Spaceflight-Induced Intracranial Hypertension

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INTRODUCTION: Although once a widely speculated about and largely theoretical topic, spaceflight-induced intracranial hypertension has gained acceptance as a distinct clinical phenomenon, yet the underlying physiological mechanisms are still poorly understood. In the past, many terms were used to describe the symptoms of malaise, nausea, vomiting, and vertigo, though longer duration spaceflights have increased the prevalence of overlapping symptoms of headache and visual disturbance. Spaceflight-induced visual pathology is thought to be a manifestation of increased intracranial pressure (ICP) because of its similar presentation to cases of known intracranial hypertension on Earth as well as the documentation of increased ICP by lumbar puncture in symptomatic astronauts upon return to gravity. The most likely mechanisms of spaceflight-induced increased ICP include a cephalad shift of body fluids, venous outflow obstruction, blood-brain barrier breakdown, and disruption to CSF flow. The relative contribution of increased ICP to the symptoms experienced during spaceflight is currently unknown, though other factors recently posited to contribute include local effects on ocular structures, individual differences in metabolism, and the vasodilator effects of carbon dioxide. This review article attempts to consolidate the literature regarding spaceflight-induced intracranial hypertension and distinguish it from other pathologies with similar symptomatology. It discusses the proposed physiological causes and the pathological manifestations of increased ICP in the spaceflight environment and provides considerations for future long-term space travel. In the future, it will be critical to develop countermeasures so that astronauts can participate at their peak potential and return safely to Earth.

KEYWORDS: increased intracranial pressure, intracranial hypertension, spaceflight, space adaptation syndrome, VIIP, visual impairment.

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Although once a widely speculated about and largely theoretical topic, spaceflight-induced increased intracranial pressure (ICP) has gained acceptance as a distinct clinical phenomenon, yet the underlying physiological mechanisms are still poorly understood. This review article attempts to consolidate the literature regarding spaceflight-induced intracranial hypertension and distinguish it from other pathologies with similar symptomatology. It will discuss many of the proposed physiological causes and the pathological manifestations of increased ICP in the spaceflight environment and provide future considerations for long-term space travel.

Since the advent of manned spaceflight, many terms have been used to describe a collective group of seemingly related neurological, ophthalmological, and neurovestibular symptoms. Up to one-half of astronauts are incapacitated by malaise, nausea, vomiting, and vertigo within the first few hours or days spent in space.[22] This constellation of symptoms, first described by Titov,[52] was formerly referred to as "space motion sickness"[41] because of its similarity to motion sickness in the terrestrial environment. It is hypothesized that two physiologically distinct mechanisms converge to produce the symptoms of space motion sickness:[17,49] cephalad fluid shifts are thought to alter the response properties of vestibular receptors while loss of tilt-related otolith signals in microgravity create a conflict between the actual and the anticipated signals collected from the external environment. The breadth of symptoms that astronauts report is likely due to a complex interaction between the neurovestibular system and the autonomic nervous system.[57] A separate yet related term, "space adaptation syndrome," had

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similarly been used to include not only motion sickness, but also symptoms of head congestion and headaches brought on by a cephalad fluid shift into facial structures.[7]

Most astronauts require only 2 to 3 d to acclimate to motion sickness in microgravity and few continue to have residual symptoms during short-term spaceflight.[17] As more time is spent in space, physiologically distinct yet overlapping symptoms seem to arise, including headache and visual disturbance. These findings are similar to cases of intracranial hypertension in the terrestrial environment that are caused by an elevation in ICP.[14] The advent of the International Space Station (ISS) has dramatically increased the time that astronauts spend in space (about 6 mo per mission) and thus has increased the prevalence of this newfound pathology. In addition, a new partnership between the United States and Russia established the concept of 1-yr missions onboard the ISS, with the first astronaut and cosmonaut spending 1 yr in space in 2015. Long-duration exposure to microgravity has brought forth concern from the aerospace medicine community because its effects on the central nervous system are unknown.

From postflight surveys of 300 astronauts, Mader et al.[31] found that approximately 29% reported deficits in distant and near visual acuity following short-duration missions (less than 2 wk), while 60% reported deficits with long-duration space travel (typically 6 mo). Detailed clinical data were collected for seven astronauts following 6 mo of continuous orbital flight onboard the ISS. Complete visual and structural eye examinations before and after spaceflight revealed pathological changes in the eye, including optic disc edema, nerve fiber layer thickening, choroidal folds, posterior globe flattening, cotton wool spots, and decreased near vision accompanied by hyperopic shift. Of these seven crewmembers, lumbar punctures performed in the four cases with disc edema revealing opening pressures of 220, 210, 280, and 285 mm H_2O at 60, 19, 12, and 57 d postmission, respectively. It should be noted that no in-flight opening pressures have ever been attempted. With this clinical evidence, the authors hypothesized that the observed findings were due to cerebral venous congestion due to cerebrospinal fluid (CSF) flow disturbance from spaceflight-induced cephalad fluid shifts. A retrospective review of data has since identified eight additional cases of pathological visual changes[4] since the original publication.

In a follow-up study, Kramer et al.[25] evaluated 27 postflight crewmembers using T2-weighted orbital and conventional brain sequences. They found various combinations of optic nerve sheath distention, posterior globe flattening, optic disc protrusion, increased optic nerve diameter, and greater concavity of the pituitary gland with posterior stalk displacement. Optic disc protrusion was only found with longer mission duration, indicating that clinical severity is associated with increasing spaceflight exposure. Repeat scans showed that some crewmembers continued to have posterior globe flattening 100 d after spaceflight, suggesting that this condition may have a prolonged course or may not entirely return to normal. The authors determined that these findings were representative of intracranial hypertension due to elevated ICP.

Clinically, visual pathology is considered a sensitive measure of increased ICP, as the perineural subarachnoid space of the optic nerve is contiguous with the intracranial subarachnoid space and therefore vulnerable to ICP fluctuations. This contiguity has been verified in a cadaver study which found that the subarachnoid pressures of the optic nerve sheath have a linear relationship to ICP.[14,29] The National Aeronautics and Space Administration (NASA) has since referred to this spaceflight pathological phenomenon as vision impairment and intracranial pressure (VIIP)[4,37] and recognizes it as a serious threat to long-duration spaceflight.

Factors Contributing to Increased ICP

Microgravity-induced fluid shifts. Although evidence may exist for the presence of increased ICP in the spaceflight environment, the underlying physiological mechanisms remain a topic of debate. Early studies found that exposure to both microgravity and simulated microgravity led to a cephalad shift of plasma fluid into the interstitial spaces of the head and neck.[39,50] This led researchers to believe that microgravity-induced cephalad fluid shifts caused increased ICP and were a prominent contributor to both space adaptation syndrome[22] and space motion sickness.[51] The initial support for this mechanism was sought through the use of the head-down tilt (HDT) method, which simulates the fluid shifts that occur in the spaceflight environment. In an early study by Murthy et al.,[34] 10 min of 6° HDT was found to significantly increase the ICP of six healthy men as indicated by tympanic membrane displacement. Increasing the angle to 15° HDT generated a further increase in ICP. Although no long-term monitoring of the HDT method has been attempted in humans, ICP was evaluated for 7 d of 45° HDT using a subarachnoid catheter in rabbits.[47] An immediate increase in ICP was observed which peaked at 12 h of HDT and then decreased gradually toward the pre-HDT baseline value. These findings suggest that rabbits begin to adapt to HDT within the first few days.

Since cephalad fluid shift has been found to increase fluid in the interstitial soft tissue space of the head, it may seem intuitive that the increased filtration of plasma into the intracranial interstitium would lead to increased ICP. However, when autoregulatory mechanisms are intact, they prevent a sustained increase in cerebral blood flow (CBF) in the presence of an elevated cerebral perfusion pressure.[2,48] Kawai et al.[23] used transcranial Doppler to examine CBF in the middle cerebral artery of humans following 6° HDT. CBF velocity was found to increase immediately upon initiation of HDT, reach a peak at 3 h, and then begin to decrease toward baseline after 9 h of HDT. Similarly, no significant differences in CBF velocity were found on transcranial Doppler measurements after up to 2 wk of spaceflight when compared to preflight baseline values.[7,20,23] These findings suggested preserved or possibly improved cerebrovascular autoregulation during short-duration spaceflight. When time spent in microgravity is extended, though, there is evidence that autoregulation may become altered.

Ex vivo examinations of mice following HDT technique in the terrestrial environment revealed increased intrinsic vasoconstrictor responsiveness of cerebral arteries,[15,58,60] thickening of the medial smooth muscle cell layer in some cerebral arteries,[45,56] and decreased cerebral blood flow.[56,58] These findings provide histological evidence for appropriate autoregulatory increases in the sympathetic tone of cerebral vessels. However, similar examination of post-spaceflight mice, following 13 d on board the STS-135 shuttle mission,[48] differed from terrestrial HDT technique by exhibiting less vasoconstriction, more vascular distensibility, and lower effective elastic modulus and stiffness. These findings suggest a decrease in cerebral vascular resistance (CVR) and thus an increase in CBF [CBF = (P_a – ICP)/CVR, where CBF is proportional to arterial pressure (P_a) and ICP and inversely proportional to CVR]. This finding supports the fact that increased arterial perfusion pressure alone, as in the HDT, does not lead to increased CBF, but that CBF may still be elevated in microgravity and may further contribute to an increase in ICP.[48]

Endothelial breakdown. Although autoregulatory mechanisms in the cerebrovasculature have evolved to provide a steady CBF in the face of wide fluctuations of cerebral perfusion pressure, endothelial dysfunction may lower the threshold pressure required to increase deposition of fluid into the intracranial interstitial. Using an in silico model for intracranial pressure dynamics, Stevens et al.[44] originally determined that increased interstitial fluid volume in the brain lead to a decrease in ICP in microgravity. After modifying the model to account for reduction in the integrity of the blood-brain barrier, they found a much more significant increase in intracranial interstitial fluid as well as elevation of ICP high enough for symptoms to manifest.[26]

Endothelial cell gap junctions are held closed by the combined pressure of the interstitial fluid in the brain and the intracranial capillary pressure. Lakin et al.[26] proposed that in a 1-G environment, hydrostatic pressure is transmitted from the brain to the capillaries, thus increasing the pressure needed to close endothelial cell junctions. In spaceflight, the brain is unable to contribute its weight to maintaining the pressure balance, thereby allowing fluid to leak from the intracranial capillaries into the interstitial fluid.

Carbon dioxide (CO_2), a natural byproduct of cellular respiration, is known to be a potent vasodilator in the cerebral vasculature. This normal physiological event occurs during increased CBF in the brain in times of respiratory compromise.[3] Nominal CO_2 levels on the ISS are between 2.3–5.3 mmHg[21] and the astronauts presenting with VIIP symptoms were exposed to levels less than 5 mmHg.[4] Although these levels are 20× higher than the normal 0.23 mmHg CO_2 on Earth, this CO_2 level is still relatively low and not thought to have detrimental physiological effects. However, as there is no natural convection in microgravity, astronauts may be exposed to localized areas of high CO_2 when working in a small space, during exercise,[21] and possibly during sleep.[42] In a computational fluid dynamics analysis, Son et al.[42] determined that without natural convection of gases and ventilation, Pco_2 could rise above 9 mmHg around a sleeping astronaut's mouth within just 10 min. These pockets of CO_2 would not be detected by the major constituent analyzers onboard the ISS and therefore would go unreported. Regular exposure to slightly increased ambient CO_2 as well as potential exposure to pockets of high concentrations of CO_2 may compromise the integrity of the blood-brain barrier, impairing cerebrovascular resistance, thus leading to increased CBF and ICP.[3,53] The response of CBF and CVR to CO_2 was found to be reduced after long-duration missions on the ISS, indicating impaired autoregulation and reduced cerebrovascular CO_2 reactivity.[48,61]

It has also been proposed that radiation exposure outside of Earth's atmosphere may disrupt the integrity of the blood-brain barrier.[26] The two cosmic sources of radiation that are considered to impact mission success are solar particle events and galactic cosmic rays. Sanzari et al.[40] found that exposure to doses of ionizing radiation similar to that experienced by astronauts during a solar particle event led to significant long-term elevation in ICP in a porcine model. Experiments involving cell phone radiation found that small amounts of radiation may activate endothelial cell proteins, causing the endothelial cells to shrink and widen the gap junction.[27,28,36] Increased vessel permeability in turn leads to extravasation of albumin into brain parenchyma, leading to cerebral edema.[36] There is little evidence, though, that the radiation generated by solar particle events or galactic cosmic rays produce effects similar to that of radiofrequency waves.

Venous outflow obstruction and CSF hydrodynamics. Aside from increased CBF, it has also been proposed that cephalad fluid shifts contribute to elevations in ICP by increasing the post-capillary venous pressure[22] through downstream venous congestion.[18,58] While supine, a majority of the cerebral outflow occurs through the internal jugular veins. However, internal jugular veins collapse in the standing position and blood is shunted through secondary venous channels (e.g., the vertebral plexus and deep cervical veins). This has been confirmed using time of flight MRI techniques in the sitting versus supine positions.[5,6] Termed "Space obstructive syndrome," Wiener[55] proposed that internal jugular vein compression along with loss of gravitationally induced cranial outflow of venous blood in the vertebral veins may lead to venous hypertension. Cerebral outflow may divert through the internal jugular veins when standing if there is a significant increase in central venous pressure (e.g., with a Valsalva maneuver).[16] This is relevant to spaceflight as the gravitational unloading of the thoracic space causes central venous pressure to paradoxically decrease.[10,11,13] Decreased venous flow may lead to a rise in pressure high enough to disturb the gradient between the CSF and cerebral venous sinuses. CSF normally circulates through the subarachnoid space and is absorbed through arachnoid granulations into the cerebral venous sinuses. Similarly, Cine phase-contrast MRI examining CSF flow in the upright posture found that a considerably smaller amount of CSF oscillated between the cranium and the spinal canal than in the supine position.[5,6,16]

Vision Impairment and Intracranial Pressure

The focus of spaceflight-induced intracranial hypertension thus far has revolved around the identification and prevention of optic manifestations. The Space Life Sciences at Johnson Space Center convened a summit in February of 2011 to address the topic of VIIP. At that meeting a research and clinical advisory panel was created to provide guidance for the future clinical and fundamental research. After considering all evidence, the panel concluded that the increase in ICP may not be the sole cause of visual disturbances following spaceflight and further chose to pursue mechanisms that may influence vision in addition to elevated ICP.[12] Projects are currently planned to characterize fluid distribution and compartmentalization during long-term space travel to determine systemic and ocular factors of individual susceptibility to the development of ICP elevation, and to evaluate noninvasive ICP monitoring devices for the clinical evaluation of ICP preflight, in flight, and postflight.[35]

Intraocular pressure. Local orbital effects have also been proposed to explain ophthalmic structural and functional changes following spaceflight without an accompanying rise in ICP. This hypothesis purports that a local disruption of CSF dynamics at the level of the optic nerve sheath results in an orbital compartment syndrome.[46] A microgravity-induced cephalad fluid shift may lead to choroidal engorgement and subsequent expansion of the choroid against the rigid scleral tissue, leading to a sudden increase in intraocular pressure (IOP).[30,32] There is an initial spike in IOP followed by a decrease over a period of days, likely due to a compensatory decrease in aqueous volume.[32] Thus, in-flight, postflight, and HDT studies suggest the possibility that a lowering of IOP may occur during extended microgravity exposure. Ocular hypotony, generally defined as an IOP of < 6.5 mmHg, is well-documented to cause disc edema, posterior globe flattening, choroidal folds, and a hyperopic shift very similar to some of our observed changes.[46]

The lamina cribrosa is a mesh-like structure that acts as a pressure barrier between the intraocular space and cerebrospinal fluid space of the optic nerve sheath.[9] The difference in IOP and CSF pressure across the lamina cribrosa is known as the translaminar pressure difference. Small yet chronically elevated CSF pressure in combination with ocular hypotony would lead to a significant pressure gradient toward the intraocular space and could thereby be responsible for the ophthalmic structural and functional changes seen in astronauts secondary to spaceflight exposure.

One-carbon metabolism. It has also been shown that variations in an important metabolic pathway, the one-carbon metabolism cycle, are associated with the occurrence of the VIIP syndrome in astronauts.[62] Zwart et al.[62] found significantly higher serum levels of several one-carbon metabolites in astronauts affected by the VIIP syndrome compared to unaffected astronauts, including serum homocysteine, cystathionine, 2-methylcitric acid, and methylmalonic acid. These findings suggest that polymorphisms in enzymes of the one-carbon pathway may interact with microgravity to cause ophthalmic changes.

Future Considerations

Increased ICP imposes a short-term risk to mission operational success by contributing to headaches, malaise, and visual impairment and may further lead to long-term risks that have not yet fully been elicited. The long-term risks of spaceflight-induced intracranial hypertension may be best estimated through observations of chronically increased ICP on Earth. Individuals with idiopathic intracranial hypertension (IIH) are plagued with well documented symptoms of severe headache and vision loss, but may also experience pulsatile tinnitus, ataxia, memory disturbances, and cognitive dysfunction.[1,33,59] Several small population studies have revealed significant cognitive deficits in patients with IIH, especially within verbal and memory tests.[26,44] In a study by Yri et al.,[59] 31 patients with IIH performed significantly worse on tests of reaction time, processing speed, visuospatial memory, and attention compared to a demographically matched healthy control group. Individuals with IIH continued to exhibit cognitive dysfunction after 3 mo of pharmacological therapy despite improvement in ICP and headache. Further, quality of life measurements have been found to be lower compared with population norms.[54]

At this time, there is no evidence for gross structural damage as a cause of cognitive dysfunction in IIH as brain morphometric and volumetric analysis have also been insignificant compared to healthy controls.[19] Subtle disturbances to white or gray matter substance due to mechanical compression similar to that in normal pressure hydrocephalus has also been proposed.[59] If this condition may serve as a predictor for future long-term spaceflight sequelae, astronauts must be educated on the potential psychomotor and cognitive problems they may face as a result of exposure to spaceflight conditions.

Intracranial hypertension may also pose a risk to future commercial spaceflight. As space tourism increases, there will be spaceflight participants that are less healthy and less screened than NASA astronauts. The incidence of intracranial hypertension may rise with the increase in civilian space travelers who are not as physiologically adept as their astronaut counterparts. Further, increased ICP in the spaceflight environment may become more concerning in someone who has a predilection, or underlying disease process that, combined with increased ICP, could cause in-flight or postflight problems.[55]

Conclusion

Many terms have been used to describe the symptoms of head congestion, nausea and vomiting, and visual disturbance in the spaceflight environment. Over the years, attempts have been made to connect these seemingly related symptoms to a number of diverse pathophysiological origins. Spaceflight-induced increased ICP may be a significant pathological mechanism, especially in the setting of prolonged exposure to microgravity. Although direct measurements of CSF pressure have not been performed in actual spaceflight conditions, the best evidence comes from the presentation of symptoms shared with cases of known intracranial hypertension on Earth as well as the documentation of increased ICP in symptomatic astronauts upon return to gravity. Documentation of CSF opening pressure via a

lumbar puncture during spaceflight would provide definitive proof of elevated ICP during spaceflight, but carries with it inherent procedural risks of postlumbar puncture headache, hemorrhage, infection, and spinal cord injury.[8] Noninvasive techniques for in-flight ICP measurements are currently being investigated.

Spaceflight-induced visual disturbance, termed by NASA as VIIP, is thought to be a serious risk to astronauts during future long-duration space travel, having already affected over 40% of ISS inhabitants.[38] Although VIIP was originally attributed to spaceflight-induced increased ICP, further factors now seem to influence visual pathology. At this time, the contribution of increased ICP to the symptoms experienced during spaceflight is unknown. Although prior research has provided better insight into the mechanisms of increased ICP in space, the exact pathophysiology is still unclear. It is likely that no entity discussed previously is the sole contributor to the neurological phenomena experienced in long-term spaceflight but a combination of multiple. Cephalad fluid shift plays a large role, along with major contributions from venous outflow obstruction, blood-brain barrier breakdown, alterations in cerebrovascular tone, and disruption of CSF flow. Since not every individual manifests with symptoms, it is likely that a combination of genetic, anatomical, and lifestyle related factors make some astronauts more susceptible to spaceflight-induced visual pathology as well as intracranial hypertension.[4]

Little is known as to how the spaceflight environment setting will alter the anatomical and physiological integrity of our nervous systems and related structures, but aerospace physicians and astronauts should be educated in the current understanding of how human physiology reacts to this extreme environment. The goal of extending the duration of missions and sending individuals further into space than ever before will challenge the current capabilities of aerospace medicine. It will be critical to develop countermeasures to these known obstacles so that astronauts can participate at their peak in these missions and return safely to Earth. The literature has called for a more comprehensive study of the problem of intracranial hypertension in the actual spaceflight environment so that this phenomenon can be properly understood.

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