated by balance between the formation and outflow of AH. In 1963, Barany (22) predicted from a theoretical study that in the absence of vasoregulatory influences, AH formation is suppressed by elevation of IOP. However, subsequent studies have reported contradictory results and are currently disputed. For example, slight changes of body position do not alter AH flow as measured by fluorescein clearance, although respective IOP changes occur (48). However, AH outflow as measured by weighted tonometer technique does not show significant differences between supine and sitting positions (251). It is evident that the AH outflow resistance within the conventional outflow pathway is continually adjusted to maintain IOP homeostasis (3, 135). Both ex vivo and in vivo studies demonstrate that acute IOP elevation significantly reduces cross-sectional area of Schlemm’s canal (139). Transient IOP increases due to the cardiac pulse, blinking and eye movement cause deformation in the elastic structural elements of the juxtacanalicular cells, and the inner wall endothelium of Schlemm’s canal. When the pressure spike decays, these elastic elements return to their original configuration, thus inducing a pulsatile AH flow from the valves into the canal. However, long-term homeostasis requires mechanotransduction through biomechanical coupling of IOP, flow, and wall stresses to optimize tissue biomechanics that define the aqueous pump performance (135, 136). Using perfused ex vivo human and mouse eyes, or cell culture model, Acott et al. (3) document that the trabecular meshwork and/or Schlemm’s canal inner wall cells sense the mechanical stimulus due to sustained IOP elevation and respond by initiating a complex extracellular matrix turnover process to adjust AH outflow resistance to restore IOP to acceptable levels.

2. IOP adaptation in microgravity and bed rest

Experiments in parabolic flight have observed an instantaneous IOP elevation during acute microgravity exposure. Draeger and associates document a mean of 5-mmHg increase of IOP during the free-fall phase of parabolic flight using a handheld applanation tonometer (cited in Ref. 8). Mader et al. (181) measured IOP during parabolic flight using a TonoPen. They found a 58% increase in IOP, from a mean baseline value of 12 mmHg to a mean of 19 mmHg within 20 s of exposure to microgravity. Moreover, a 4% reduction in the caliber of retinal arteries was also noted. More recently, Anderson et al. (13) found that IOP in microgravity (16.3 ± 2.7 mmHg) was significantly elevated above that in seated (11.5 ± 2.0 mmHg) and supine (13.7 ± 3.0 mmHg) positions and was significantly less than IOP in the prone position (20.3 ± 2.6 mmHg).

Several studies during short-duration spaceflight document that IOP is elevated in the first few days and moderates over time and then decreased below preflight levels upon returning to Earth. The first IOP readings were obtained during D1 Spacelab mission by Draeger et al. (78). They reported an IOP rise of 20–25% at 44 min after entry into microgravity, followed by a decrease in IOP. In subsequent studies, they measured IOP at 15 min after entry into microgravity and documented a 92% increase in the German-Russian MIR mission and a 114% increase in IOP in the Spacelab D2 mission (79). A postflight decrease of IOP compared with preflight measurements was also observed in Apollo astronauts (184, 220). According to data for 11 subjects over 6 Shuttle missions, it seems that the largest IOP values
were recorded during the first 6 days of flight, revealing a sharp rise in IOP over baseline values (8, 77, 78). Chung et al. (58) measured the IOP of a woman astronaut during ISS flight using a pressure phosphene tonometer. They reported a mean IOP rise of 26.3% that was maintained until Launch +8 days.

In general, analogs of head-down tilt and horizontal bed rest are not very good models for simulating the visual changes that occur in space (112). However, supine posture, when compared with upright posture on Earth, may offer useful data to understand IOP and its diurnal variations (8, 271). For example, similar to space, an immediate increase in IOP is well documented in short-duration bed rest studies (48, 89, 138, 176, 184, 301). Several bed rest studies suggest that elevated IOP resolves over time. For example, in a 10° HDT bed rest study for 48 h, Mader et al. (184) report that IOP increased 4.7 mmHg within seconds of assuming the HDT position and decreased 6.7 mmHg when they sat up 48 h later, apparently explained by a compensatory decrease in AH volume. They also note that a circadian rhythm in IOP is maintained despite sustained elevations of IOP. In addition, the calibers of retinal arteries and veins immediately decrease during 10° HDT (89, 184). Chiquet et al. (57) measured IOP in 25 women subjects using a noncontact tonometer during a 6° HDT bed rest study for 7 days. They note that, after an initial immediate rise, IOP exhibits a slight and progressive decrease of 1.3 mmHg. In a 120-day horizontal bed rest study, Kuz’min (159) reports that IOP increased in two subjects with visual disorders, but returned to the control level at the end of the experiment and during recovery. The first known study to test the outcomes of bed rest on visual function is from Drozdova and Nesterenko (80). They report that prolonged bed rest reduces visual acuity, visual field, and IOP with an enlarged blind spot area. However, Mekjavic et al. (197) report that no significant changes in visual function were noted during a 35-day horizontal bed rest study. More recently, Taibbi et al. (273) report a reduction in IOP associated with subtle changes in ocular structure and visual function in a healthy subject after 30-day 6° HDT bed rest. They further document that 14 days of 6° HDT bed rest initially raises IOP with a tendency to return to baseline levels without clinically relevant visual changes (272).

Altered body position studies demonstrate the relation between the ocular venous pressures due to hydrostatic pressure redistributions along the vasculature and the relevant IOP changes. Draeger and Hanke (77) reported that postural changes from 90° HUT to 90° HDT position almost tripled IOP from ~12 to ~34 mmHg in 20 subjects. Similar effects of inverted body position on IOP were also reported by other studies (90, 91, 171, 289). Friberg et al. (90) found that the IOP rise during gravity inversion is closely related to increased venous pressure in the orbit: for each 0.83 ± 0.21 mmHg increase in episcleral venous pressure, there is a rise of 1 mmHg in IOP. The caliber of retinal arterioles is also decreased following body inversion (91). In animal studies, Aihara et al. (5) successfully measured the episcleral venous pressure of the mouse eye based on the detection of erythrocyte reflux from an episcleral vein into Schlemm’s canal. They found that both episcleral venous pressure and IOP increased with the degree of the HDT body position. Usually choroidal deposits of blood are removed by vortex veins. With the head in supine posture, venous blood may stagnate in the choroid due to gravity. Because the choroidal circulation is without autoregulation, fluid accumulates unabated except for the counteracting effect of higher IOP. The passive response of the choroidal circulation to altered posture is also supported by the linear relationship between the subfoveal choroidal blood flow and the calculated ocular perfusion pressure (138, 176, 301). The increase in choroidal blood flow is primarily due to an increase in the nonpulsatile component of the blood velocity (176). As noted by Smith and Lewis (265), a sudden rise in choroidal blood volume of 20 µl may result in an immediate rise in IOP of more than 20 mmHg because the rigid sclera is not compliant with this increase in ocular volume. Using spectral domain-optical coherence tomography, Shinojima et al. (254) find that the subfoveal choroidal thickness and IOP are increased during a brief HDT, while the foveal retinal thickness is unaffected, indicating that the venous blood is easily pooled in the choroidal stroma by greater venous pooling and pressure during HDT. However, measuring the pulsatile component of the choroidal ocular blood flow synchronized with each cardiac cycle, Kerfoot and Lovasik (144) document that HDT reduces choroidal pulsatile ocular blood flow, suggesting a retinal hypoperfusion to the outer retinal layers. This also reflects a reduction in the compliance of choroidal vasculature due to blood pooling in the choroidal stroma. In animal studies, Gotoh et al. (104) show that transient microgravity exposure during free fall elicits increases in the cephalic perfusion pressure and iris capillary blood flow of anesthetized rats being kept at the 30° HUT position. It provides further evidence that the autoregulatory capacity of the ciliary artery/uveal circulation is weaker than the central retinal artery/retinal circulation.

It is apparent that the almost instantaneous IOP rise and the initial peak upon entry into microgravity is due to an immediate loss of hydrostatic pressures due to the removal of gravity (288, 311, 316). Moreover, the subsequent passive choroidal congestion is due to lack of autoregulation in the uveal circulation, while the ocular perfusion pressure is increased upon entering microgravity (71, 138, 176, 265). Other weightlessness effects such as elevated cephalic venous pressure due to increased extracranial venous backflow, loss of weight of eyeball, and periocular fluid volume change will require further investigation. It is hypothesized that the decrease of IOP after the initial peak may be due to a compensatory decrease in AH formation and aequous
and IOP is of critical importance in the pathogenesis of disorders that lead to glaucomatous-optic neuropathy. In the 1970s, Volkov (286) pointed out that CSF pressure is associated with glaucomatous optic neuropathy. Berdahl and co-workers (26, 27) demonstrated for the first time that ICP is decreased in primary open-angle glaucoma compared with controls. Ren et al. (242) also demonstrated in a prospective study that ICP in normal-tension glaucoma patients was significantly lower than in open-angle glaucoma. Their study also suggested that in ocular hypertensive patients without glaucomatous optic nerve damage, an abnormally high CSF pressure may represent an increased counterpressure to the elevated IOP (243). In animal studies, it was documented that reducing ICP in cats had a similar effect on the optic nerve as raising IOP (Yablonski et al., 1979; cited in Ref. 25). More recently, Yang et al. (304) found that chronic reduction of CSF pressure in monkeys was associated with the development of an optic neuropathy in some monkeys.

In contrast, if ICP is higher than IOP, due to either elevated ICP or lower IOP, papilledema may occur (117). The reversal or reduction of the normal TLPD may lead to anterior movement of swollen optic nerve that bulges forward with edema present in the surrounding retinal nerve fiber layer (118, 280). Jinkins (130) reported that, regardless of the cause of intracranial hypertension, certain features were noted repeatedly in an orbital CT study. These features included dilation of the optic nerve sheath, “bulging” of the terminal optic sheath subarachnoid space into the posterior aspect of the globe at the ONH, and a depressed perfusion of the optic disk/nerve junction. A positive correlation between ICP and IOP is found in some clinical studies, and hence, IOP is proposed as a noninvasive measure of ICP for clinical utility (214), but it seems to lack the accuracy necessary for close management of intracranial pressure in emergency medicine (267, 306).

### 2. Structure and function of the optic nerve head

In normal adults, the average length of the optic nerve is ~40 mm, and its average diameter, with and without the nerve sheath, is ~4 and 3 mm, respectively. The optic nerve travels through two pressurized regions, the intracranial space and the intraocular space. Under normal conditions, a small volume of CSF fluid is contained along the entire length of the optic nerve. The ONH faces the intraocular space, and the optic nerve itself lies within the subarachnoid space (SAS) and is surrounded by CSF that enters the SAS via the chiasmal cistern. The periretinal SAS of the optic nerve is contiguous with the intracranial SAS and therefore, when ICP increases, the optic nerve is distended. Measurements of the SAS pressure of the optic nerve on fresh cadav-
ers find interindividual variations and a linear relationship with ICP (172).

The meninges and the orbital SAS surrounding the optic nerve transforms into a distensible blind end (a cul-de-sac structure) behind the ocular globe, ending at the sclera. Killer and co-workers (145, 147, 148) demonstrate that the optic nerve SAS (ONSAS) is a multichambered system, divided by arachnoid trabeculae and septae that may play a role in the hydrodynamics of the CSF inside the ONSAS. The pressure within the ONSAS is caused by an influx of CSF from the chiasmal cistern and the tissue pressure in the orbit. The immediate retrobulbar space is more distensible due to the absence of pillars and septae found in the less distensible intraorbital and canalicular portions of the optic nerve sheath. This arrangement allows a buildup of physiological pressure within the retrobulbar space, thereby facilitating the periodic reverse flow and thus circulation of CSF within the ONSAS (145, 148). In addition, lymphatics in dura of the optic nerve may be involved in the regulation of pressure in the ONSAS, especially during eye movements (145, 149, 177). Hansen et al. (108) have determined the elasticity of isolated human optic nerve sheaths and predict that the optic nerve function is reversibly impaired after episodes of prolonged elevated ICP. In some pathological conditions the ONSAS width is increased with elevated ICP, and there is a relative stasis of CSF flow, probably due to thickened trabeculae. This reduced flow may have metabolic consequences by reducing removal of toxic metabolites and reduced delivery of metabolites to regions, particularly near the termination of the ONSAS. ICP may also affect the lymphatic and neural tissues at the ONSAS termination (146, 150, 204).

The lamina cribrosa (LC) is the primary structure that forms a pressure barrier between the two pressurized compartments, the intraocular space and the retrobulbar space (42, 137, 209). Bundles of nerve fibers with a latticelike anatomy with successive and porous cribiform plates pass across the optic nerve canal. These cribiform plates are lined by basement membranes and contain fibrillar collagens and elastic fibers. The LC permits the retinal ganglion cell axons and central retinal vein to exit the eye, allowing the central retinal artery to enter the intraocular space and support the IOP by a barrier between intraocular and extraocular spaces. Due to the barrier function of the LC, leakage of aqueous humor is counteracted from the intravitreal volume into the retrobulbar CSF volume encompassing the retrobulbar aspect of the optic nerve. Hence, the LC and its constituent elements are also very sensitive to alterations in pressure across this region with a major influence upon the eye, particularly in the ONH region.

The difference between IOP and the retrolaminar tissue pressure pressure creates a translaminar pressure gradient (TLPG) [TLPG = (IOP–ICP)/LC thickness] across the LC. In the normal eye, the TLPG is ~1 mmHg per 100 μm, as the thickness of the normal LC averages 458 μm (209). The TLPD and TLPG gradient determines the position and the tissue mechanical stress of the LC and helps determine the surface shape of the optic disk (209). Forces acting upon tissues are due to TLPGs, and thus, these forces and their effects are reduced by minimizing TLPG. A higher TLPG may cause abnormal function and damage of optic nerve due to changes in axon transport, deformation of the LC, altered blood flow, or a combination of them all. Morgan and associates (208–210) have determined the relationships between intraocular, ONSAS, and retrolaminar tissue pressure to CSF pressure using a servo-null micropipette system in dogs. There is a strong linear relationship between optic nerve SAS pressure, retrolaminar tissue pressure, venous pulsation pressure, and the lateral ventricle CSF pressure above certain CSF pressure levels. However, when CSF pressure is less than −0.5 mmHg, there is no fluid communication between the intracranial and optic nerve SAS. Acute alterations in TLPG are associated with certain changes in optic disk. Elevations in IOP may reduce rapid orthograde and retrograde axonal transport across the LC (198, 236) and alter ganglion cell axon neurofilament properties (20). Contrarily, raised CSF pressure can lead to impaired axonal transport with axonal material accumulation within the prelaminar tissue (280), and to raised retinal venous pressure (211). Morgan et al. (205) document that elevation in IOP displaces the posterior aspect of the optic disk surface significantly, whereas elevated CSF pressure produces significant anterior displacement. For any alteration of pressure, an increase of CSF pressure produces larger IOP elevations. Most optic disk translocation is due to altered pressures at low TLPDs, consistent with collagen mechanical properties. Recently, Morgan et al. (207) highlighted the fundamentals of retinal vein pulsation. They found that retinal venous collapse is in phase with CSF pressure pulsations. Using recently-developed techniques, they suggest that noninvasive measurement of CSF pressure is possible.

Quigley (237) has defined open-angle glaucoma as a disease of retinal ganglion cells, characterized by structural change in the optic disk and by a typical, slowly progressive loss of function. The level of IOP is no longer a defining criterion for this disease, but an important risk factor. A common site of injury is the axonal level of the ONH where orthograde and retrograde axonal transport is inhibited (237, 238). The typical field loss pattern is explained, in part, by regional laminar architecture. In addition, altered connective tissue of LC is also central to the understanding of pathogenesis of this injury (235). It is documented in monkeys that IOP elevation causes loss of elastic compliance of the ONH early in the course of acute and chronic IOP elevation (43). During aging, LC shows an increase in nonenzymatic glycation, a process that weakens collagen and changes in the amounts of types I, III, and IV collagen (6, 7). A change...
in LC mechanical behavior towards decreased resilience may compromise the ability of LC to support the nerve axons that pass through it. The change in the compliance of LC is most marked after 40–50 yr of age and may be implicated in the susceptibility of the elderly LC to pathogenic factors.

3. Biomechanics of the optic nerve head

Special attention is focused on the biomechanics of the ONH and the LC specifically, because it is the principal site of retinal ganglion cell (RGC) insult in glaucoma. Importantly, we need to understand how altered ocular biomechanics affect the biological response and glaucomatous injury. Because noninvasive imaging technology for direct measurement of deformations interior to the ONH is unavailable at present, modeling is the primary approach for studying the biomechanics of ONH and LC. Relevant studies have pointed out the crucial role of IOP-related stress/strain within the load-bearing connective tissues in ONH aging and glaucomatous damage. It shows that the underlying mechanisms may involve mechanical failure of the connective tissues of the LC, sclera canal wall, and peripapillary sclera and axonal transport compromise within the LC by a variety of mechanisms. On the other hand, chronic IOP-related remodeling of the extracellular matrix of the laminar beams may limit the diffusion of nutrients to RGC axons in the ONH (42, 76, 257).

IOP generates a pressure normal to the eye wall inner surface, producing hoop and compressive stresses. This IOP-generated in-wall stress is primarily borne by the stiff, collagenous sclera, while the more compliant retina and nerve fiber tissues are exposed primarily to the compressive or tensile stress of IOP. In addition, shear stresses are maximal at the border between the sclera and the LC and minimal at the center of the ONH, because the majority of the posterior displacement in the LC occurs near the periphery of the ONH (303). This is also consistent with clinically observed patterns of visual field loss in glaucoma.

This modeling approach indicates that peripapillary sclera properties have a strong influence on ONH biomechanics. IOP is borne in the ONH by the fenestrated connective tissues of the LC that span the scleral canal opening and tether into the stiff outer ring of circumferential collagen and elastin fibers in the peripapillary sclera. Therefore, the ONH in the corneo-scleral shell is a discontinuity ("weak spot"), typically giving rise to stress or strain concentrations in mechanical systems. Most research that helps understand glaucoma pathophysiology and vision loss and optic nerve head cupping relates to retinal ganglion cell axon injury within the LC. Finite element models document IOP-related stress within connective tissues of the ONH at low levels of IOP and suggest that scleral canal size, shape, and thickness determine the magnitude of IOP-related stress within the ONH (24). Monkey eye LCs exhibit local strains dependent on laminar beam microarchitecture. Smaller-scale modeling documents beam-level stresses and strains that are much higher than for models without LC beams. In brief, peripapillary sclera thickness and stiffness of the laminar beams strongly affect the mechanical damage to interior LCs (257). Recently, Sigal et al. (258) obtained high-resolution (trabecula-scale) eye-specific measurements of the displacements and deformations induced within the LC by an acute increase in IOP in uncut and unfixed human eyes. Elevated IOP produces substantial in-plane LC stretch and compressive strain. In addition, recent progress in imaging technology may add a useful tool for future three-dimensional analysis of the LC microarchitecture in vivo. An automated segmentation of the three-dimensional LC scanned by adaptive optics spectral domain optical coherence tomography (OCT) is now proposed and validated (216). (FIGURE 2, B AND C).

V. IOP/ICP MISMATCH HYPOTHESIS AND POTENTIAL COUNTERMEASURES

A. IOP/ICP Mismatch Hypothesis for Space V2iP Syndrome

In a 1-G environment, normally there is a low positive pressure difference between IOP and ICP. This pressure differential helps maintain the shape of the eyeball and the fixed distance of the refractive surfaces from the retina. However, during long-duration spaceflight, chronic microgravity may cause a mismatch between IOP and ICP, characterized by a chronic, mildly elevated ICP. Hence, the normal TLPD is altered due to changes in the pressure relationship between compartments on either side of the LC, thus leading to refractive changes and ONH pathological changes, such as papilledema (28, 157, 182, 204, 316).

Our hypothesis is depicted in FIGURE 3. First, we propose that a chronic, mildly elevated ICP in space is most likely accounted for by the hydrostatic and hemodynamic changes in the cranial circulation and the cerebral CSF space due to the removal of gravity. Upon entry into microgravity, the pressures within the cranial and ocular blood vessels and the cerebral CSF space immediately rise due to the loss of hydrostatic pressures and the increase of blood and CSF pressures (compared with these pressures during normal-upright daily activities on Earth) is maintained during weightlessness. Thus, as a secondary consequence to these chronically increased pressures, a headward fluid volume shift occurs while a stable cerebral blood flow is well-maintained as efficient autoregulatory mechanisms (17, 97, 288, 311, 313). Second, with reference to ocular circulation and AH homeostasis, the rapid IOP rise and the initial peak are due to an immediate elevation of episcleral and vortex venous pressures and choroidal congestion upon entering
microgravity (5, 90, 138, 231, 254, 265). Whereas a direct hydrostatic effect on the AH fluid is negligible (height of this fluid column is quite short), it is most likely that there exists a mechanism to protect the retina, sclera, and optic disk from elevated IOP beyond tolerable limits by lowering AH formation and reducing the compressive or tensile stress and in-wall circumferential stress due to the high IOP load (41, 42, 76, 86, 212). But the possibility that there is a compensatory failure of the homeostatic mechanisms for maintaining IOP/ICP matching cannot be excluded. Third, regarding the crucial role of the adaptive change of the ONH in the pathogenesis of space VIIP syndrome, we agree with the view proposed more recently by Berdahl et al. (28) and Morgan et al. (204). Thus a long-standing pressure mismatch between spaces on each side of the LC may reverse or reduce the normal TLPD leading to an anterior movement of the optic disk with refractive and peripapillary retinal changes and papilledema. However, acclimation-induced mechanical failure of the connective tissues within the LC needs further elucidation. Fourth, there may be yet additional factors that aggravate this maladaptation of eyes and vision due to prolonged microgravity exposure. For example, in upright posture on Earth, orbital pressure (2 mmHg) is greater than CSF pressure, causing the ONSAS pressure to be dependent on orbital tissue pressure at low CSF pressures. However, in weightlessness, this appears not to occur, because the weight of the eyeball disappears, and the CSF pressure at the level of ONSAS is probably chronically higher (28, 209). Also, the chronic absence of periodic pressure changes in cerebral CSF space and ONSAS in space decreases CSF removal from terminal ONSAS lymphatics. This may also accentuate the pressure and CSF translocation in regions of the ONSAS, thus accumulating toxic metabolites and reducing delivery of necessary nutrients (28, 204). An occupational surveillance analysis of ISS astronauts reveals that VIIP cases have greater optic nerve sheath diameter compared with non-VIIP cases (8). Other cranial vascular and lymphatic changes in weightlessness, such as increased venous outflow from the extracranial organs and the subcutaneous edema in facial and neck regions, may also contribute, leading to the reduction of the cranial lymphatic drainage and elevation of ICP. Contrarily, a significant increase in the compliance of the craniospinal space may occur in space due to loss of spinal curvature (249) and hence the ICP elevation may be attenuated. We also suggest that weightlessness may constitute another type of “constant condition” whereby the absence of gravity may eliminate the Zeitgeber of diurnal, thus affecting the circadian rhythm of IOP and ocular processes associated with the eye growth regulation and emmetropization (49, 219). Whether the ICP rhythm (221) or even the IOP/ICP phase relationship is altered in space remains unknown.

To integrate our knowledge about cardiovascular adaptation to microgravity (109, 111, 288, 311, 313) and the recent progress in studies on terrestrial glaucoma and IIH (25, 28, 137, 204, 209, 237), we need a working hypothesis to explain the etiology and pathogenesis of space VIIP syndrome. Three key issues should be addressed with a strategy of interaction between spaceflight and ground-based, multidisciplinary experimental studies at different levels. First, can a chronic, mildly elevated ICP during long-duration spaceflight be sufficiently accounted for by the physical principles of hydrostatics and subsequent acclimation changes in both the cranial hemodynamics and the CSF dynamics? More inflight data collected by novel on-orbit imaging and noninvasive ICP measurement with required preflight and postflight tests will help to ascertain the exact magnitude and temporal characteristics of the postulated chronic, but mild ICP elevation in space. Microgravity-induced pressure and flow changes within the CSF fluid column along the cranio-spinal axis should be explored by space and ground-based animal and human studies in association with physical and mathematical models (81, 152, 185, 186, 247). It remains unknown how CSF homeostasis is adjusted to a new set point to adapt a sustained, mildly elevated ICP in space. Several animal studies suggest that adaptation to microgravity reduces CSF production in rats (47, 93, 194). Second, is the long-duration spaceflight-induced translaminal pressure gradient between IOP and a mild, but chronically elevated ICP well validated? Inflight IOP should be measured during a long-duration spaceflight by novel technology such as continuous 24 h IOP monitoring (188, 189, 263) and compared with preflight and postflight data. Such results may provide an overall picture indicating the decreasing trend towards a reduced IOP relative to a chronic, mildly elevated ICP in space. Attention should be further focused on whether AH formation is suppressed after the initial elevated IOP upon entry into microgravity. Furthermore, how do AH formation and outflow resistance adjustment mechanisms of the astronauts undergo adaptive changes to achieve a new set point in space (3, 48, 59, 101, 139)? Third, can the hypothesized ONH changes from an IOP/ICP mismatch in space be proven by experimental evidence obtained from multidisciplinary space and ground-based studies? For example, recent progress in imaging technology make it possible to gain three-dimensional analysis of the LC microarchitecture (216) and direct measurements of the deformation of the peripapillary retinal pigment epithelium layer (158) of astronauts in space. In addition, ground-based simulation analogs may provide useful tools to clarify the chronic microgravity-induced acclimation changes of the ONH, LC, and ONSAS and to elucidate the underlying mechanisms by in vivo, ex vivo, and in vitro experimental studies. Rat models now cause chronically elevated IOP; and the resulting IOP elevation is measurable, thus quantitating damage to the retina and optic nerve. For example, Bui et al. (41) have established a rat model to study the retinal dysfunction produced by chronic IOP elevation. In this model, the electroretinogram is an index to assess the severity of the retinal dysfunction and the underlying pathological
changes. Morrison et al. (212) have demonstrated that the low-cost rat model is more manageable and allows treatments to alleviate optic nerve damage. Recently, Chowdhury and co-workers (248) report a novel rat model, the intraventricular cannula model, that can study the effect of altered ICP on optic neuropathies and the interplay between IOP and ICP. Furthermore, Aihara et al. (4) document similar AH production and turnover rate in mice as in human eyes. The occurrence of both conventional and uveoscleral outflows indicates the mouse model is a fruitful tool for AH dynamics. Fortunately, Chen and co-workers (52, 53, 314) have modified the tail-suspended rat model established by Morey-Holton and co-workers (201, 202) and thus have extended the simulation period up to 120 days.

These animal studies will be of great help to gain deeper insights into the IOP/ICP matching homeostasis mechanism on Earth and the pathogenesis of the terrestrial glaucoma and IIH as well. It is a significant challenge to study the homeostasis of IOP and ICP in an integrated conceptual framework, instead of an isolated mode, even though fluid volumes and formation rates of the AH systems are far smaller than those of the CSF system by about three magnitudes and the entire cerebrospinal fluid space is more compliant than the rigid eye ball (FIGURE 2D).

However, novel experimental studies along with mathematical modeling are required because the regulatory systems maintaining a physiological IOP/ICP matching in a 1-G environment involve many interactive positive- and negative-feedback loops. Thus it is difficult to elucidate the underlying homeostatic mechanism by simple and linear reasoning based on traditional understandings of the CSF and AH systems. Until recently, simulation studies have been restricted to regulatory networks of small size and modest complexity. The modeling of the CSF or AH fluid systems is from an isolated perspective, for example (22, 64, 83, 105, 161, 191, 283, 284). Wakeland and Goldstein (287) reviewed the literature regarding modeling of ICP dynamics and discussed the methodology, limitations, and opportunities for further simulation studies. The whole body, lumped-parameter model introduced by Lakin et al. (161) is now used to simulate the effect of microgravity on ICP. Simulation results suggest that ICP in microgravity is elevated but is less than that in HDT on Earth (160, 269).

To our knowledge, no simulation study attempts to elucidate comprehensively the regulatory system regarding the homeostasis of IOP/ICP matching on Earth from a systems physiology perspective.

B. Rationale of Artificial Gravity as a Potential Countermeasure

Given that microgravity-induced adaptation/acclimation of the cerebral and ocular vasculature and the CSF and AH fluid systems may play a significant role in the pathogenesis of VIIP syndrome, the countermeasure efficacy of intermittent artificial gravity (IAG) generated by a short-arm centrifuge (60, 307) or exercise within lower body negative pressure (LBNP) (109, 114) for preventing VIIP should be evaluated. Moreover, the possible efficacy of LBNP alone (109, 178) and thigh cuff placement (18) also merits consideration.

Over the past 20 yr, microgravity adaptations of the circulatory end organs (heart and vessels) are primarily responsible for postflight orthostatic intolerance (33, 34, 73, 111, 113, 169, 311, 313). For vascular adaptations, loss of transmural pressures along the arterial vasculature in microgravity is the primary factor for vascular remodeling. Furthermore, daily short-duration IAG prevents these vascular adaptations (311, 312) such as postflight cardiovascular deconditioning (109, 111). Current exercise countermeasures cannot produce an acceleration field and, thus, cannot restore tissue stresses and blood hydrostatic pressures to their daily levels on Earth (109, 255, 307, 308, 311). Exercise with some form of IAG should provide the most effective countermeasure to maintain physiological structure and function for future deep-space missions (164, 307).

However, due to technical difficulties, IAG on a short-arm centrifuge is presently feasible as an alternative to continuous artificial gravity, as depicted in Kubrick’s “Space 2001 Odyssey,” as provided by spinning the entire spacecraft (44, 60, 155, 285, 307). However, a human centrifuge is not now available for long-term spacecraft (164, 307). Exercise within LBNP is another form of artificial gravity (109, 111, 113, 288), allowing normal and even higher than normal stresses on the musculoskeletal system with Earth-like transmural pressures across blood vessels of the lower body. This exercise concept prevents loss of aerobic capacity, altered submaximal exercise responses, and decreased physiological performance with short- and long-term simulations of microgravity (106, 109, 111, 163, 250). Moreover, recent separate studies by Macias et al. (178) and Petersen and co-workers (personal communication) demonstrate that LBNP reduces ICP during HDT of normal volunteers. Combining LBNP with negative pressure respiration is proposed as a possible countermeasure to generate normal Earth-like blood pressures over the body in space (21, 297). Using a rat model to simulate the effectiveness of IAG, Zhang and co-workers (270, 312, 317) show that the minimum gravity (G) exposure requirements vary greatly in different systems. It is worth mentioning that daily simulated IAG by -Gx gravitation for 60 min, or 4% of the total unloading time, is sufficient to prevent vascular adaptation during 28 days of simulated microgravity, even though the minimum effective exposure time is yet undefined. In addition, the effectiveness of simulated IAG in preventing vascular adaptation is further demonstrated in an ex vivo study using artery culture (95) for biomechanical studies on isolated mesenteric and middle cerebral arteries (56, 94) and
for an integrative study with conscious rats (315). It seems that central to these mechanisms is the extracellular matrix-integrin-cytoskeletal axis, which provides anchoring mechanisms for cell-cell and cell-extracellular matrix interactions (166, 193). It is also possible that multiple self-stabilizing tensegrity modules in the heart and vascular tissues possess a strong resilience or “memory” function towards restoring to their original prestress and tensegrity state at 1-G environment that are quickly triggered by a brief periods of IAG (125, 126).

With respect to thigh cuff placement, Herault et al. (119) report that repeated applications of thigh cuffs over the 6-mo Mir spaceflight do not prevent the development of orthostatic intolerance. The reason may be that these cuffs can only create a more Earth-like fluid distribution mainly in the venous system and the body fluid system, but cannot affect the transmural pressure redistribution along the arterial vasculature in weightlessness.

VI. SUMMARY AND PROSPECTS

Evidence thus reviewed supports that a chronic, mildly elevated ICP may exist in space and is largely accounted for by the loss of hydrostatic pressure gradients. It seems most likely that the subsequent elevated pressure gradient across the lamina cribrosa caused by a chronic, but mildly elevated ICP may be adaptive in nature. A chronic IOP/ICP mismatch thus built up in space might induce acclimation changes in the ONH, LC, and ONSAS, thus playing a central role in the pathogenesis of space VIP syndrome. Using new theories and noninvasive technology for measuring CSF pressure will also aid validation of the IOP/ICP model for VIP (207). It is reasonable to assume that the IAG is efficacious in preventing VIP syndrome as in the case of cardiovascular deconditioning during long-duration spaceflight. In both cases, tissue remodeling via cell-mechanotransduction mechanisms is involved which may be prevented by daily short-duration restoration of 1-G pressure gradients within body fluid systems.

In the future, several key issues should be addressed with a strategy of interaction between spaceflight and ground-based studies and between experimental and simulation studies as well. First, the IOP/ICP mismatch phenomenon in space and its underlying mechanisms should be firmly established and understood. Second, the acclimation changes in ONH, LC, and ONSAS and eye structure and visual function should be further revealed using novel imaging technology during long-duration spaceflight. Third, the underlying mechanisms of altered ONH, LC, and ONSAS and their possible prevention by artificial gravity should be elucidated by in vivo, in vitro, and ex vivo experimental studies. Additionally, these studies may offer a better understanding of the pathogenesis and treatment of IIH, glaucoma, and other diseases of the optic nerve head on Earth.

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DISCLOSURES

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REFERENCES


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