Title: Intracranial Pressure in Outer Space: Preparing For the Mission to Mars.

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Introduction

The constant force of gravity is an often overlooked, yet profound, biophysical stress on the human body. Gravity has substantial effects on blood volume and pressure within the human vasculature. For example, when moving from a 90 degree head-up position (i.e. standing) to a 90 degree head-down position (i.e. upside down), there is an approximate 20% shift in blood volume from the lower extremities into the upper extremities. Similarly, during microgravity exposure (e.g. parabolic flight, and outer space), there is a shift of fluid from the lower-body to the upper-body. However, there are several integrated, rapid responding intrinsic reflexes in place to accommodate shifts in blood volume in order to maintain adequate delivery of oxygen and nutrients to organs and tissue.

Despite the human body's exemplary adaptive capabilities, several physiological problems persist upon return to earth such as bone density loss, reductions in muscle mass, and alterations in vision. Visual impairment (VI) is currently the National Aeronautics and Space Administration's (NASA) top health risk for long duration spaceflight, and millions of dollars has been allocated for research funding to investigate the mechanisms responsible for VI after space flight. One of the proposed mechanisms for post-spaceflight VI is due to microgravity related fluid redistribution resulting in a greater elevation in intracranial pressure (ICP), compared to intraocular pressure. The proposed differential change between ICP and intraocular pressure results in a pressure gradient between the brain compartment and the eye, similar to what is observed in those afflicted by idiopathic intracranial hypertension. As seen in clinical populations, this gradient results in flattening of the optic globe, dilation of the optic nerve sheath, optic disc oedema, and decreased visual acuity. Risk of VI from short-term exposure to microgravity (i.e. 3-4 months) is mild (~ 23%), however, risk of VI increases (~ 48%) with prolonged exposure (i.e. >6 months), and can persist for years upon return (Mader *et al* 2011). In the past decade, with exponential advancements in space technology, NASA has begun planning and investigating what will become arguably the greatest scientific feat in human history – a successful mission to Mars. Such a mission would take anywhere in-between one-to-three years, or potentially even decades, which could result in a significant visual deterioration that would impose a tremendous risk for the astronauts' health, and consequently,

their mission upon arrival on Mars. For these reasons, there is urgency to progress space-related VI research forward in order to: 1) Identify the underpinning mechanism(s) responsible for spaceflight associated VI, and 2) Determine potential preventative actions/treatments in order to reduce the prevalence of VI in astronauts.

Is intracranial pressure elevated in space?

It has been long thought that due to microgravity associated shifts in body fluid, ICP is elevated in outer space which could lead changes in the optic globe, and thus, causing VI. A recent publication in the *Journal of Physiology* by Lawley *et al*. (2017) reports the most eloquent data set currently available describing the consequences of microgravity on ICP in humans during: 1) changes in posture – supine to 90º upright sitting, 2) microgravity simulated by parabolic flight, 3) microgravity simulated by 24-hours of -6º head down tilt, and 4) inhalation of mild ambient carbon dioxide (0.7%) combined with resistance leg exercise. The authors are commended for publishing such a comprehensive study. Undoubtedly, one of the author's greatest challenges would have been recruiting patients where direct measurements of ICP were possible. The participant's recruited (five men; three female) each had an Ommaya reservoir (a surgical implant connecting the lateral ventricles with an easily accessible reservoir under the scalp), making direct measurements of ICP possible. The authors main findings were the following: 1) ICP was lower in the seated upright position, compared to supine position, 2) in the supine position, ICP was reduced by ~20% during parabolic flight, 3) microgravity simulated with -6 degrees head down tilt transiently increased ICP, which then decreased during sleep but returned to baseline (simulated microgravity) values after waking, and 4) mild increases in the ambient CO_2 did not alter ICP, and leg exercise substantially increased ICP only when Valsalva maneuvers were performed.

Several aspects of this meritorious study deserve further comment. First, the baseline ICP of these 'healthy' participants was seemingly quite high with a mean ICP of 15 mm Hg compared to previous upper limits in neurologically healthy populations being reported as 14 mm Hg to18 mm Hg (Malm *et al.* 2011). This raises the question of whether the recruited population of patients with previous haematological malignancy, truly reflect a healthy intracranial hydrodynamic system considering that the mean ICP of 15 mm Hg is similar to the reported lumbar cerebrospinal fluid pressures in the cohort of visually impaired astronauts (13 and 21 mm Hg) (Mader *et al.* 2011). It is possible that these participants are on the steep portion of the intracranial-spinal compliance curve, meaning that changes in intracranial volume will translate into greater changes in intracranial pressure, compared to individuals with a lower resting ICP. However, there is evidence that the slightly elevated resting ICP reported in the current is trivial since the author's raw data demonstrates that an individual with the lowest resting ICP had the greatest reduction in ICP during parabolic flight in the supine position. Additionally, the current study did not examine ocular specific measure (e.g. optic nerve sheath diameter, intraocular pressure), which would be insightful on whether an ICP-intraocular pressure gradient was present during acute microgravity. Furthermore, investigation into the frequency spectrum of the intracranial pressure signal during parabolic flight may have been useful; analysis of pulse waveform morphology can give indication

of reduced intracranial compliance, which could be relevant for the visual impairment. However, the authors did measure intracranial compliance during simulated microgravity (i.e. head down bed rest) and demonstrated that intracranial compliance was unaltered prior and during sleep. While some of the findings of this study need to be treated cautiously given certain experiments contained only four participants, the major finding that short-term acute microgravity does not increase ICP is a major step forward in the field. However, the question of long-term (>24 hours) effects of microgravity on ICP remain unexplored. This will undoubtedly be an area of significant interest for NASA and integrative physiologists; it is a topic of extreme importance due to the long-term planning of future space explorations, such as the exploration of Mars.

How can we quantify intracranial pressure in space?

The gold standard for testing the hypothesis that microgravity induced changes in ICP are the root cause of the VI requires estimation of ICP in space. Invasive approaches could include insertion of a subdural telemetric probe prior to the mission, although insertion in healthy individuals is not without precedent, it does raise ethical concerns. Alternative approaches could include assessment of ophthalmic artery blood flow pulsatility in response to changes in intraocular pressure, non-invasive transcranial Doppler ultrasound based approaches or evaluation of optic nerve sheath diameter (Robba *et al.* 2015). With such non-invasive approaches, we must consider the relative lack of sensitivity for detecting small but perhaps clinically significant alterations in ICP.

Future Directions

As stated previously, the long-term effects of microgravity on ICP remains unclear. An important observation from the current study is that ICP was reduced from ~15 to ~5 mmHg when moving from the upright position to supine, on earth. This means that ICP is ~10 mmHg lower for ~2/3 of the day when an individual is upright, compared to when they are asleep (~1/3 of the day) in supine position. In the microgravity environment, data from Lawley *et al*. (2017) indicates that ICP is ~13 mmHg, slightly lower than ICP during supine on earth, meaning that 24hr ICP is likely elevated during long-term microgravity compared to earth since ICP is no longer reduced with upright posture. An approach to simulate microgravity (i.e. fluid shifts) on earth used by Lawley *et al*. (2017) and others (e.g. Chiquet *et al.* 2003), involves -6º of head down tilt bed. This degree of head down tilt redistributes blood volume from the lower limbs into the upper body and results in resting ICP being ~15 mmHg. A long-term bed rest study (e.g. >3 months) in human participants, where 24hr ICP is elevated, with direct ICP and IOP measurements, would be insightful on the long-term adaptation to microgravity. Potentially, it is the long-term, mild elevation in 24hr ICP that is responsible for VI in astronauts.

In addition to finding the physiological mechanism responsible for VI, a potential treatment for VI will need to be developed. Assuming that a small, fluctuations in the gradient between the intracranial and intraocular pressures are the stimulus for VI, potential solutions to the VI would be titration of the either the intraocular or the ICP. Conceivably, medications targeting

cerebrospinal fluid secretion, cerebral blood volume or volume of aqueous humor could be relevant (e.g., Indomethacin, Acetazolamide), as could physical devices to increase intraocular, or decrease ICP such as pressurised goggles or lower body negative pressure. In light of the current study, such approaches would need to be considered cautiously given the potentially small effects of microgravity on ICP. Clearly, further research focussing on mechanisms of VI need to be considered, especially with a focus on the optic nerve, which has been shown to be altered in space.

Perspective and Significance

Visual impairment upon return to Earth is extremely common in astronauts, and although there has been significant research aimed at determining the underpinning mechanism(s) responsible for VI, it remains unclear. On earth, although undesirable, VI is a relatively benign condition since it can be cured with corrective lenses. However, VI becomes a very serious condition in regards to the future Mars missions, as the condition appears to be degenerative and corrective lenses may not be obtainable while astronauts are on a mission in outer space, or on Mars. The study by Lawley and colleagues (2017) is a major step forward in research in this area, and they should be commended for attempting to address this current issue. Moving forward, this area of research should be viewed as a global issue, as it is one of the many obstacles that need to be overcome in order to reduce the risk of long-term space travel, which will contribute to a successful mission to Mars, and potentially, in the foreseeable future, human habitation on Mars.

Competing Interests:

None declared

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