

Increased Intracranial Pressure and Visual Impairment Associated with Long-Duration Spaceflight

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List of Acronyms

ARED	Advanced Resistive Exercise Device
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CDRA	Carbon Dioxide Removal Assembly
CO ₂	Carbon Dioxide
CPP	Cerebral Perfusion Pressure
CSF	Cerebrospinal Fluid
CVP	Central Venous Pressure
CVR	Cerebral Vascular Resistance
GAG	Glycoaminoglycan
ICP	Intracranial Pressure
IH	Intracranial Hypertension
IIH	Idiopathic Intracranial Hypertension
IOP	Intraocular Pressure
iRED	Interim Resistive Exercise Device
ISS	International Space Station
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MRI	Magnetic Resonance Imaging
NASA	The National Aeronautics and Space Administration
NRC	National Research Council
OCT	Optical Coherence Tomography
OD	Oculus Dexter (the right eye)
PaCO ₂	Partial Pressure of Arterial Carbon Dioxide
ppCO ₂	Partial Pressure of Carbon Dioxide
SMAC	Spacecraft Maximum Allowable Concentration
STS	Space Transportation System

1. Introduction

Although humans have been flying in space since the 1960s, more recent missions have revealed a new suite of physiological adaptations and consequences of space flight. Notably, 60% of long-duration crewmembers (ISS/MIR) and >25% of short-duration (Shuttle) crewmembers have reported subjective degradation in vision (based on debrief comments) (Gibson 2011). Decreased near-visual acuity was demonstrated in 46% of ISS/Mir and 21% of Shuttle crewmembers, resulting in a shift of up to 1-2 diopters in their refractive correction. It is likely that the recently revealed ophthalmic changes have been present since the first days of human space flight, but have been overlooked or attributed to other causations.

The reported changes in vision have occurred at various time points throughout missions, with ranging degrees of visual degradation. Although some cases resolved upon return to Earth, several astronauts have not regained preflight visual acuity, indicating that the damage may be permanent. While observing these changes over the years, without other overt symptomology and with the given age range of the flying population, this has largely been attributed to an expected hyperopic shift due to aging. However, the availability of onboard analysis techniques, including visual acuity assessments, retinal imagery, and ultrasounds of the eye and optic nerve tracts, along with more detailed post-flight techniques, has led to the recent recognition of a wider syndrome. Along with vision changes, findings include flattening of the globe, swelling of the optic disc (papilledema), choroidal folds in the retina, swelling of the optic nerve sheath, and visual field defects. It is widely hypothesized that this constellation of findings may be explained by an elevation of intracranial pressure (ICP). Out of the 60% of long-duration astronauts that have reported a subjective degradation in vision, a subset (currently 10 astronauts) have developed this syndrome.

The National Aeronautics and Space Administration (NASA) has made it a high priority to understand this syndrome and provide mitigation techniques to protect crewmembers from visual impairment. While there are many possible factors that could contribute to intracranial hypertension associated with spaceflight, the relative contribution of these, as well as the processes by which eye damage occurs as a result of intracranial hypertension, are not fully understood. The observed pathophysiological phenomena are extremely complex and it is likely that multiple factors contribute to their incidence, rather than one simple mechanism. This paper will define and examine the findings in detail, and expound upon the potential contributing factors and their relative contribution to this syndrome.

1.1 Relevant Anatomy and Physiology

The Intracranial Space

The skull is a rigid structure with a fixed volume, containing the brain, cerebrospinal fluid (CSF) and blood. Because these components are housed in a non-distensible vault (the cranium), an increase in fluid (CSF or blood) will cause pressure to rise quickly.

The brain is the largest component of the skull, with a mass of 1400 g, and is encased in three membranes (pia matter, arachnoid and dura matter)(Gwinnutt and Saha 2005). The brain is supplied with blood via the internal carotid and vertebral arteries, and venous drainages occur via the cerebral veins, sinuses and internal jugular veins. Under normal conditions, there is about 150 ml of blood in the skull, most of which (100 ml) is within the venous system.

CSF is produced constantly, at a rate of 0.3 ml/min, and flows within the ventricles and sub-arachnoid space (Figure 2). CSF is reabsorbed into the venous circulation via the arachnoid villi in the sagittal and sigmoid sinuses. Under normal conditions, the pressure of CSF is 11mmHg, and the pressure in the venous dural sinus is 6mmHg, creating a pressure gradient that facilitates CSF absorption across the villi (Gwinnutt and Saha 2005).

The Monro-Kellie Hypothesis

The Monro-Kellie hypothesis demonstrates the relationship between intracranial volume and pressure, given that its components are incompressible. More than two centuries ago, Alexander Monro applied physics concepts to the intracranial space and hypothesized that that any increase in the volume of one of the three components within the intracranial space must be offset by an equal decrease in the volume of another component, otherwise ICP will increase (Monro 1783). This hypothesis was then supported by experiments by Kellie, giving rise to the Monro-Kellie doctrine.

In persons with normal tissue elasticity, a small increase in volume of CSF or blood does not result in a sustained increase in ICP. However, once the compensation mechanisms have been exhausted or eliminated, ICP rises dramatically. The pressure-volume curve displays the result of continued increases in intracranial volume, and at a critical volume, pressure begins to rise steeply (Figure 1). Before the critical volume is reached, a given change in intracranial volume (Δv) will result in a small increase in intracranial pressure (ΔP_1). After the critical volume has been surpassed, the same change in volume (Δv) will result in a much larger increase in intracranial pressure (ΔP_2) (Figure 1).

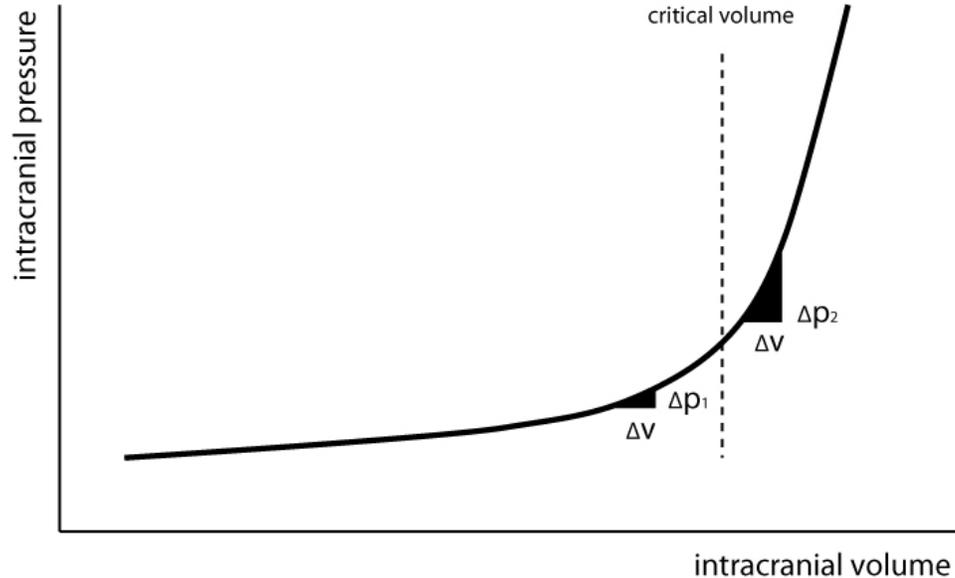


Figure 1: Intracranial pressure-volume relationship

1.2 Terrestrial Pathophysiology of Increased ICP

Increased intracranial pressure, also known as Intracranial Hypertension (IH), is a rise in the pressure inside the cranial cavity and can be caused by a variety of factors including bleeding in the brain, traumatic injuries, a rise in cerebrospinal fluid pressure, increased cerebral blood flow, and impairment of cerebral venous drainage. Idiopathic intracranial hypertension has no known cause, and its estimated incidence in the USA is about 1 per 100,000 people (Dhungana, Sharrack and Woodroffe 2010).

In a normal adult, ICP is <10-15 mmHg (100-200 mmH₂O), varying with posture, respiration, coughing and straining (Gwinnutt and Saha 2005). To diagnose IH, the lumbar CSF opening pressure (a measurement of intracranial pressure) should be more than 18.4 mmHg (250 mmH₂O), however, most cases in the clinical population have an ICP well above this opening pressure (Corbett and Mehta 1983). Symptoms include nausea/vomiting, pulsatile tinnitus, visual disturbances, and headache aggravated by coughing or straining. Papilledema, swelling of the optic disc, is the ophthalmic hallmark of raised intracranial pressure.

The increase in intracranial pressure takes place in the subarachnoid space, a space between the brain and the meninges where CSF flows (Figure 2). The subarachnoid space continues up to the optic nerve head in the back of the eye, and when intracranial pressure increases, the optic nerve sheath is distended. This causes fibers in the optic nerve to be compressed, which impedes venous drainage and axoplasmic flow in optic nerves, resulting in swelling of the optic nerve head (papilla) (Gwinnutt and Saha 2005).

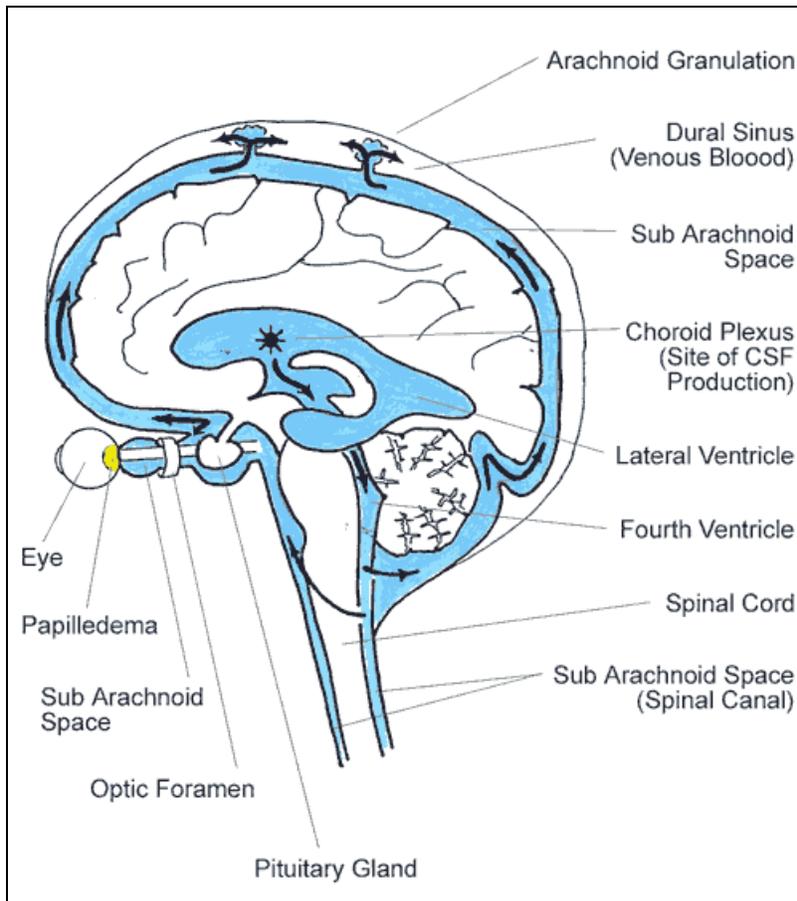


Figure 2: Schematic drawing of CSF flow through the ventricles and subarachnoid space (Source: <http://www.ihrfoundation.org/intracranial/hypertension/info/C16>)

Increased ICP also affects the microcirculation of the eye, and decreased blood flow to the optic nerve can result in vision loss. In papilledema, features of central retinal vein obstruction are typically seen, including dilation of pre-papillary retinal capillaries, dilation of retinal veins and cotton wool spots (Acheson 2006). In addition to papilledema, other retinal changes may contribute to visual disturbances, including choroidal folds (grooves in the choroid layer of the eye), serous retinal elevation around the nerve head, and flattening of the globe.

Changes in vision due to increased intracranial pressure and papilledema depend greatly on the severity and duration of IH. Typically, central vision is preserved and perimetry shows blind spot enlargement. However, uncontrolled intracranial hypertension and persistent papilledema can result in blindness.

1.3 Pathophysiology of Increased ICP in Microgravity

The physiological and anatomical changes observed in the ten cases of visual impairment presented by astronauts during and after long-duration missions are unlike any clinical entity seen on Earth. Fundoscopic examinations of affected individuals revealed optic disc edema,

choroidal folds, and cotton wool spots (Figure 3). Magnetic Resonance Imaging (MRI) and ultrasound examinations showed posterior flattening of the globe (Figure 4), papilledema and optic nerve sheath distension (Figure 5).



Figure 3: Fundoscopic picture of the back of the eye post-flight (R+19) showing a cotton wool spot (black arrow), choroidal folds (white arrow), and optic disc edema (yellow arrow) (Photo courtesy of Dr. Robert Gibson)

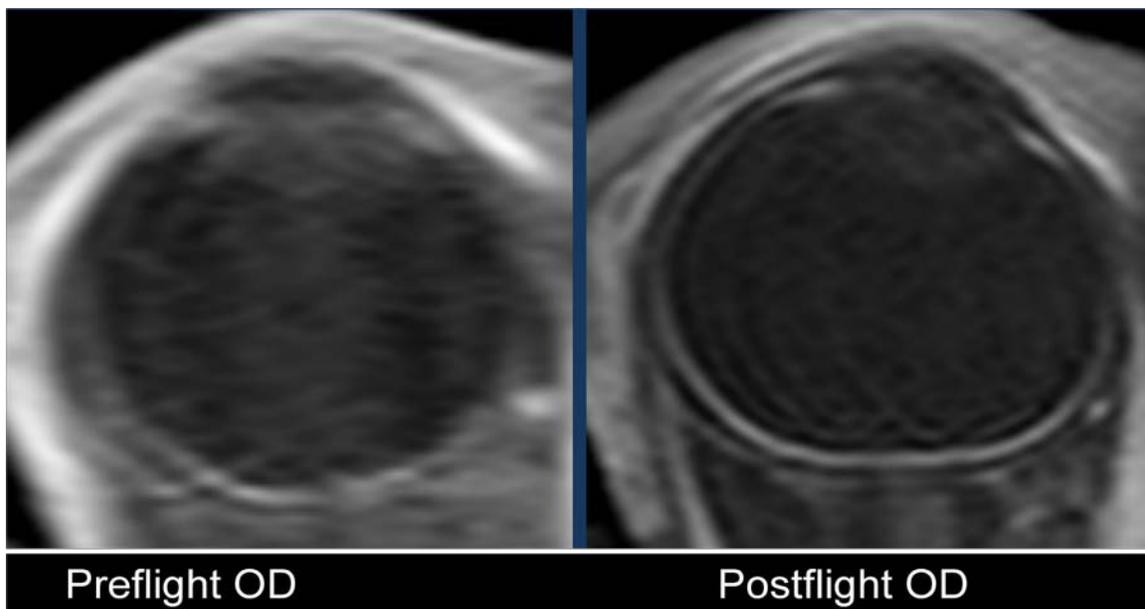


Figure 4: MRI of the OD (right eye) pre-flight and post-flight, showing significant flattening of the globe post-flight (thought to be caused by increased ICP) (Photo courtesy of Dr. Robert Gibson)

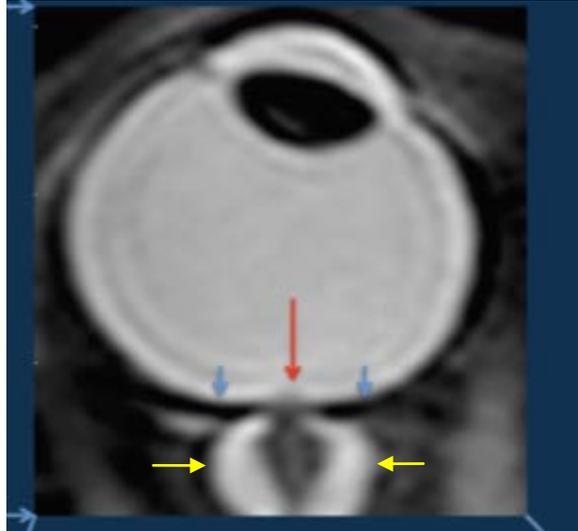


Figure 5: Post-flight MRI picture of the eye showing papilledema (red arrow), globe flattening (blue arrows) and optic nerve sheath distension (yellow arrows) (Photo courtesy of Dr. Robert Gibson)

These ophthalmic changes are similar to those seen in clinical patients on Earth with idiopathic intracranial hypertension, leading to the hypothesis that increased intracranial pressure could be causing the observed changes in astronauts. However, ICP is typically much higher in clinical cases with much more severe symptomology including headaches, reduced cognition and nausea/vomiting. Just a handful of astronauts presenting with visual impairment have had ICP measurements taken pre- and post-flight via lumbar puncture (a routine clinical procedure performed with local anesthetic). The affected astronauts presented mild to moderately increased ICP upon return to Earth (between 210-285 mmH₂O), with the only known symptom being vision changes (R. Gibson 2011).

In 2009, upon realizing that vision changes may be a consequence of space flight, NASA began anatomically studying crewmembers using onboard visual acuity assessments, eye ultrasounds, retinal imagery, and post-flight optical coherence tomography (OCT). While the number of cases still remains small, a significant amount of information on long-duration crewmembers and their ophthalmic changes is accumulating rapidly.

Papilledema

The lamina cribrosa sclera (Figure 6), a mesh-like structure that lies between the optic nerve and the intraocular space, forms a pressure barrier between the intraocular space and the retrobulbar cerebrospinal fluid space (surrounding the retrobulbar part of the optic nerve)(Jonas, Berenshtein and Holbach 2003). Normally, the lamina cribrosa is in a state of posterior displacement (bulges slightly outwards towards the optic nerve) because intraocular pressure (IOP) is higher than

intracranial pressure (approximately 15mmHg and 10mmHg respectively). However, if IOP or ICP are altered, the lamina cribrosa will respond elastically. An abnormal pressure gradient will influence the physiology of the optic nerve fibers, specifically the orthograde and retrograde axoplasmic flow, and the pressure in the retinal veins (Jonas et al. (2003) and references 4-9 within).

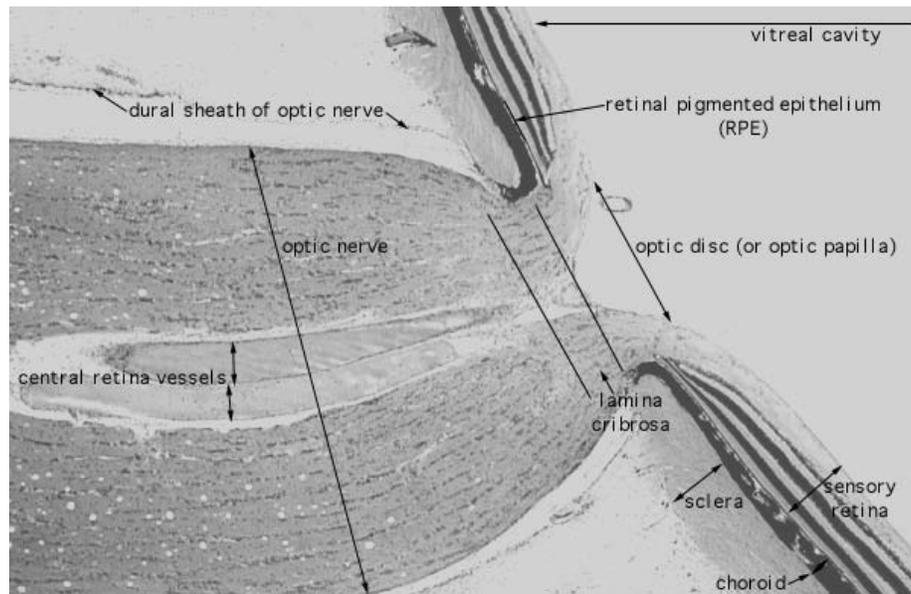


Figure 6: The lamina cribrosa, between the optic nerve and intraocular space in a normal state of posterior displacement
(Source: <http://www.bu.edu/histology/p/08009loa.htm>)

If the lamina cribrosa is displaced too much, it can pinch the traversing nerve fibers and blood vessels, causing nerve damage and visual disturbances. In people with glaucoma, IOP is increased, pushing the lamina cribrosa out further, pinching the nerves that run through it. The opposite occurs in persons with severe intracranial hypertension. Increased ICP pushes the lamina cribrosa towards the intraocular space, pinching the nerves and vessels, causing optic disc swelling (papilledema). Both glaucoma and intracranial hypertension can cause lasting vision changes, especially if the lamina is not elastic and stays in the abnormal convex or concave position.

A person's anatomy can predetermine their vulnerability to various syndromes and diseases. It is thought that vascular elasticity and preexisting ophthalmic health may contribute to susceptibility of increased ICP and/or visual impairment on-orbit. Age and genetics are the primary determinants of tissue elasticity within the body. Elasticity, also known as compliance, refers to vessels' and tissues' ability to expand and contract with volume changes and return to normal. Elasticity also contributes to how pressure changes are transmitted within the body. The more elastic a tissue is, the less likely it is that a large pressure change will have a harmful effect on sensitive organs like the brain or eyes. In more rigid vessels and tissues, high pressure is transmitted to other structures instead of being absorbed by the blood vessels. It is therefore thought that persons with less elastic vessels and tissues are at a greater risk of developing

intracranial hypertension and subsequent vision changes. It is possible that the astronauts that have experienced visual changes have less compliant vessels and tissues and cannot tolerate intracranial pressure changes as well as astronauts with more elastic vessels and tissues.

It is therefore hypothesized that all astronauts experience an increase in ICP as a part of 0-G adaptation, and that a select few are more susceptible to the eye effects due to local anatomical predispositions. Astronauts that do not present symptoms of visual impairment on-orbit may in fact be experiencing increased ICP, but their vessels and tissues are more compliant and so the pressure is not being transmitted to the eye.

Emphasis has been placed on establishing the role of increased intracranial pressure in the changes in vision and eye anatomy seen on-orbit. During the Visual Impairment Intracranial Pressure Summit (hosted by NASA's Johnson Space Center on February 8-10, 2011), a panel of experts suggested that ICP measurements be taken before, during and after flight for all long duration astronauts. This way, ICP can be correlated to the visual disturbances experienced by some astronauts.

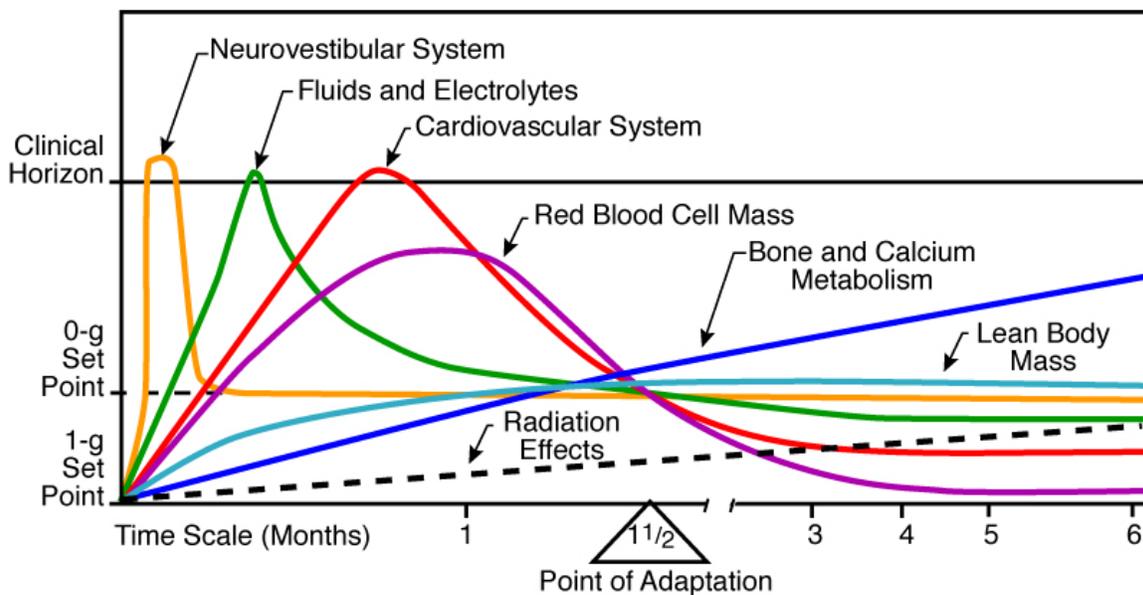


Figure 7: Physiologic changes of various systems during adaptation to microgravity. (Source: <http://asgsb.org/slidesets/slidesets.html>)

It is imperative to remember that this syndrome is occurring against a backdrop of an overall adaptation of the body to microgravity (Figure 7). Almost every major body system is altered, and adaptive changes towards new set points help the body to function more efficiently in its new environment. In regards to the cardiovascular system, the newly adapted state represents a basic euvoletic set point, with a 10-15% reduction in plasma volume and 10% reduction in red blood cell mass (Baker, Barratt and Wear 2008). The “newly” reported vision changes represent a maladaptive aspect of spaceflight, reminding the space medicine community of the vast possibilities of unknown entities occurring in the human body in space. As discussions of 500+

day missions to mars circulate, new risks must be addressed including the danger of unknown maladaptations bound to occur during extensive periods of time in space.

1.4 Pathology

Demographics

Currently, 10 crewmembers have experienced the aforementioned suite of ophthalmic changes during a 6-month ISS mission. Based on these cases, the likelihood of developing this syndrome does not appear to be equal and clear trends have emerged upon analyzing the demographics of the affected astronauts. Thus far, all of the affected astronauts have been males over the age of 45 with a mesomorphic, muscular build. It is interesting to note that idiopathic intracranial hypertension on Earth predominantly affects overweight women (Dhungana, Sharrack and Woodroffe 2010). It is therefore apparent that microgravity is playing a central role in the alteration of anatomical and physiological processes in the human body, making a different population more susceptible to this problem.

Pre-flight tests revealed that all affected astronauts were negative for systemic hypertension, connective tissue disorders, iron deficiency, diabetes mellitus and renal disease, and none had ever used any medications that could produce increased ICP (e.g., vitamin A, tetracycline, corticosteroids, or nalidixic acid). It is currently unclear what, if anything, makes an astronaut more susceptible to increased ICP and/or visual impairment, and it is too premature to declare that certain traits equate to a being at a larger risk for of increased ICP.

Anatomy

Anatomical Shifts

Basic anatomical responses to microgravity including changes in blood volume and pressure, upward organ shifting and cephalad fluid shift may all affect intracranial pressure to some degree.

Upon entry into weightlessness, a cephalad body fluid shift occurs, thought to be the underlying mechanism behind several immediate effects of weightlessness inducing space motion sickness. The cephalad fluid shift notably induces changes in blood volume and fluid regulation within the body, but its influence on ICP is currently unknown (discussed in detail in Chapter 2). It is tempting to blame increased ICP on venous outflow obstruction due to increased central venous pressure. However, contrary to popular belief, CVP has actually proven to decrease upon entry into microgravity, even with a cephalad fluid shift (Buckey, et al. 1996). This suggests that there may be striking changes in the mechanical characteristic of the circulatory system in space.

With a loss of gravity, the chest relaxes with a concomitant shape change, increasing the volume of the closed chest cavity, and organs drift upward (White and Blomqvist 1998). The redistribution of intrathoracic components could possibly result in obstruction of the jugular vein, causing outflow obstruction and a subsequent increase in ICP. This could explain the visible distension of the external jugular veins that accompanies transitioning to zero-G.

Along with increased blood volume in the intracranial space, increased CSF volume could cause ICP to rise. Obstruction of the jugular venous outflow would also affect CSF absorption, as it is driven by a pressure gradient. However, until the paradox of decreased CVP alongside visible jugular venous distension is explained, no conclusions can be drawn.

Tight fit hypothesis

In 1985, Ross accounted for the random nature of cerebral mountain sickness by suggesting that individuals with more atrophic brains and larger ventricles could accommodate more hypoxic cerebral swelling, and hence be more protected from increased intracranial pressure (Ross 1985). The tight-fit hypothesis suggests that individuals with smaller ventricles and cerebrospinal fluid spaces have a greater increase in ICP for a given increase in volume in one of the three intracranial components, giving an anatomical predisposition to intracranial hypertension.

In 1985 Brian Cummings performed an experiment, relating ventricle size, ICP, and acute mountain sickness susceptibility during a climb of Hagshu Peak (21 300 ft) in India. CT scans were taken of 10 subjects before the expedition to determine ventricular size. It was found that the subjects with the smaller ventricular sizes reported higher acute mountain sickness (AMS) and headache scores (Wilson and Milledge 2008). ICP was also measured via burr hole in select individuals and monitored as they climbed Hagshu Peak. The subject with the largest ventricular size had its ICP remain within normal levels at all altitudes. The subject with the smallest ventricles experienced increased ICP upon minimal exertion, and was the only one to develop headaches (Wilson and Milledge 2008).

These experiments support Ross's "tight-fit" hypothesis, and show the possibility of an anatomic predisposition to AMS. It would be interesting to perform a similar study on astronauts to determine if smaller ventricles equate to increased susceptibility to intracranial hypertension and therefore visual impairment during spaceflight. It is possible that astronauts with smaller ventricles are not able to handle the intracranial volume increase experienced during spaceflight, resulting in a spike in ICP. These astronauts may then be more susceptible to sustained ICP, causing visual disturbances.

Secondary Contributory Factors

Microgravity is the dominant physiological modifier experienced by all astronauts. However, it is hypothesized that secondary mechanisms not related to microgravity may also contribute to raised ICP.

One possible contributory factor is carbon dioxide (CO₂). Spacecrafts are known to have a magnitude higher concentration of carbon dioxide than nominal Earth levels, and have proved to have no real serious consequences thus far. However, CO₂ is a potent vasodilator, increasing cerebral blood flow, and has been considered as a contributory mechanism to increased intracranial pressure in space (detailed in Chapter 3).

Another identified secondary contributor is on-orbit resistive exercise. Implementation of the Advanced Resistive Exercise Device (ARED) into the astronaut's exercise routine in 2008 has led some to blame heavy weight lifting for visual impairment on-orbit. Resistive exercise is

associated with an increase in mean arterial pressure and intrathoracic pressure and could have effects on cerebral blood flow and venous outflow (detailed in Chapter 4). However, many astronauts reported vision changes long before the ARED was even flown.

Another possible contributing factor is the high levels of sodium intake on-orbit. Space food has historically been extremely high in sodium, and astronauts consume about 5,000 mg/day of sodium, well above the U.S. recommended 2,300 mg/day of sodium. High sodium intake has been linked to various disorders including hypertension and studies have shown that low sodium diets along with weight-reduction have actually reversed vision loss in patients with idiopathic intracranial hypertension (detailed in Chapter 5).

The last contributory mechanism discussed in this report is the possibility of enzymatic dysfunction in an important biochemical pathway on cerebral dynamics and ICP. It is thought that an enzymatic polymorphisms occurring in the one-carbon metabolism cycle could lead to an increase in the neurotoxin homocysteine, and decreased levels of folate and vitamin B6 and B12. All of these effects are known to have serious consequences on the body, and have been coupled to numerous disorders. It has been hypothesized that polymorphisms could be present in the affected astronauts and contributes to visual disturbances (detailed in Chapter 6).

It is not thought that one of the aforementioned mechanisms is the sole contributor to increased ICP and therefore visual changes, but rather, the described ophthalmic phenomenon is caused by a combination of factors. It is possible that a combination of cephalad fluid shift, increased carbon dioxide exposure, resistive exercise, increased sodium intake, and enzymatic dysfunction could lead to increased ICP. Subsequent chapters will discuss each of these contributory factors in detail, and explain how they could contribute to ICP changes.

2. Microgravity Induced Cephalad Fluid Shift

2.1 Introduction

On Earth, the human body has a hydrostatic pressure gradient along its vertical axis. The mean arterial pressure in a healthy human is about 70mmHg at head level, 100mmHg at heart level, and 200mmHg at the feet (Hamilton 2008). The human body has adapted to live in a 1-G environment and has many physiological mechanisms to keep blood flowing against the pull of gravity to reach one of its most vital organs, the brain. The body also works with gravity to deliver blood to the lower extremities. Millions of years of evolution and adaptation have produced a human body that works in sync with Earth's natural environment, especially gravity. However, upon entry into a weightless environment, the body must re-adapt to its new environment and create new homeostatic set points.

Immediately upon reaching weightlessness, a cephalic fluid shift of roughly 2L occurs, representing an 11.6% volume change (Figure 8) (Moore and Thornton 1987). Physical manifestations of this shift can be seen including facial puffiness, diminished leg volume (Kirsch, et al. 1993), engorged superficial vascular system of the upper body (Baker, Barratt and

Wear 2008), increased forehead tissue thickness by 7%, and increased intraocular pressure by 92% (J. C. Buckey 2006). Also, a sensation of fullness in the head and nasal congestion has been reported by astronauts between minutes and hours after entry into microgravity. Cephalad fluid shift is believed to be a major contributor to many of the physiological effects seen during spaceflight.

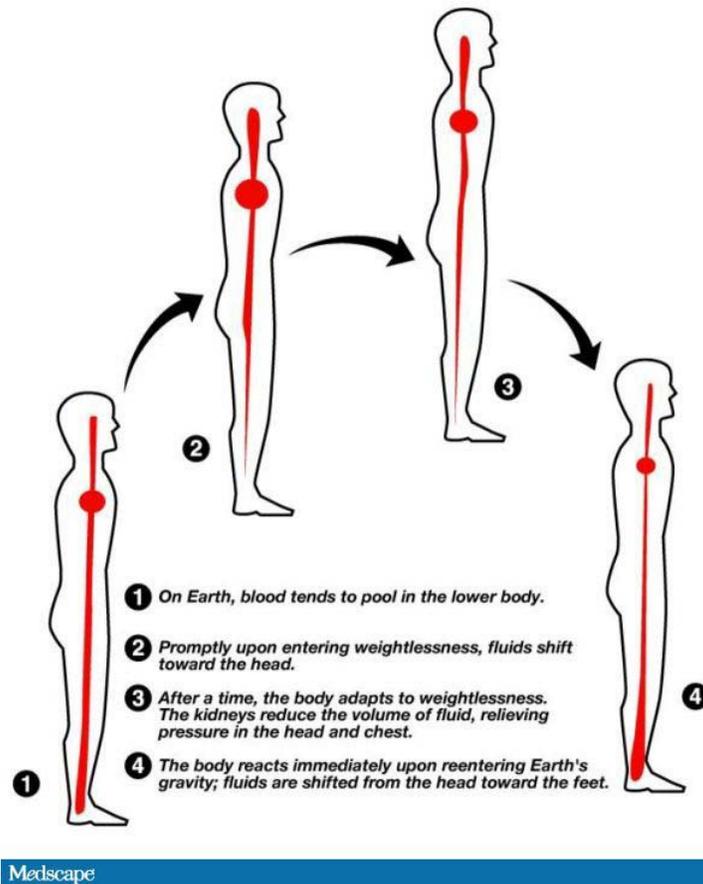


Figure 8: Fluid shifting during gravity and microgravity exposure (Source: <http://asgsb.org/slidesets/slidesets.html>)

The human body, specifically stretch receptors in the atria and pulmonary arteries, perceives this upward fluid shift and increased central blood volume as a state of hypervolemia, even though total body water and intravascular volumes are normal by terrestrial standards. The body begins to adapt to its new environment, and reduces fluid volume (Figure 8). Plasma volume decreases about 17% within the first 24 hours of spaceflight, and then stabilizes at a reduction of 10-15% by flight day 5 (Leach, et al. 1996). The reduction in plasma volume leads to increased hematocrit, which inhibits erythropoietin secretion. This results in a decrease in red blood cell mass by 10% within the first week (Alfrey, et al. 1996). This decrease is achieved by decreasing renal sympathetic nerve activity, plasma rennin activity and aldosterone secretion (Fortney, Schneider and Greenleaf 1996). Also, atrial stretch releases atrial natriuretic peptide, which

causes salt and water loss, to decrease fluid volume (J. C. Buckey 2006). This moves central blood volume back towards a standing level on Earth.

Eventually, the body reaches a state of microgravity-induced euvoemia and the newly decreased volume of body fluid is perceived to be normal (Hamilton 2008). Astronauts are able to continue living and working normally in space as the body adapts to its new environment. However, upon return to Earth, gravity takes its effect on the human body once again. This pulls blood back down to the lower extremities, and because astronauts have a significant reduction in blood volume, many experience orthostatic intolerance and lose consciousness.

2.2 Space Motion Sickness and ICP

It has been hypothesized that elevated ICP and cephalad fluid shift may play a role in the development of symptoms associated with space motion sickness (Jennings 1990). The symptoms include headache, stomach awareness, nausea, vomiting, and dizziness (Ortega and Harm 2008). The fact that these symptoms occur early in-flight, and usually resolve themselves within a week suggests that the symptoms could be associated with the onset of upward fluid shifting (which also is 'resolved' in less than one week). It has been proposed that cephalad fluid shift causes an increase in the post-capillary venous pressure, which decreases the egress of water from the brain, raising intracranial pressure (Jennings 1990).

2.3 Adaptations of The Cardiovascular System

To truly understand the physiological changes associated with this fluid shift, central venous pressure (CVP) and cardiac filling pressure needed to be continuously monitored in spaceflight. In 1996, Buckey, et al. directly measured CVP in three subjects aboard the shuttle with a 4-Fr catheter for continuous CVP measurements (before, during launch, and in microgravity) The mean CVP was 8.4 cmH₂O seated before flight, 15.0 cmH₂O while in the supine legs-elevated posture in the shuttle, and 2.5 cmH₂O after ten minutes in microgravity (Buckey, et al. 1996). Through this revolutionary in-vivo study, it was determined that CVP actually decreases in microgravity, contrary to the original hypothesis that cephalad fluid shift would cause increased CVP. Distension of the external jugular veins is noted immediately upon entry into microgravity, and continues throughout short and long-duration missions. This implies that CVP is always greater than 0 cmH₂O (Hamilton 2008).

Also, stroke volume, cardiac output and heart size all increase, while heart rate is unchanged. Left ventricle end diastolic dimension was also measured by echocardiography and was found to increase from a mean of 4.60 cm to 4.97 cm within 48 hours of exposure to microgravity. Left ventricle stroke volume also increased from 56mL preflight to 77mL during spaceflight (Buckey, et al. 1996).

It is hypothesized that during weightlessness, the chest relaxes with an associated shape change which increases the volume of the thoracic cavity. The rib cage widens, decreasing intrathoracic pressure, and there is a slight upward movement of the diaphragm (Michels, Friedman and West 1979). The reduction of central venous pressure in combination with an increase in cardiac output seen in space has been suggested to result from this decreased intrathoracic pressure,

causing a decrease in external cardiac constraint greater than the decrease in CVP. This effectively increases cardiac chamber transmural pressure (Foldager, Andersen and Jessen 1996)(White and Blomqvist 1998). The increase in transmural filling pressure of the heart is then responsible for the observed increases in heart size, left ventricular end-diastolic volume, stroke volume and cardiac output (White and Blomqvist 1998).

It is important to note that many of the cardiovascular changes associated with microgravity exposure, for example heart size and stroke volume, return to preflight sitting levels over time (Verbanck, et al. 1997).

2.4 Cephalad Fluid Shift Effects on the Cerebral Hemodynamics

The cranium is a rigid structure containing brain tissue, blood and cerebral spinal fluid (CSF). If there is an increase in volume in any of these three, the cranium is unable to stretch to adapt to the increased volume shift, and pressure increases. It has therefore been hypothesized that cephalad fluid shift due to microgravity could contribute to intracranial hypertension. Exposure to microgravity alters the degree of distension of cranial blood vessels and when ICP rises, it compresses the blood vessels and increases vascular resistance, causing a reduction of cerebral blood flow (Kawai, et al. 2003).

Impaired cerebral autoregulation has been documented in several studies involving head-down tilt studies, and has been proposed as a mechanism for possible post-spaceflight orthostatic intolerance. However, Iwasaki, et al. (2007) determined that resting middle cerebral artery blood flow velocity did not change significantly during short-duration spaceflight from pre-flight values or after spaceflight. The results are counter the hypothesis that exposure to microgravity impairs cerebral autoregulation and suggest rather that microgravity actually improves it (Iwasaki, et al. 2007). However other mechanisms such as increased CO₂ and resistive exercise may affect cerebral autoregulation in spaceflight (further discussed in Chapters 3 and 4).

Lakin et al. (2007) used a validated mathematical model that embeds the intracranial system in whole-body physiology to predict ICP in response to various microgravity induced stimuli. Simulation results predict a significantly elevated ICP, within the symptomatic range for benign intracranial hypertension. This was combined with a drop in blood colloid osmotic pressure and a reduction in the integrity of the blood-brain barrier in microgravity (Lakin, Stevens and Penar 2007). However, it is important to note that models cannot predict outcomes, but rather help to formulate hypotheses.

2.5 Conclusion

Overall, it is possible that cephalad fluid shift contributes to increased ICP immediately upon entry into weightlessness and could contribute to the minor vision changes experienced by short-duration astronauts. However, fluid shift cannot explain vision changes occurring three months into a mission after blood volume has been decreased significantly. Adaptations of the cardiovascular system to microgravity, specifically venous dynamics, need to be more deeply studied to understand how CVP can decrease, yet there is visible jugular venous distension.

3. Carbon Dioxide

3.1 Introduction

Atmosphere revitalization in any closed environment is an essential and integral part in the maintenance of human health and safety. Of particular interest is Carbon Dioxide (CO₂) removal, as it can have adverse and potentially toxic effects if levels become too high. CO₂ is a natural byproduct of metabolism and humans generate about 1kg of it per day, although this varies greatly with physical activity. CO₂ is expelled through respiration, and therefore its levels will naturally increase in a closed system, such as a spacecraft or submarine. Carbon dioxide is a potent vasodilator, causing decreased vascular resistance and increased blood flow. Side effects of hypercapnia include rapid breathing, diminished mental alertness, faulty judgment, fatigue, headache, and nausea.

CO₂ makes up approximately 0.039% of the terrestrial atmosphere (partial pressure of 0.228 mmHg), and indoor air typically contains about 0.08% to 0.1% CO₂. Unfortunately, “scrubbing” of spacecraft air is extremely power intensive, and the required power and ventilation needed to maintain CO₂ at terrestrial levels in a closed environment is impractical. Therefore, a compromise must be struck between crew health and life support system realities/operational feasibility. The United States Navy and NASA have set regulations on allowable CO₂ levels in submarines and spacecrafts respectively to ensure crewmember safety.

Although normal CO₂ levels in spacecrafts and submarines are usually 20-50 times higher than Earth levels, no evidence exists to suggest that these levels lead to any short or long-term deficits (Bacal, Beck and Barratt 2008). Studies in healthy individuals demonstrate no residual effects of breathing low to moderate CO₂ levels (<11 mmHg) for periods of 30-40 days (Malkin 1993). However, it is not uncommon for CO₂ levels to rise above the allowable concentrations in these enclosed environments. Prolonged exposure to higher levels results in several physiological adaptations including a compensatory metabolic alkalosis and a respiratory acidosis that leads to various electrolyte and metabolic alterations (Malkin 1993)(Bacal, Beck and Barratt 2008).

Only when the CO₂ level reaches about 12mmHg do detrimental physiologic effects become noticeable. Table 1 displays the symptoms and performance effects of increased atmospheric CO₂ during varying exposure durations. A ppCO₂ below 7.5mmHg produces few changes. Above 11 mmHg, subtle changes in acid-base equilibrium, ventilation, and electrolyte balance are seen. Above 22 mmHg ppCO₂, obvious abnormalities are noted, and at 38 mmHg, CO₂ is directly toxic. NASA has identified 15mmHg as the upper limit for off-nominal ppCO₂ level and 20 mmHg as the emergency level (Bacal, Beck and Barratt 2008).

Table 1: Symptoms and performance effects of increased atmospheric CO₂ at varying exposure durations

TABLE 22.7. Symptoms and performance effects of increased atmospheric CO₂.

PCO ₂ (mmHg)	Exposure Duration	Symptoms	Exercise performance	Mental performance
≤7.5	3–4 months	No unpleasant sensations; no functional impairments	Possible (all levels)	Possible
<15	Up to 30 days	No perceived symptoms; some increase in respiratory minute volume; slight acidosis	Light and moderate; heavy is difficult	Possible
25–30	Up to 7 days	Discomfort; dyspnea, especially on exertion; respiratory minute volume elevated by 2–2.5 at rest; exposure up to 3 days leads to easily reversible changes in metabolism due to acidosis	Light possible; moderate limited; heavy extremely difficult	Possible, if well learned
35–40	up to 15 h	Dyspnea, even at rest, “heaviness” of head, vertigo; respiratory minute volume elevated by a factor of 3–4; parameters of cardiovascular function relatively stable; respiratory acidosis; impaired cerebral functioning; sleep disorders	Light limited; moderate extremely difficult	Limited, even for familiar tasks
<50	up to 3–4 h	Dyspnea, headache, vertigo, visual impairments, sleep disorders; respiratory minute volume increased by a factor of 4–5; respiratory acidosis; marked changes in cardiovascular function; tachycardia, elevated blood pressure; disruption of central nervous system function	Light limited; moderate and heavy impossible	Difficult
<60	Up to 1 h	Drastic worsening of symptoms	All types impossible	Impossible
>60, <75	None acceptable	Drastic worsening of symptoms	Precluded	Precluded

Source: Malkin [2]. Used with permission.

Carbon dioxide removal on the ISS is performed by two American Carbon Dioxide Removal Assemblies (CDRAs) and the Russian Carbon Dioxide removal assembly, Vozdukh. Additional CO₂ removal systems, including Lithium Hydroxide (LiOH) canisters, are available while the Shuttle Orbiter is docked to the station. Unfortunately, CDRA failures are not uncommon and CO₂ levels have risen well beyond the appropriated safe threshold on the ISS.

The microgravity environment poses an additional challenge in CO₂ removal in that a ventilation system is required to carry CO₂ away from the nose and mouth, as there are no gravitationally driven convection forces in space. Forced ventilation and air flow is crucial in microgravity to mix atmospheric components and to prevent pockets of CO₂. Crewmembers are frequently required to work behind racks and in tight spaces where airflow can be compromised and are consequently exposed to pockets of concentrated CO₂.

Reports of visual impairment in astronauts have triggered new concerns over the connection between increased intracranial blood flow via vasodilatation induced by high ppCO₂ and intracranial hypertension. A classic “chicken/egg” debate exists on whether exposure to high levels of CO₂ induces increased ICP, or if existing ICP accentuates CO₂ symptom manifestation and positive feedback effects of high ICP (including eye effects).

3.2 Carbon Dioxide Exposure Limits in Confined Spaces

A plethora of information exists on the physiological effects of excess CO₂ on human subjects and in submariners habitually exposed to concentrations exceeding 1% (at 760 mmHg normal atmospheric pressure, 1% is roughly equal to 7.5 mmHg) (James, Carbon dioxide 2008). With the current data showing adverse effects above this level, the National Research Council (NRC) proposed revised guidelines to the U.S. Navy and NASA regarding exposure limits in confined spaces, in 2004 and 2008 respectively. The Spacecraft Maximum Allowable Concentrations (SMACs) for carbon dioxide levels have been adjusted and depend on the duration of exposure (from one hour to 1,000 days). It is very difficult to set safe exposure limits though as the database regarding CO₂ and its effects suffer from a scarcity of robust data in-flight. Figure 9 shows the recommended exposure limits for various lengths of exposure for the Navy and NASA.

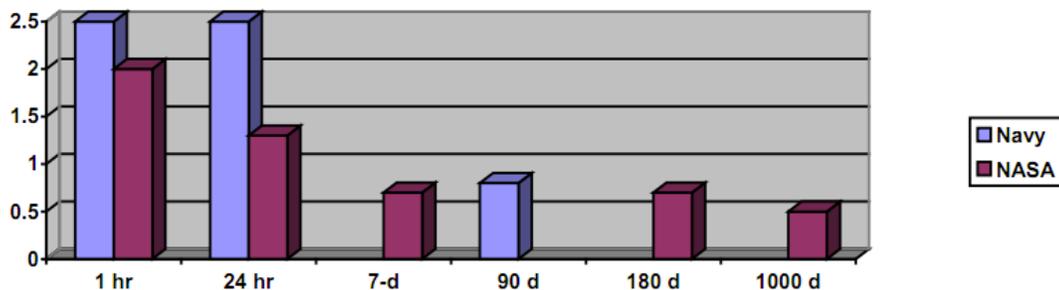


Figure 9: CO₂ exposure limits (%) proposed for various times in submarines and in spaceships adopted by the National Research Council (%CO₂ vs. time of exposure)(James, Carbon dioxide 2008).

The basis for the values recommended by the NRC to the Navy is very different from the basis for limits recommended to NASA. The NRC began with the lowest observed adverse effect level of 2.5% for visual effects for 1hr exposure limits. The 24hr exposure limit was drastically reduced for NASA because astronauts may need to repair the CO₂ removal system, and it is crucial that they not be mentally impaired. Submariners on the other hand could engage additional scrubbers or possibly surface. The 1000-day SMAC level was set at 0.5% because of anecdotal reports of behavioral changes at levels higher than 0.5% (James, Carbon dioxide 2008). Behavioral issues are of great concern for future exploration missions, and every precaution must be taken to avoid them. However, more research is warranted on the effects of long-duration exposure to high levels of CO₂.

3.3 Physiological Effects of Increased Carbon Dioxide Levels

Carbon dioxide is a powerful vasodilator, and exposure to high levels of CO₂ has many physiological implications including changes in cerebral hemodynamics and visual disturbances. Numerous studies have been performed to understand these changes, but limited data is available on the effects of excess CO₂ to the human body in microgravity.

As discussed in previous chapters, cerebral circulation takes place within a closed, rigid space of fixed volume, with limited capacity to buffer blood volume changes. Therefore, any modification

in cerebral vessel diameter, changes in cerebral blood flow (CBF), and cerebral blood volume (CBV) may affect ICP. Normally, there is about 150 mL of blood in the skull, of which about 100 mL is within the venous system, and CBF is approximately 50 mL/100 g/min (Gwinnutt and Saha 2005).

The relationship between the partial pressure of carbon dioxide in arterial blood (PaCO_2) and CBF is almost linear (Figure 10). At a PaCO_2 of 80 mmHg, CBF is approximately doubled and no further increase in CBF is seen because cerebral vessels are maximally vasodilated.

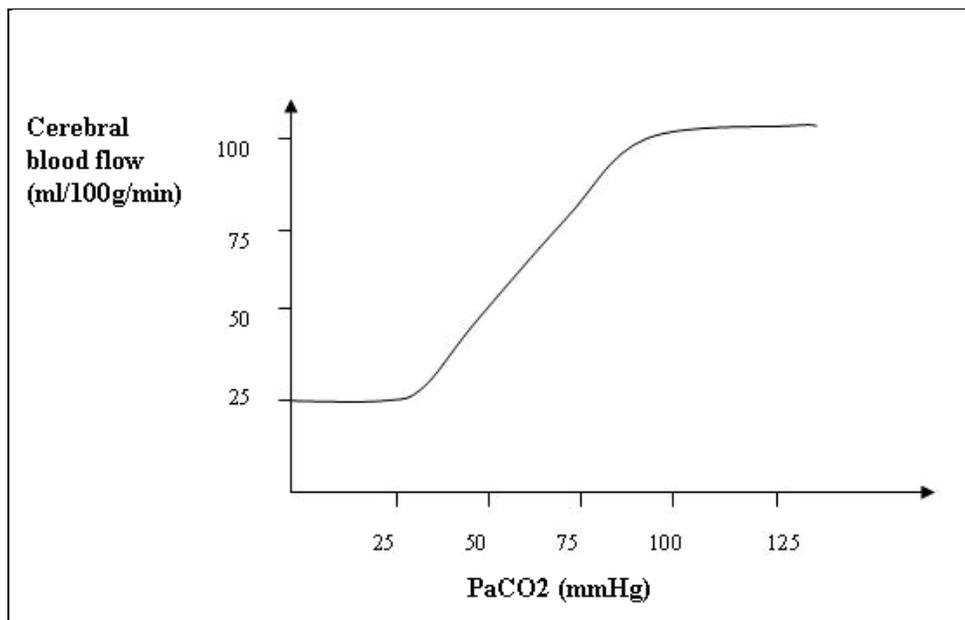


Figure 10: Relationship between cerebral blood flow (ml/100g/min) and PaCO_2 (mmHg)(Hill and Gwinnutt n.d.)

Ursino and Lodi (1998) used a mathematical model to simulate cerebrovascular reactivity to CO_2 and demonstrated the relationship between CO_2 , cerebral autoregulation, and ICP. It was determined that hypercapnia-induced vasodilation causes an increase in cerebral blood volume, leading to a sudden rise in ICP. Subsequently, ICP returned towards the baseline after about one hour (Ursino and Lodi 1998). However, it is important to remember that there are probably existing cerebral blood drainage issues during spaceflight, and so even a small increase in cerebral blood flow may cause a large, lasting increase in intracranial pressure. It is also important to remember that within the first week of spaceflight, blood volume is also decreased by 17%, which would help to buffer this effect. However, at the onset of weightlessness, there would be a double whammy of headward fluid shift plus the CO_2 exposure increase from the Earth atmospheric level (0.039%) to the spacecraft level (1%). This is one of the main reasons it would be imperative to measure ICP immediately upon entry into weightlessness.

In another study, Edwards et al. (2004) found that the dynamic cerebrovascular autoregulatory response depends on the steady-state level of arterial ppCO_2 . A small increase in ppCO_2 caused

a reduction in the amplitude and a marked slowing of the cerebrovascular resistance response to change the middle cerebral artery blood pressure (Edwards, Devitt and Hughson, Two-breath CO₂ test detects altered dynamic cerebrovascular autoregulation and CO₂ responsiveness with changes in arterial PCO₂ 2004). Cerebral autoregulation is extremely important to maintain a constant CBF, and if it is compromised or altered, there could be detrimental effects. In another study demonstrating the effects of 5-7% CO₂ inhalation, cerebral blood flow underwent a striking and consistent increase, averaging 75%, and a marked reduction in mean cerebrovascular resistance was seen (Kety and Schmidt 1947). A direct relationship has also been shown between increased ppCO₂ and increased ICP in pigs (Schob, et al. 1996). All of these studies demonstrate increased cerebral blood flow associated with increased exposure to carbon dioxide. In spaceflight, exposure to high levels of carbon dioxide could cause a marked increase in cerebral blood flow, contributing to increased intracranial pressure.

James et al. (2010) demonstrated a link between private medical conference-reported headaches and 24-hr average CO₂ levels on the ISS. A direct relationship between CO₂ dose and percentage of headaches was observed. It is unknown if the astronauts experiencing headaches were also the ones experiencing vision disturbances. Headache is a known side effect of hypercapnia on Earth, and is likely occurring in space due to CO₂ overexposure. It is also noteworthy that James et al. (2010) found no convincing behavioral response to higher CO₂ levels through analysis of the WinSCAT system (James, Meyers, et al. 2010).

Hypercapnia is known to have visual symptoms on Earth, with no association to increased ICP. Hypercapnia results in increased retinal, choroidal, and retrobulbar blood flow. Sponcel et al. (1996) showed reduced temporal contrast sensitivity in response to hypercapnia (Sponcel, et al. 1997). Sun et al. (1996) exposed subjects to 2.5% CO₂ for about 30 minutes, and found a subsequent decrease in depth perception (Sun, Sun and Yang 1996). In a similar experiment, Yang et al. (1997) found that exposure to 2.5% CO₂ impaired one's ability to detect coherent motion (Yang, Sun and Sun 1997). In these studies, the effects disappeared when subjects discontinued breathing carbon dioxide. These visual disturbances are not the same ophthalmic changes seen on-orbit though, and the acute effects are due to sudden exposure to high levels of carbon dioxide. Astronauts, on the other hand, are immersed in a relatively hypercarbic environment for weeks to months at a time. Therefore CO₂ is not thought to contribute directly to visual disturbances.

3.4 Future Research

Although ground studies help in the understanding of hypercapnia and its effect on ICP, bed-rest studies may not provide sufficient or accurate data in regards to astronaut response to CO₂ levels and ICP. This is because subjects on Earth do not have the same underlying physiological adaptations as astronauts in space do. What may be thought of as a safe level of CO₂ on Earth may not be the same in space due to an existing increased susceptibility to CO₂ effects. Individuals vary greatly in their response to excess CO₂, and therefore it is difficult to determine a threshold at which NASA should set CO₂ levels.

However, it would be extremely valuable to look at a population experiencing CO₂ levels similar to those on the space station for extended periods of time. Submariners live in enclosed, high CO₂ environments for months at a time, and it would be beneficial to perform ophthalmic tests and ICP measurements before, during and after their expeditions. This way, results could be compared to those of astronauts, and it could be determined if CO₂ is in fact a primary mechanism for vision changes/increased ICP, or whether gravity (or lack thereof) plays the major role.

3.5 Conclusion

There is discussion on whether increased CO₂ levels induce increased ICP or whether existing increased ICP accentuates CO₂ symptom manifestation. There is still much to be researched and discovered regarding the cause of increased intracranial pressure in space. It is thought that physiological adaptations to the microgravity environment can make the body more susceptible to harmful effects of increased CO₂. Crewmembers have reported CO₂-related symptoms at levels far lower than at levels reported terrestrially. These symptoms then tend to resolve when CO₂ levels are decreased. It appears that the body has a heightened sensitivity to CO₂ in microgravity. This can be attributed to individual predisposition to CO₂ retention, adaptation to microgravity, and/or local fluctuations in CO₂ that are not measured by fixed sensors (Law, Watkins and Alexander June 2010). It is therefore thought that high CO₂ levels are not the primary cause of increased intracranial pressure, but rather are a contributing factor that may affect some more than others.

4. Resistance Exercise

4.1 Musculoskeletal Adaptations to Space and Resistance Exercise Countermeasures

The human musculoskeletal system is adapted to a 1-G environment, with constant compression from gravity and impact forces from ambulation. Changes in mechanical loading during exposure to microgravity result in a cascade of biochemical and structural changes in bone, muscle and connective tissues. Notably, the removal of these forces induces bone resorption and decreased bone formation.

Decreased bone mass and muscle atrophy are well-known and highly researched physiological consequences of long-duration spaceflight. Historically, human spaceflight has seen an evolution of exercise countermeasures attempting to counteract these adaptations. Weight-bearing bones such as the hip, lumbar spine, femur, tibia and calcaneal bones suffer the most bone loss in space, as these areas usually receive substantial loading during daily activities in a 1-G environment. Medical data from long-duration Mir and ISS missions show an average bone density loss of 1-2% per month on the weight-bearing bones, and no bone loss in the arms.

There is consensus among the exercise science community that both aerobic and resistance exercise are needed to maintain crew health. Studies show that impact loading and resistance

exercise are extremely important in the mitigation of bone loss and provide the most osteogenic stimulus (Taaffe, et al. 1997)(Shackelford, et al. 2004). However, it is important to remember that prevention of bone loss is not yet possible and therefore countermeasures focus on slowing the process.

Resistance exercise has always been a routine part of long-duration space missions. Skylab utilized a friction rope, and the Mir station had 80lb bungee cords and full-body loading suits. The standard suite of exercise countermeasures (treadmill, cycle ergometer, and bungees) are available on the ISS, however, due to compelling ground data with bed rest subjects, heavy resistance exercise capabilities have also been added. A resistive device capable of producing 300lbs of force, the interim resistive exercise device (iRED), has been available since the first expedition crew on the ISS. Resistive exercises include squats, heel raises and dead lifts. However, restrictions due to load capabilities and hardware failures have limited the effectiveness of the iRED (L. C. Shackelford 2008). 300 lbs may seem like a large load, however, in space, the body is in a state of weightlessness and a large portion of the load is used to offset the body mass, and not used in muscle and bone loading. The iRED also lacks isolation, and therefore imparts undue loads on the structure of the ISS.

4.2 Advanced Resistive Exercise Device (ARED)

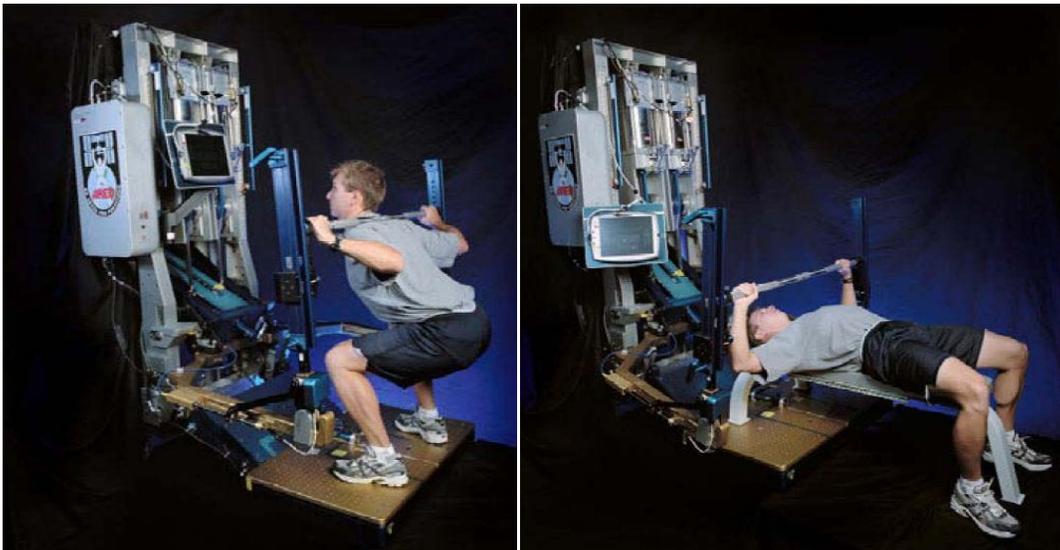


Figure 11: The ARED being used for a squat and bench press (Photo courtesy of NASA)

In a ground-based study comparing the effectiveness of the iRED vs. free weight exercise in increasing muscle strength and bone mineral density, it was found that high-intensity training with the iRED produced muscle responses similar to free weight exercise, but was not effective in stimulating bone (Schneider, et al. 2003). The importance of heavy loading and resistance exercise to prevent musculoskeletal losses, especially bone density loss, was recognized by NASA, and the Advanced Resistive Exercise Device (ARED) was flown to the ISS in 2008. The ARED (Figure 11) uses vacuum cylinders and inertial flywheels to simulate the constant mass and inertia of free weight exercise in the absence of gravity. It provides feedback to the astronaut

during use and concentric workloads up to 600 lbs. In a study comparing the effectiveness of exercising with the ARED vs. free weights, no significant difference was found between the two, and both forms of exercise showed an increase in muscle strength, muscle volume, and lumbar spine bone mineral density (Loehr, et al. 2011). The ARED is also an isolated system, transmitting less than 10^3 G onto the stack structure, which is extremely important for the ISS structure integrity and lifetime.

4.3 Physiology of Resistance Exercise

Breathing Techniques and Cerebral Blood Flow

Cerebral blood flow autoregulation is a natural biological mechanism in place to keep the brain protected from over- or under-perfusion during large blood pressure changes in the body. Autoregulatory mechanisms maintains cerebral blood flow at ~45-50 mL/100g/min, despite systemic changes in blood pressure (Giles and Whitfield 2007). It is initiated in response to changes in mean arterial pressure (MAP) within three to five seconds and it acts between pressures of approximately 50-160 mmHg (Figure 12) (Paulson, Strandgaard and Edvinsson 1990). Outside of this range, autoregulation is not able to maintain normal cerebral blood flow and it becomes dependent on arterial blood pressure.

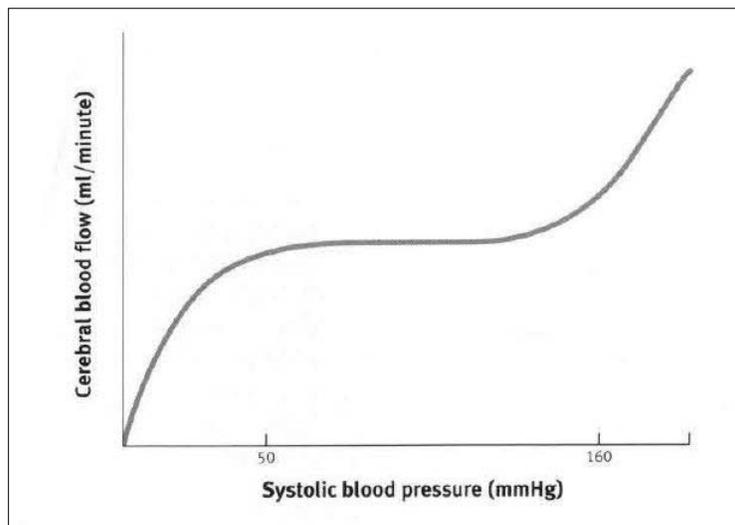


Figure 12: Cerebral blood flow over a range of systolic blood pressures (Source: Giles and Whitfield 2007)

Heavy resistance exercise is associated with a large increase in MAP. It is thought that spikes in MAP due to resistance exercise may exceed the ability of cerebral autoregulation to maintain normal blood flow velocity to the brain (MacDougall, et al. 1992). This however depends on the percentage of maximum load the person uses to exercise and their breathing technique. Edwards, et al. (2002) found that the average flow velocity through the middle cerebral artery (MCA) oscillates directly with changes in MAP during leg press exercise (at 75% of each subject's theoretical maximum voluntary contraction with continuous breathing) (Edwards, Martin and Hughson, Cerebral hemodynamics and resistance exercise 2002). However, the overall average

MCA blood flow velocity remained constant during leg press exercise, even though the MAP increased with successive repetitions. This shows that rapid oscillations in MAP transmit directly to mean cerebral blood flow velocity, but systemic increases in MAP are countered by cerebral autoregulation.

Changes in MAP and cerebral blood flow during heavy resistive exercise depend greatly on the mode of ventilation of the person exercising. During a Valsalva-like maneuver, a forceful exhalation against a closed airway, blood flow to the brain is critically reduced. A Valsalva maneuver leads to a sudden increase in intrathoracic and central venous pressure (F. Pott, J. J. Van Lieshout, et al. 1999). This rise in central venous pressure, which impedes cerebral venous outflow via the jugular venous system, results in a simultaneous and equal rise in ICP, causing a reduction in cerebral perfusion pressure (Haykowsky, et al. 2003). When looking at the equation:

CPP decreases and CVR increases, resulting in a lower CBF. Even when a Valsalva maneuver is performed in the supine position, middle cerebral artery mean blood velocity is reduced ~35% (Tiecks, et al. 1996). Some weight lifters performing a Valsalva maneuver experience black-outs and pass out due to reduced cardiac output because of reduced venous return and decreased cerebral blood flow (Dickerman, et al. 2000)(Compton, Mcn. Hill and Sinclair 1973). Fighter pilots also perform straining maneuvers under high G-loads to keep cerebral pressure up, however, they must let go periodically to prevent blacking out.

Another study demonstrated that increased intra-abdominal pressure in swine caused significant increases in intracranial pressure (7.3mmHg to 16.4mmHg) and central venous pressure (6.6mmHg to 10.7mmHg) and a decrease in cerebral perfusion pressure (75.6mmHg to 62.0mmHg) (Bloomfield, et al. 1997). The increase in ICP is due to cerebral venous outflow obstruction via the jugular venous system.

Continued ventilation during resistance exercise results in a much smaller increase in intracranial pressure, and also lowers the initial rise in middle cerebral artery blood flow velocity, MAP and central venous pressure (F. Pott, J. Van Lieshout, et al. 2003).

Resistance Exercise, Intraocular Pressure and Intracranial Pressure

Studies have shown that aerobic, anaerobic and static isometric exercises lead to a decrease in intraocular pressure (IOP) after exercise (Vieira, et al. 2006 and references 1-9 within). However, during weightlifting, IOP increases significantly, both during a Valsalva maneuver (increases ~4.3 mmHg) and continued respiration (increases ~2.2 mmHg) (Vieira, et al. 2006).

As previously mentioned, during a Valsalva maneuver, there is a sudden increase in intrathoracic venous pressure. This is transmitted through the jugular, orbital and vortex veins to the choroid,

bringing about vascular engorgement, an increase in the choroidal volume, and an increase in IOP (Vieira, et al. 2006)(Schuman, et al. 2000). The larger increase in IOP during a Valsalva maneuver may be due to a larger increase in intrathoracic pressure from air being retained in the lungs. It is thought that similar mechanisms of increased ICP and IOP due to increased intrathoracic pressure occur in resistance wind instrument player and people with chronic asthma (Schuman, et al. 2000)(Krist, Cursiefen and Junemann 2001).

If the rise in IOP is due to venous outflow congestion because of increased jugular venous pressure, one would expect ICP to rise simultaneously (due venous outflow obstruction and impaired CSF reabsorption). A correlation between IOP and ICP has been suggested in some studies (Vieira, et al. 2006 and references 1-3 within), however, it is still highly debated. If both rise, then there will be no change in trans-lamina cribrosa pressure (Jonas, Berenshtein and Holbach 2003). On Earth, a rise in IOP and not ICP will cause the lamina cribrosa to be pushed outward, towards the optic nerve, pinching the nerves that run through it. This is referred to as Glaucoma and can lead to complete blindness. In spaceflight, ICP is raised, and the lamina is pushed towards the intraocular space. It is thought that this is due to the ICP being greater than the IOP. It is possible that the rise in IOP (although still less than ICP) is actually being caused by a rise in ophthalmic venous pressure due to increased ICP.

4.4 The ARED and Astronaut Vision Changes

The ARED was delivered to the ISS on STS-126 in November, 2008. Expedition 19 was the first crew to use it as a consistent part of their exercise schedule for an entire flight routine, along with the treadmill and cycle ergometer.

Literature on resistive exercise and weight lifting shows that it contributes to increased ICP. However, on-orbit, 4 out of the 10 astronauts having visual symptoms experienced these changes before the ARED was even on the ISS. It is therefore very difficult to omit or include resistance exercise, specifically the ARED, as a contributing factor to increased ICP and visual impairment in space. Just like increased levels of CO₂, it is possible that slightly increased ICP due to strenuous exercise over repetitive, daily exertions could have a much larger affect on-orbit than on the ground due to underlying physiologic adaptational changes and already increased ICP present in the astronauts.

Onboard the ISS, astronauts are trying to counteract the body's natural adaptation to microgravity by loading the muscles and bones with forces. They are not trying to body build, and therefore are not using the ARED to do maximum lifts. They usually perform 12 repetitions for any given exercise, and not maximal exertions. In a study of 11 athletes doing maximal isometric contractions while holding their breath, an IOP increase of 15.0 mmHg from rest was seen (Dickerman, et al. 1999). The subjects in the study by Vieira et al. (2006) lifted weights at 80% of maximal load, which greatly reduced the IOP during the lift (increased IOP 4.3 mmHg from rest during Valsalva maneuver and 2.2 mmHg during continued respiration). Because astronauts are not lifting at maximal exertion, it is unlikely that the straining is producing a large enough intrathoracic pressure to cause a significant increase in IOP and/or ICP. It would be

beneficial to look at the specific exercise techniques of the astronauts experiencing visual impairment, to see how close they were lifting to their max, breathing techniques, etc.

It would be extremely valuable to have an on-orbit experiment to measure the IOP and ICP before, during, and after using the ARED. This would help determine if resistance exercise is causing increased ICP just during the exercise, or if it produces lasting pressure changes. It would also be interesting to look at the ophthalmic data from Russian cosmonauts that never used the ARED during their long-duration missions to determine if the ARED could have a contributing affect to ocular health.

4.5 Conclusion

Overall, research has shown that there is an increase in mean arterial pressure but decrease in mean flow velocity of the middle cerebral artery associated with resistance exercise on Earth. Increased intrathoracic pressure and increased in central venous pressure is also seen when exercise is performed with a Valsalva maneuver. This results in cerebral venous outflow disruption, causing increased ICP. Astronauts are trained to never use a Valsalva maneuver though, greatly reducing the potential of exercise contributing to increased ICP in space. Increased IOP has also been linked to heavy resistive exercise, which could possibly be a secondary factor of increased ICP. These physiological changes associated with resistance exercise depend greatly on the percent of maximum weight lifted and breathing technique used. Vision changes are not frequently seen in the weight lifting community, even though ICP and IOP can increase greatly during exercise. It is therefore concluded that the ARED is most likely not a large contributor to visual disturbances seen on the ISS, however it must be considered as a secondary contributing mechanism.

5. Excess Sodium Intake

5.1 Introduction

Salt (40% sodium and 60% chloride) is an essential and integral part of the human diet. The dietary guidelines for Americans created by the U.S. Department of Health and Human Services and the U.S. Department of Agriculture recommends a daily sodium intake of no more than 2,300 mg/day (5,750 mg of salt), but the average American consumes almost 4,000 mg/day. Although sodium is naturally present in many foods, 75% of a person's sodium intake is from salt added by manufacturers for added flavor and preservation.

Sodium is a vital mineral and plays an important role in the function of nerve impulses, muscle physiology, maintaining water balance within cells, and pH balance. However, excess sodium and its effects on acid/base physiology have been associated with many health issues including hypertension, bone loss, increased risk of kidney stones, impaired muscle performance, and altered glucose and vitamin D metabolism.

Epidemiologic data shows a direct relationship between dietary sodium intake and blood pressure (Stamler 1997)(Elliott 1991), and it is recommended that people with hypertension

reduce their sodium intake to 1,500mg/day. Even though some experts oppose recommendations to decrease sodium intake in the general population and question the universality of negative effects on everyone (McCarron 2000), top level organizations such as the American Medical Association, American Dietetic Association, Institute of Medicine of the National Academies and Center for Disease Control and Prevention highly recommend decreasing sodium intake (American Medical Association 2008)(American Dietetic Association 2010)(Institute of Medicine of the National Academies: Food and Nutrition Board 2005).

5.2 On-Orbit Diet

Nutrition is closely, if not directly, related to many of the physiologic consequences of spaceflight. The diet in place for astronauts is, and has historically been, very high in sodium. Nutritional requirements for missions lasting 30 days to 1 year recommend that sodium intake be less than 3,500 mg/day (NASA Johnson Space Center 1996). In reality, sodium intake is much higher than the recommended amount during space flight (Figure 13), and has been documented up to 14,000 mg/day in some cases. This is primarily due to the fact that majority of space foods are commercial the off-the-shelf and have a very high sodium content, both for taste and shelf-life. Also, calorie intake on-orbit has proven to be much larger than expected, and with sodium levels already too high in on-board food, this by default translates an excessively high sodium intake.

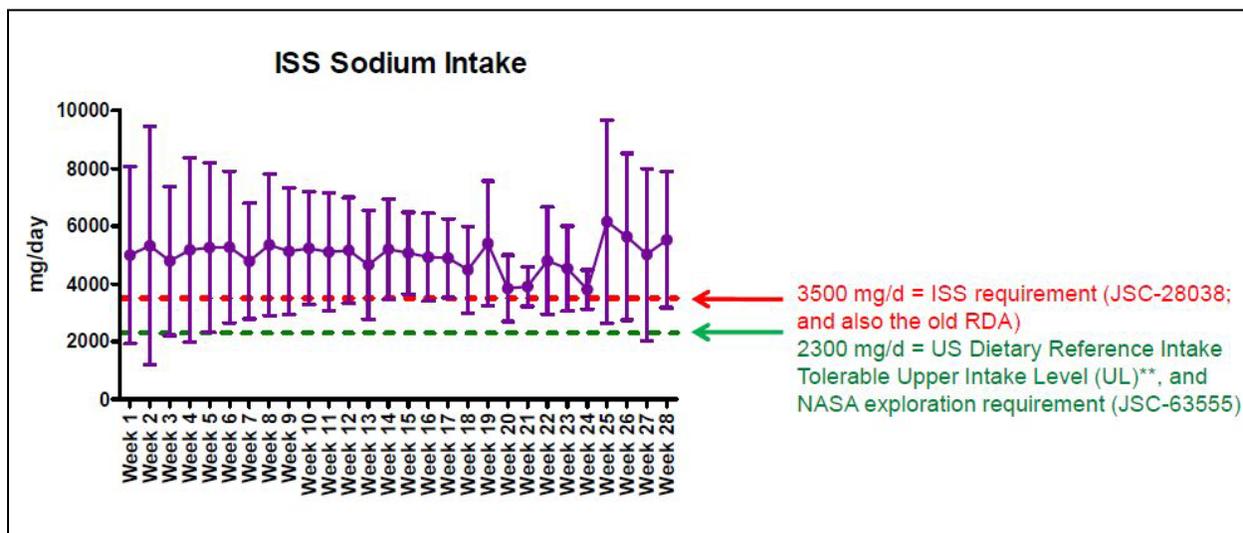


Figure 13: Average ISS Sodium intake (in purple), compared to the ISS requirement (red) and recommended U.S. sodium intake (green) (Figure courtesy of Dr. Scott M. Smith)

In 2010, the NASA food lab started an on-orbit diet reformulation initiative in attempts of lowering sodium in the prescribed astronaut diet. The baseline menu started at approximately 5,600 mg Na/day, and has a goal of being lowered to 3,000 mg/day. All space food reformulations are scheduled for completion in September, 2011, however, the food currently on-orbit will feed the crew until 2012, so it will be some time before low sodium foods are an integral part of crew diet on the ISS.

5.3 Health Effects of High Sodium Intake

The high sodium diet of astronauts onboard the ISS can have many physiological consequences. For example, high sodium intake can exacerbate bone loss, an existing consequence of space flight, and is associated with increased amounts of calcium in the urine, increasing the risk for developing kidney stones (Massey and Whiting 1996)(Heer, Zitterman and Hoetzel 1995).

Also, population based studies show a direct relationship between dietary sodium intake and blood pressure, although this varies between subgroups (Elliott 1991)(Vollmer, et al. 2001)(Stamler 1997). Several studies suggest that African Americans and older adults are more salt-sensitive (have a greater blood pressure response to sodium intake) (Weinberger, et al. 1986)(Ishibashi, et al. 1994). Findings from the Dietary Approaches to Stop Hypertension (DASH) Sodium Trial demonstrated that lower sodium intake decreased blood pressure in all participants. Even though this decrease in blood pressure was seen in all participants, variations existed in the degree of change based on age, race, existing hypertension, body mass, etc (Svetkey, et al. 1999). Effects tended to be greatest in persons with preexisting hypertension, those older than 45 years of age, and women (Vollmer, et al. 2001). Pre-ISS, the mean astronaut age was 38 and missions were generally 5 to 17 days (Skylab being a notable exception). Nowadays, the mean age of active U.S. astronauts is 46.7, making them more susceptible to hypertension and salt-sensitivity.

In healthy adults, the osmotic pressure of body fluids is maintained within a narrow range, and its principal determinant, serum sodium concentration, rarely varies by more than 2%. This consistency is achieved by elevating or lowering the total body water to counteract changes in the serum sodium concentration and its anions. It is a commonly accepted hypothesis that a high sodium diet expands the intravascular and total extracellular volume. However, Heer et al. (2000) found no increase in extracellular volume or total body fluid due to the increased salt intake (Heer, Baisch, et al. 2000). They did however find a stepwise increase in plasma volume with increases in salt consumption, and increases in blood volume. This new finding shows that high salt intake leads to preservation of body sodium that is not paralleled by an increase in total body water. This has also been observed on-orbit during the MIR 1997 mission, where the daily determination of sodium balance cumulated to a retention of 740mmol of sodium within 15 days aboard MIR, compared with the two week simulation on ground, where 65mmol were retained. This shows that microgravity may be playing a unique role in sodium handling (Drummer, et al. 2000). The SODium LOading in Microgravity (SOLO) experiment, currently being performed on the ISS, will study the mechanisms of fluid and salt retention in the body during space flight. One possible mechanism for water free sodium retention has been proposed, in which excess sodium is bound to glycoaminoglycans (GAGs), exchanging with a hydrogen ion. This H⁺ release contributes to the acidification of blood pH. Heer et al (2009) found that mRNA expression of GAG polymerization genes increased with a rise in salt intake (Heer, Frings-Meuthen, et al. 2009).

High sodium levels cause a body fluid shift from the interstitial to the intravascular space to compensate for transiently increasing serum sodium concentration and serum osmolality. This

increase in blood volume and plasma volume could be a contributor to increased venous volume and congestion, causing jugular venous outflow obstruction.

There are also other pressure phenomena besides vascular hypertension that can be addressed by low sodium diets. For example, Meniere's disease is a disorder of the inner ear resulting in hearing loss associated with excess fluid in the inner ear (endolymphatic hydrops). Although there is no cure, physicians frequently prescribe a low-salt diet to reduce the amount of sodium in the body, and therefore reduce the amount of overall fluid in the body.

Moreover, a low sodium diet has long been a suggested treatment for idiopathic intracranial hypertension (IIH). The main morbidity for IIH is visual loss (due to papilledema) and can often be reversed if recognized early and treated promptly with weight reduction, a low-sodium diet, and acetazolamide (Bekavac and Goel 2011). Newborg (1974) reported remission of papilledema in all nine patients placed on a restricted diet of less than 100 mg of sodium per day (Newborg 1974). It is not yet clear whether improvement occurs because of the weight loss per se or the changes in diet. However it is suggested that astronauts consume a lower sodium diet in attempt to improve papilledema and prevent long term damage.

5.4 Conclusion

An individual's preference for salt is not fixed, and after consuming foods lower in salt for a period of time, taste for salt tends to decrease. Reducing the sodium intake on-orbit will decrease the risk of developing hypertension and reduce the amount of sodium retention in the body. Although new research demonstrates that sodium retention does not lead to an overall increase in body fluid, an increase in blood volume is still seen. This increase in blood volume could be a contributor to increased ICP, or worsen existing intracranial hypertension in astronauts. However, sodium appears to be a soft contender on the contributors list. Even if high sodium intake is not playing a large role in increased ICP, it is safe to say that it is most definitely not making anything better, and reducing sodium intake could enhance the overall health of astronauts.

6. Enzymatic Polymorphism

6.1 Introduction

Through examining data from the Nutritional Status Assessment Supplemental Medical Objective (SMO), it has been hypothesized that variations in an important metabolic pathway could be a possible contributing factor to these cerebrovascular and optical medical issues (Smith, et al. 2011). The pathway is called the one-carbon metabolic pathway (Figure 14), and is critical for nucleotide and amino acid synthesis, and biological methylation reactions (Shane 1995).

One noteworthy effect of enzyme dysfunction in the one-carbon metabolic cycle is a consequential buildup of metabolites, including plasma homocysteine. Elevated plasma homocysteine is an independent risk factor for serious cardiovascular related diseases,

cerebrovascular events, cancer and several neurologic disorders (Chen, et al. 2005)(Suzuki, et al. 2007)(Fuso and Scarpa Article In Press)(Guilliams 2004).

6.2 Sources of Dysfunction in the One-Carbon Metabolic Pathway

Modifications in the one-carbon transfer pathway can be attributed to several sources. For example, deficiencies in vitamins B6 and B12 and folic acid can contribute to alterations. However, astronaut diet and nutritional intake is closely monitored and therefore this is not thought to be a contributing factor in one-carbon pathway dysfunction.

Another cause of one-carbon pathway dysfunction is alteration of the actual enzymes that regulate the pathway. A one-letter change in the section of the genetic code responsible for a particular enzyme, known as a single nucleotide polymorphism, can cause significant changes in the enzyme structure and function. Smith, et al. (2011) has linked six known polymorphisms, occurring in four genes involved in the one-carbon pathway, to be the cause of enzymatic dysfunction and metabolite accumulation. Dysfunction in these enzymes could potentially lead to vision changes seen in astronauts, discussed in more detail in subsequent sections. Figure 14 highlights the enzymes affected by these polymorphisms in red font.

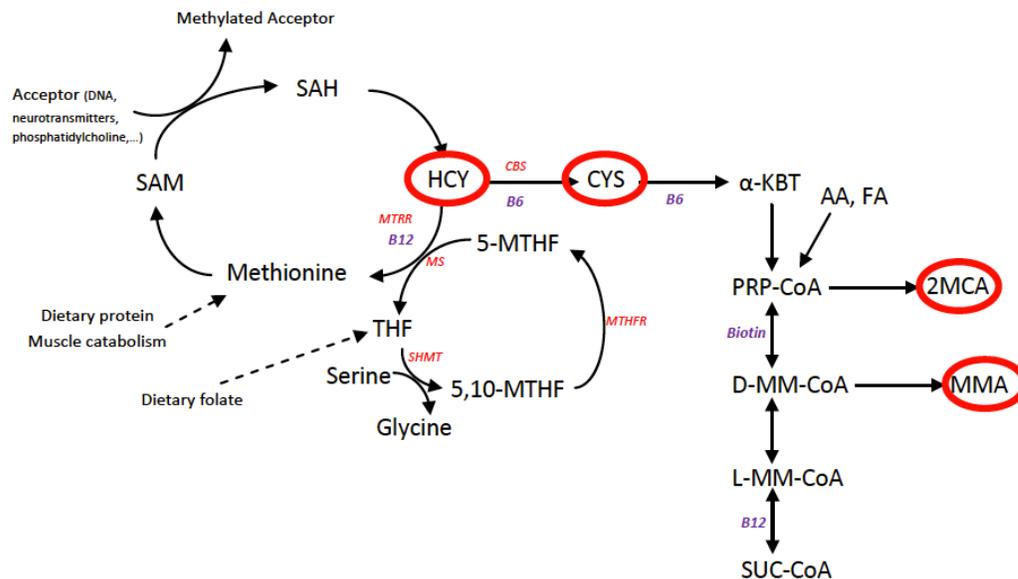


Figure 14: Overview of the 1-carbon metabolic pathway. Enzymes affected by the polymorphisms are in red font, and metabolites that accumulate as a result of enzyme dysfunction are circled in red (Source: Smith, et al. 2011).

The polymorphisms Smith et al. has linked to enzymatic dysfunction include:

1. 5,10-methylenetetrahydrofolate reductase (MTHFR) 677C→T, 665C→T, and 1298A→T
2. serine hydroxymethyltransferase 1 (SHMT1) 1420C→T
3. cystathionine β-synthase (CBS) 844ins68
4. 5-methyltetrahydrofolate homocysteine methyltransferase reductase (MTFF) 66A→G

Altering the one-carbon cycle is similar to altering an assembly line in a factory; if a modification occurs in the beginning, everything downstream will also be affected. Also, if the production of one piece slows, it affects the rate of the entire cycle and pieces further down the line being to build up in excess. In regards to the one-carbon cycle, dysfunction of the MTHF, MS, SHMT, MTHFR and CBS enzymes slow down the entire cycle, causing a buildup in downstream constituents including homocysteine (HCY), cystathionine (CYS), methylcitric acid (MCA) and methylmalonic acid (MMA)(Figure 14).

Data also shows that serum folate and vitamin B6 levels were lower in affected crewmembers than crewmembers without symptoms in-flight (Smith, et al. 2011). This is most likely due to disruptions and slowing down of the cycle, rather than nutritional deficiencies. A possible mitigation could be to provide vitamin B6 and folate supplements to astronauts thought to be predisposed to one-carbon pathway polymorphisms (Sugiyama 2005) to prevent further issues that could develop due to vitamin B6 and folate deficiencies.

The identified polymorphisms are quite common in normal populations, for certain ethnic backgrounds. For example, the MTHFR C677T polymorphism occurs is less than 1% in those of African descent, 11-15% in Anglo-Americans, and >20% in Italian, Hispanic, and Columbians (Guilliams 2004). It is therefore plausible that given the number and ethnic background of astronauts affected, these polymorphisms could be present in the selected astronauts.

6.3 Relevance to Astronauts and Preliminary Data

Smith, et al. (2011) has hypothesized that the incidence of these polymorphisms, occurring in genes involved in one-carbon metabolism, can be associated with the incidence of in-flight and post-flight vision changes in long-duration crewmembers. Preliminary data is available from 4 of the crewmembers that experienced significant vision changes, and 10-20 crewmembers of which did not experience vision changes. Plasma levels of cystathionine, methylcitric acid and methylmalonic acid, all intermediates of one-carbon metabolism, were higher in crewmembers that experienced visual or intracranial pressure issues (Smith, et al. 2011). Also, a lower status of relevant vitamin cofactors has been identified between the two groups.

Most notably, pre, in- and post-flight data show a higher plasma homocysteine concentration in astronauts that experienced vision changes than those who did not (Figure 15). Increased homocysteine levels has been identified as a risk factor for ischemic stroke, intracranial aneurysms, migraine headaches, occlusive disease of the retina and some types of glaucoma (Smith, et al. 2011, and references 2-7 within). Negative effects of excess homocysteine in the body have been well documented, as it is a known neurotoxin.

One hypothesis explains that a buildup of homocysteine can lead the body to incorrectly select homocysteine instead of methionine in protein biosynthesis (Fredriksen, et al. 2007). Incorporation of homocysteine-thiolactone into a protein could cause issues in its function and folding patterns. Two hypothesized protein targets include hemoglobin and ferritin. Data from Smith, et al. (2011) show a decrease in both of these proteins in astronauts with vision changes

relative to astronauts with no vision changes. Further research is warranted to understand the effects of decreased hemoglobin and ferritin on spaceflight induced vision changes.

Ganapathy, et al. (2011) also provides a mechanism of homocysteine-mediated ganglion cell death induced by NMDA receptor stimulation and oxidative stress (Ganapathy, et al. 2011).

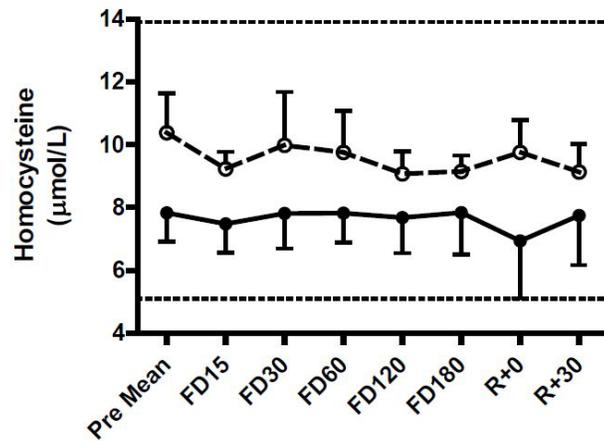


Figure 15: Plasma homocysteine levels before, during, and after spaceflight. The open circles and dashed line represents the mean of the four crewmembers with reported vision changes. The filled circles and solid line represents the mean of the eleven crewmembers with no reported changes in vision post flight.

It is important to note that while the homocysteine levels found in astronauts with vision changes is consistently higher than in astronauts with no vision changes, the levels are still considered to be within normal levels (between 6-12 µmol/L) (Guilliams 2004). Elevated plasma homocysteine is known to be an independent risk factor for several cardiovascular diseases, cancer and neurologic conditions. In patients recovering from either unstable angina or myocardial infarction, there was a statistical decrease in survival in patients with homocysteine levels above 12 µmol/L (Stubbs, et al. 2000). Homocysteine is also an independent risk factor for ischemic stroke. The Framingham Heart Study identified individuals in the highest quartile (>14.24 µmol/L) had a relative risk of 1.8 compared to the lowest quartile (<9.25 µmol /L) in incidence of stroke (Bostom, et al. 1999). In another Framingham study, it was found that the risk for Alzheimer’s dementia doubled when plasma homocysteine exceeded 14 µmol/L (Seshadri, et al. 2002). Astronauts experiencing vision changes had average homocysteine levels of about 9.5 µmol/L (Smith, et al. 2011). This is below any aforementioned clinical levels associated with serious disease risk. However, one cannot ignore the statistically significant difference between homocysteine levels in astronauts experiencing vision changes, and those that do not.

6.4 Polymorphisms and Vision

Homocysteine and other one-carbon metabolites are known vascular toxins. However, the exact mechanisms of how increased levels of one-carbon metabolites can induce vision changes are

unknown. First, the research proposed by Smith et al. (2011) needs to be carried out to determine whether these polymorphisms occur solely in astronauts with vision changes. If this is true, the discovery would then propel ample research to determine the exact mechanisms of vision changes during spaceflight.

Because these enzymatic modifications are due to genetic polymorphisms, one cannot help but wonder why it is occurring in space, and not on Earth to these particular astronauts. It is thought that these polymorphisms are not a singular mechanism causing vision changes, but rather are a contributing, or secondary effect. The physiological stresses of spaceflight, coupled with intracranial hypertension, upward fluid shift, increased levels of carbon dioxide, and strenuous exercise could trigger this system to have more profound effects on the human body and ocular system.

One hypothesis is that adaptation to microgravity may alter astronaut's vascular drainage on a very local area, especially in the central nervous system. This could then affect the microvasculature, such as drainage of the choroid plexus or renal vasculatures. Therefore, even a slight increase in homocysteine may have significant effects due to the stagnant blood flow in the cranial cavity.

It is also worth noting that the degree of vision degradation varied greatly between the nine affected crewmembers. It is possible that one polymorphism (out of the 6 aforementioned polymorphisms) could have greater affects than others. Also, a certain combination of the listed polymorphisms could be more detrimental than others.

Human adaptation to microgravity causes the body to change in numerous ways. It is therefore likely that factors that do not have an effect on someone on Earth, such as slightly increased homocysteine levels, may have significant effects on that person in space.

6.5 Conclusion

Enzymatic activity tests and/or genotyping needs to be performed on astronauts who experienced vision changes, and those who did not to determine if the proposed polymorphisms could be a contributing factor to vision changes in spaceflight. There also needs to be more research done to explain exactly how alterations in the one-carbon cycle (i.e. the buildup of homocysteine) directly affect ocular health, and the mechanisms that could cause the observed vision changes. It is currently not thought that these polymorphisms alone could cause significant visual issues, but rather that they are a contributing factor. If it is determined that these polymorphisms are present in astronaut with vision changes, researchers could then look further into other provoking factors, such as increased carbon dioxide or increased intracranial pressure, that coupled with enzymatic polymorphisms could trigger vision changes.

7. Overall Conclusions

Overall, the newly recognized suite of ophthalmic changes seen in astronauts onboard the ISS and Space Shuttle has reminded the space community how much is still unknown regarding

human adaptation to space. This phenomenon has most likely existed since the beginning of human space flight, but is just recently being recognized as a major consequence of adaptation to microgravity. Nearly every bodily system changes upon entry into microgravity, and new homeostatic set-points are adapted accordingly to help the body function more efficiently. The majority of adaptations are beneficial, but vision changes are an example of a maladaptive aspect.

Increased intracranial pressure is hypothesized to be the main causation of visual disturbances on-orbit, however, this remains a theory until direct measurements can be taken. Pre-flight, on-orbit and post-flight ICP measurements are imperative to truly understand its role in vision changes. Nevertheless, this report has aimed to identify factors that potentially contribute to increased intracranial pressure and/or visual impairment. It is concluded that the vision changes seen in-orbit are most likely not caused by one single mechanism, but rather a combination of contributory factors. Anatomical changes, demographic predisposition, cephalad fluid shift, exposure to high levels of carbon dioxide, resistive exercise, high sodium intake, and enzymatic polymorphisms have all been identified as possible contributors to the syndrome, although some factors are thought to play a larger role in causing vision changes than others.

The exact mechanisms of vision changes and susceptibility factors are currently not known, however, there is an expectation that a significant fraction of crewmembers will be affected, presumably following the identified demographic. Along with ICP measurements, clinical monitoring of this phenomenon must be installed including pre-, in-, and post-flight visual acuity testing, high fidelity retinal imagery and topography, OCT, eye ultrasound, etc. With more information, pieces of the puzzle will begin to fall into place and mitigation strategies can be formulated. Countermeasures may be required for future crews including flying adaptive glasses for flight operations, nutritional supplements, tighter CO₂ regulations, and new crew selection standards.

The next logical step for NASA would be to fly experiments to help determine the principle contributors. Of most benefit would be to directly measure ICP continuously during spaceflight to be able to correlate pressure changes with other adaptive milestones of the body. ICP dynamics are currently unknown, and to understand more about the when pressure rises and falls would enable correlation with other body adaptations such as the vascular volume, cardiac output, neurovestibular functions, etc. Also, the relationship between MTHFR polymorphisms and vision changes should be vigorously pursued, as mentioned in Chapter 6. Another recommended study would be to investigate analog populations, such as submariners, to determine the effects of high CO₂ exposure on vision.

Throughout one's time in space, the body begins deep adaptation to the microgravity environment. Whether it is compensating for cephalad fluid shift by reducing fluid volume, or reducing muscle and bone density because it is no longer needed, vigorous adaptation occurs. Through this adaptation, the body's physiology is changing and is under a stress, and thus the body is more susceptible to changes that might not be a problem on Earth. For example, astronauts may be more sensitive to CO₂ levels, or variations in ones genetics and metabolic pathways that do not pose a problem on Earth may become a problem in space. There is still

much to be discovered and vision changes are just one of many maladaptations of which scientists are aware. Before humans can venture on long-duration exploration missions to other worlds, these issues must be resolved and mitigated properly.

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