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Erik Seedhouse

Microgravity and Vision Impairments in Astronauts



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People often ask, why should we spend money on space when we have so many problems here on Earth? The answer, in fact, is in the question. Because we have so many diverse problems facing our home planet, we must look to space and its development if we are to envision a long-term future for ourselves. We could invest all our money in solving global warming or addressing any of the above-mentioned crises, but solving one or even several of these problems will not in any way guarantee our long-term survival. However, venturing into space gives us a real hope of solving all of the issues involved and is a natural continuation of humankind's endless quest to expand beyond current borders, to open up new territories to development, and to learn more about the universe. Dr. Stephen Hawking recently warned humankind that we must develop space or face extinction.

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Microgravity and Vision Impairments in Astronauts

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Acronyms

AGSM	Anti-G Straining Manoeuvre
A-LOC	Almost Loss of Consciousness
ARED	Advanced Resistive Exercise Device
ATP	Adenosine Tri-phosphate
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CDRA	Carbon Dioxide Removal Assembly
CPP	Cerebral Perfusion Pressure
CSF	Cerebrospinal Fluid
CVP	Central Venous Pressure
CVR	Cerebral Vascular Resistance
DRM	Design Reference Mission
ESA	European Space Agency
G-LOC	Gravity-Induced Loss of Consciousness
HDT	Head Down Tilt
HEOMD	Human Exploration and Operations Mission Directorate
HRP	Human Research Program
HRR	Human Research Roadmap
ICP	Intracranial Pressure
IH	Intracranial Hypertension
IIH	Idiopathic Intracranial Hypertension
IOP	Intraocular Pressure
iRED	Interim Resistive Exercise Device
IRP	Integrated Research Plan
ISS	International Space Station
JSC	Johnson Space Center
LoV	Loss of Vision
LSAH	Lifetime Surveillance of Astronaut Health
LSDA	Life Science Data Archive
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MRA	Magnetic Resonance Angiography

MRI	Magnetic Resonance Imaging
MRV	Magnetic Resonance Venograph
MTHFR	Methylenetetrahydrofolate reductase
NFL	Nerve fiber layer
NRC	National Research Council
OCHMO	Office of the Chief Health and Medical Officer
OCT	Optical Coherence Tomography
OD	Optical Diameter
OND	Optic nerve diameter
ONSD	Optical Nerve Sheath Diameter
PaCO ₂	Partial Pressure of Arterial Carbon Dioxide
PPCO ₂	Partial Pressure of Carbon Dioxide
PRR	Path to Risk Reduction
SMAC	Spacecraft Maximum Allowable Concentration
SMO	Supplemental Medical Objective
SOLO	SOdium LOading
SOS	Space Obstructive Syndrome
TCD	Transcranial Doppler
VIIH	Visual Induced Intracranial Hypertension
VIIP	Visual Impairment/Intracranial Pressure

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About the Author



Erik Seedhouse is a Norwegian-Canadian suborbital astronaut whose life-long ambition is to work in space. After completing a degree in Sports Science the author joined the 2nd Battalion the Parachute Regiment. During his time in the ‘Para’s’, Erik spent six months in Belize, where he was trained in the art of jungle warfare. Later, he spent several months learning the intricacies of desert warfare in Cyprus.

He made 30+ jumps from a C130, performed 200+ helicopter abseils and fired more anti-tank weapons than he cares to remember!

Upon returning to the comparatively mundane world of academia, the author embarked upon a Master's in Medical Science, supporting his studies by winning prize money in 100 km running races. After placing third in the World 100 km Championships in 1992, the author turned to ultra-distance triathlon, winning the World Endurance Triathlon Championships in 1995 and 1996. For good measure, he won the World Double Ironman Championships and the Decatriathlon, an event requiring competitors to swim 38 km, cycle 1800 km, and run 422 km. Non-stop!

Returning to academia, Erik pursued his Ph.D. at the German Space Agency's Institute for Space Medicine. While studying he won Ultraman Hawai'i and the European Ultraman Championships and completed Race Across America. As the world's leading ultra-distance triathlete Erik was featured in dozens of magazines and television interviews. In 1997, GQ magazine nominated him as the 'Fittest Man in the World'.

In 1999, Erik retired from triathlon. In 2005 he worked as an astronaut training consultant for Bigelow Aerospace and wrote 'Tourists in Space'. He is a Fellow of the British Interplanetary Society and a member of the Space Medical Association. In 2009, he was one of the final 30 candidates in the Canadian Space Agency's Astronaut Recruitment Campaign. Erik works as a spaceflight instructor for the American Astronautics Institute, professional speaker, triathlon coach, author, and Editor-in-Chief for the Handbook of Life Support Systems for Spacecraft. Between 2008 and 2013 he served as director of Canada's manned centrifuge operations.

In addition to being a suborbital astronaut, triathlete, centrifuge operator, pilot and author, Erik is an avid mountaineer and is pursuing his goal of climbing the Seven Summits. This brief is his eighteenth book. He divides his time between Vancouver Island and Sandefjord, Norway.

Chapter 1

Introduction

Some Background of the Problem

The effect of weightlessness on eyesight has a long history stretching all the way back to the Mercury program [1, 2]. Although vision tests performed during the *Gemini V* and *Gemini VII* missions showed very little change in astronaut's visual acuity, similar investigations conducted during the Apollo program noted an increase in intraocular pressure (IOP). The Apollo findings were later confirmed by Spacelab studies, which revealed an in-flight IOP increase as much as 25 % higher than pre-flight [3–5]. The results of comparable studies performed in the shuttle era (Figs. 1.1 and 1.2) echoed earlier results, but the ophthalmic changes didn't have a profound effect on vision.

Then, in 2005, the visual impairment/intracranial pressure (VIIP) problem surfaced, which was the catalyst for researchers to perform a retrospective survey of questionnaires that were submitted to 300 shuttle astronauts. The analysis of the responses revealed 23 % of shuttle astronauts had experienced near-vision changes and 11 % had experienced post-flight changes.

Following these findings, a study of long duration astronauts was performed to get an idea of the visual symptoms and physiological changes that were occurring during a typical four to six month mission on board the International Space Station (ISS). The results were striking. Five crewmembers had disc edema and globe flattening, three had cotton wool spots, five had problems with near vision, and five had choroidal folds [6].

Further investigation revealed a constellation of symptoms, including kinked optic nerves, scotoma, refractive deficits, optic disc protrusion, and elevated intracranial pressure (ICP). Some crewmembers, all of whom were males between 45 and 55, experienced symptoms so severe that they had difficulty reading checklists. And one astronaut, who suffered scotoma, had to tilt his head 15° to view instruments. His symptoms were still evident more than a year after landing. Something



Fig. 1.1 Canadian Space Agency astronaut Bob Thirsk performs an eye exam. (Illustration courtesy of NASA)

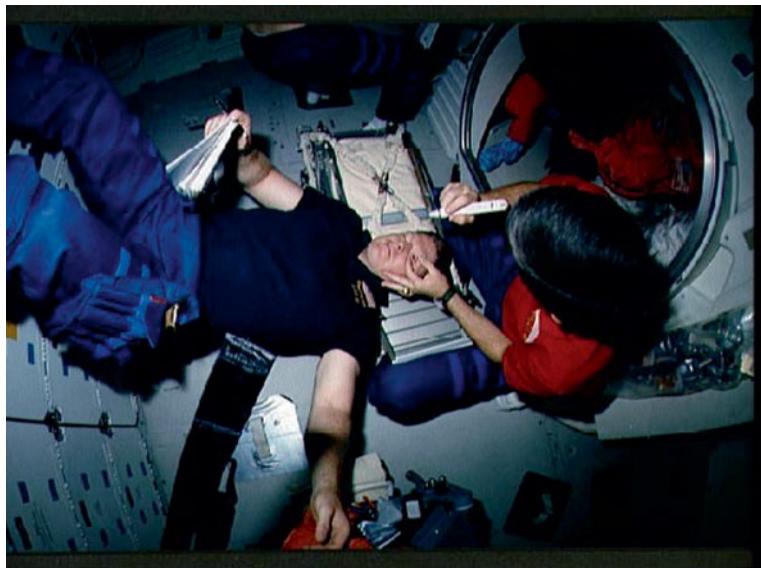


Fig. 1.2 The astronaut resting his head on the treadmill is Bill Shepherd. The astronaut holding Shepherd's eye open is Bob Cabana, who is preparing to measure intraocular pressure during STS-41. (Illustration courtesy of NASA)

had to be done. After all, there was no way NASA could plan asteroid missions and expeditions to the Red Planet when crews ran the risk of becoming half blind!

We've been sending astronauts and cosmonauts into space for more than 50 years, but we still only have a very rudimentary understanding of how the weightlessness environment affects the human body. What we do know is that there is a lot that happens up there that just isn't good. Radiation exposure can result in a three-percent increase in cancer risk for long duration crewmembers; astronauts suffer bone loss at greater rates than post-menopausal women. And despite exercising like marathoners, astronauts continue to lose muscle mass.

Then there is the problem of space motion sickness (SMS) that strikes almost three-quarters of first time flyers. Fortunately SMS symptoms resolve within three days, but most of the other adaptations do not resolve. Among them are the troubling vision changes that have been receiving a lot of press lately. Apparently, long duration astronauts are susceptible to visual deficits. Some complain of blurred vision while others have trouble focusing on checklists. The problems tend to occur after six weeks in orbit, and remain for the duration of what can be a six-month mission.

Many of those afflicted find that their vision remains affected for months after landing. The problem, which already has a family of acronyms—visually induced intracranial hypertension (VIIH), space obstructive syndrome (SOS), visually impairment/intracranial pressure (VIIP—we'll use this abbreviation in this book because this is the one NASA has adopted)—has ophthalmologists scratching their heads because there seems to be no commonality of symptoms among those affected. Some crewmembers report no vision changes in orbit but are found later to have structural changes in their eyes comparable to those who did suffer vision changes. Others recover their vision shortly after landing, while some have problems months after their mission has ended. One of the few consistencies is that the problem affects astronauts over the age of 40 [6].

Theories abound for the space-inflicted syndrome called VIIP. Some researchers reckon an increase in ICP is to blame. It sounds like a reasonable theory. After all, one of the first changes that occurs on entering orbit is a headward fluid shift on the order of two liters. All that fluid rushing to the head is bound to cause an increase in pressure. The problem is that ICP sufferers on Earth complain of a particular set of symptoms that include chronic headaches, ringing in the ears, and diplopia (double vision). None of the ISS astronauts who suffered vision changes reported these symptoms.

So researchers went back to the drawing board and tried to figure out another explanation. What about cerebrospinal fluid (CSF) perhaps? After all, any change in CSF pressure might affect the eye because an increase in CSF pressure would increase pressure on the optic nerve. CSF pressure and several other factors that could possibly explain the vision changes were assessed in a NASA survey that examined 300 astronauts. The results of that survey revealed that 23 percent of short-duration astronauts and 48 percent of long-duration crewmembers had experienced vision problems. The survey also found that for some crewmembers, the vision changes continued for months or years following return to Earth. So, to help

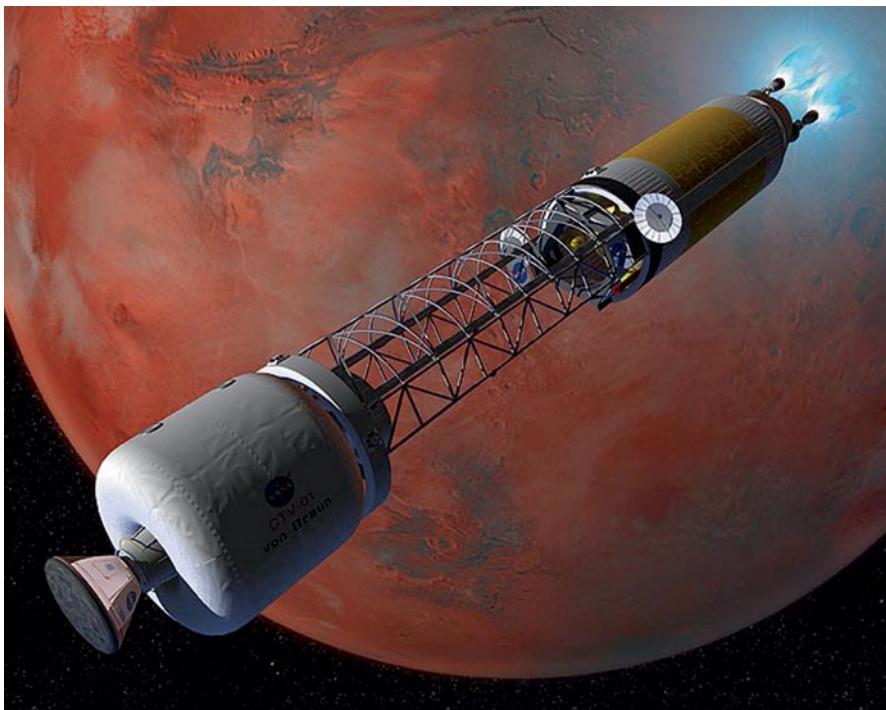


Fig. 1.3 A manned mission to Mars using chemical propulsion will be a three-year affair. It is unlikely any of the crew will be trained ophthalmologists, which is why it's so important that NASA resolve the visual impairment issue. (Illustration courtesy of NASA)

astronauts deal with the problem while researchers tried to figure out what was going on, NASA began issuing special glasses to improve visual acuity.

Although the issue of VIIP has only recently received media attention, the problem of vision changes has been known for decades, mainly through testing and the occasional crewmember report. Until the problem was highlighted by the NASA survey, the vision changes were thought to be temporary—more of a nuisance than anything else. But, thanks to a concerted research effort, combined with pre-, in-, and post-flight ocular measures, researchers have categorized the issue as a very serious problem that has implications that reach beyond the ocular health of astronauts. After all, NASA and other agencies are planning trips to asteroids and to Mars (Fig. 1.3). What happens if the crew is half blind when they arrive on the surface of the Red Planet?

At this point it is worth highlighting some of the other eye-related risks of such a mission. All that radiation is known to increase the risk of cataracts in those who eventually venture beyond low Earth orbit (LEO). The cataract risk combined with the VIIP issue is a sure-fire mission killer if ever there was one. How can mission planners expect a half-blind myopic crewmember to perform the critical entry, descent and landing (EDL) tasks, and how can a half-blind crew be expected

to conduct surface operations with any efficacy? Don't forget, these VIIP issues don't resolve for months—or years. It's quite possible that crews landing on the Red Planet will continue to suffer vision deficits, perhaps eventually going blind sometime during the mission. That's a scenario no agency wants to deal with, so it's really, *really* important that this problem is resolved.

Another component in terms of risk is that the characteristics of the VIIP syndrome are unknown. Could the syndrome cause some astronauts to lose their sight permanently? What are the exact causes and to what extent does an increase in intracranial pressure and/or changes in intraocular pressure affect symptoms? We just don't know. What we do know is that this problem has the potential to put the brakes on any plans to venture beyond Earth orbit—at least until VIIP can be resolved.

Prolonged or persistent optic disc edema is potentially sight-threatening and could theoretically limit interplanetary space travel for some astronauts.

Thomas H. Mader, M. D., was lead author on the 2011 ophthalmology study that brought the VIIP problem to the media's attention.

As you will see in this book, this is a complex problem characterized by a veritable shopping list of symptoms, ranging from choroidal folds to cotton wool spots to optic nerve distension to posterior globe flattening—we'll explain these as we examine the syndrome. Added to the complexity of the range of symptoms are the problems of susceptibility and genetic predisposition to certain visual changes. And compounding the challenge of trying to find an association between one factor and VIIP are all the exacerbating factors such as resistive exercise, sodium intake, and the effects of inflight pharmaceuticals.

NASA's VIIP Task Force

The VIIP issue may sound baffling in the extreme, but ultimately it can be condensed into a three-part story. The first part is the vascular system (fluid shifts), the second is the brain/central nervous system (ICP), and the third is the ocular system (edema and fundoscopic changes). This categorization has provided a start on the job of analyzing the VIIP issue, and it has also generated a number of hypotheses that include alterations in CSF dynamics and decreased venous compliance.

Although these hypotheses are sound there exists a knowledge gap related to the vision changes and what happens following landing. One of the reasons for this gap is the fact that researchers are dealing with very, *very* small subject (*n*) numbers. That's because only a handful of astronauts are on the ISS at any one time. On Earth, if you happen to be studying, say, papilledema, you have access to huge numbers of potential test subjects for the simple reason that there are almost 200,000 people suffering from the condition in the United States alone. But when you're dealing with subject numbers measured in twos or threes, the research becomes much more difficult, especially when you throw pharmaceuticals into the mix. What was needed was a VIIP Task Force, and that is what NASA created in 2011, appointing

Jennifer Fogarty (Johnson Space Center, JSC), Christian Otto (Universities Space Research Association, USRA, and Eric Kerstman, Cherie Oubre and Jimmy Wu (Wyle Integrated Science and Engineering, WISE) to a team charged with providing guidance for the future research of the VIIP problem. The initiative kicked off with the Visual Impairment/Intracranial Pressure (VIIP) Summit at JSC in February 2011, which presented discussions on various VIIP topics followed by a review of the proceedings and recommendations for future research.

The VIIP panel agreed that NASA was doing a good job documenting vision changes in their astronauts but that higher resolution optical imagery was required, so a recommendation was made that a greater emphasis be placed on magnetic resonance imaging (MRI). The panel also recommended that the role of ICP needed to be more accurately defined pre-, in-, and post-flight.

A review of the technology used to investigate the VIIP problem was also discussed by the panel, and it was agreed that optical coherence tomography (OCT) had the most potential to quantitatively observe pathological ocular changes. At the time of the summit, OCT was a relatively new technology. It is also very accurate, since it can measure how much individual nerve fibers have thickened, which means it is very sensitive to identifying the first signs of VIIP symptoms. One of the outcomes of the summit was the agreement of panel members to emphasize case definition based on the following four categories:

1. Microgravity-associated intracranial hypertension with visual impairment and altered ophthalmic anatomy (papilledema, choroidal folds).
2. Microgravity-associated intracranial hypertension without visual impairment.
3. Microgravity-associated visual impairment without intracranial hypertension.
4. Null case: long-duration astronauts return to Earth with neither visual impairment nor increased intracranial pressure.

Clinical Management

Another important outcome was agreeing on the clinical management of VIIP. The panel recommended that six operational sets of data be collected as follows¹:

1. Pre- and post-flight lumbar puncture of each long-duration astronaut to determine ICP (timeframe: Launch to 6 months and Return +4 to 5 days and Return +2 months).
2. Coordination of MRI and ultrasound images to enhance ability to interpret in-flight ultrasound images
3. Enhanced analysis of current pre- and post-flight OCT findings.
4. Improved in-flight fundoscopic imaging capability.

¹ Adapted from The Visual Impairment Intracranial Pressure Summit Report NASA/TP-2011-216160, October 2011.

5. Blinded readings of previous and future diagnostic imaging to minimize potential bias.
6. Consider the possibility of obtaining more than one preflight measurement of ICP.

The next step was identifying the key areas of research. The panel decided to focus on the following nine areas²:

1. Assessment of Compliance. To do this it was recommended that MRI be used to measure cranial and spinal compliance.
2. Assessment of role of jugular and parajugular vessels in cranial outflow. The aim of this assessment was to determine if venous outflow was implicated in increased ICP.
3. In-flight OCT capability. This research was to investigate the best means of assessing vision changes.
4. In-flight non-invasive ICP monitoring device.
5. Assessment of cephalad fluid shift and transmission of hydrodynamic forces on ocular anatomy and function to understand the cause(s) of altered visual acuity. This research sought to provide answers to the following:
 - Does IOP change in-flight?
 - What is the relationship between ICP, ONSD, choroidal engorgement, and IOP?
 - What is the relationship between papillary protrusion secondary to ICP and the degree of papilledema?
 - Is episcleral pressure increased, causing decreased aqueous humor outflow?
 - What is the relationship between age and ocular changes in-flight?
 - Does age and the structure of the lamina cribrosa impact the degree of visual acuity change?
6. In-flight venous congestion via ultrasound to determine whether jugular venous pressure increases in microgravity. What is jugular venous pressure in-flight?
7. Determine the etiology of post-flight cotton wool spots.
8. Options for non-pharmaceutical means to reduce cephalad blood volume.
9. Options for pharmaceutical intervention will require ground testing and intense monitoring if used pre- and post-flight.

Research Areas and Hardware

Given the VIIP problem is such a complex one, it wasn't surprising that the scope of the research covered so many topics. Six research areas were identified, the first of which was physiology and anatomy using human and animal models. In this area, the panel suggested that research be conducted to better characterize to what degree

² Adapted from The Visual Impairment Intracranial Pressure Summit Report NASA/TP-2011-216160, October 2011.

fluid shifts are implicated in the VIIP syndrome. Although that may sound fairly straightforward, in space it is anything but, because fluid shifts comprise changes in plasma volume, changes in CSF, venous congestion, changes in central venous pressure, and of course the two-liter cephalothoracic fluid shift. In addition to fluid shifts, panel members recommended that investigations into in-flight environmental factors such as sodium intake and carbon dioxide concentration be conducted.

The second line of research proposed using animal models to investigate the time course of responses to increased carbon dioxide concentration, to assess changes in the functioning of the blood-brain barrier, and to determine if choroid plexus damage could be reversed. The use of animal models also sought to evaluate the effectiveness of acetazolamide and to better characterize vascular remodeling.

To conduct all these investigations obviously required equipment, so the panelists agreed on certain items of hardware best suited for use in orbit. The list of hardware included ultrasound, OCT, a laptop-based vision test, tonometry, transcranial doppler (TCD), near infrared spectroscopy, and ophthalmodynamometry (ODN). ODN was an obvious item of equipment since the procedure measures blood pressure in the central retinal artery of the eye. This is achieved by applying pressure to the surface of the eye using a device that has a striking similarity to a plunger. As this is being done, the tester uses an ophthalmoscope to measure the flow of blood through the retinal arteries.

Two other areas of research the panel recommended were genetics and biomarkers. Genetics, which we'll discuss at some length in this brief, has an important bearing on many of the adaptations to weightlessness. For example, some astronauts have higher bone density than others, some are better responders to exercise, and some have higher resistance to radiation. Chances are there is a genetic component implicated in the VIIP syndrome, and the panel suggested that investigations in this area might provide some clues. The collation of biomarker data was also deemed important because biomarkers can provide clues to some of the mechanisms that may cause vision changes. For example, aquaporins are water channels that help control the water content in cells. We humans have more than ten different aquaporins, and certain disorders and conditions such as cataracts are caused as a result of a malfunction of these channels. So, if aquaporins biomarker data is collected it may be possible to determine if damage has occurred to the choroidal cell.

After having decided on the areas of investigations, the panel determined a suggested timeline. The highest priority recommendations the panel suggested be conducted immediately included³:

1. Correlating pre- and post-flight MRIs with ultrasound.
2. Measuring pre- and post-flight ICP.
3. Enhanced analysis of OCT data.
4. Measurement of in-flight IOP in each astronaut.
5. Improve fundoscopy imaging on board the ISS.

³ Adapted from The Visual Impairment Intracranial Pressure Summit Report NASA/TP-2011-216160, October 2011.

In the near-term, the panel suggested⁴:

1. Establishing a case definition for the VIIP syndrome based on clinical findings.
2. Developing a Clinical Practice Guideline for the VIIP syndrome based on case definition and clinical findings.
3. Establishing a reliable and accurate non-invasive in-flight means to measure and monitor ICP and cerebral blood flow.
4. Developing more sophisticated in-flight neuro-cognitive testing.

In the long term, the panel recommended:

1. Characterizing physiological and anatomical human and animal studies.
2. Developing advanced imaging capabilities such as Near Infrared Spectroscopy (NIRS), (TCD), and ODN.
3. Performing genetic testing.
4. Using biomarkers in blood and CSF.

Purpose of This Brief

This is one that we don't yet have a good handle on, and it can be a showstopper.

Mark Shelhamer, Chief Scientist for the NASA Human Research Program at Johnson Space Center, said in Houston, March 2014.

Although the VIIP problem has generated dozens of articles in the popular press and several research articles, the visual impairment issue is extraordinarily complex since it comprises a constellation of symptoms and anatomical and physiologic changes. What this brief aims to do is to distill and synthesize the complex aspects of the VIIP problem and make them accessible to the layperson. In case you're not familiar with ophthalmology a glossary of terms has been included that you can reference as you read this brief.

The book is organized to first give the reader an introduction to the theories of the VIIP syndrome together with insights into seven case studies that highlight some of the more common symptoms and signs. Chapter 2 describes the terrestrial pathophysiology of elevated ICP since ICP is implicated in the development of symptoms of VIIP. This chapter also describes what is revealed in an eye examination of a patient suffering from ICP and how ICP is treated. Chapter 3 applies some of what has been learned from terrestrial ICP to ICP observed in weightlessness. This chapter also examines the role of elevated CSF and the effect of pressure on the diameter of the optical nerve sheath (ONS). Also addressed are the effects of ICP on the structure of the eye, with particular reference to posterior globe flattening and microstructural differences.

⁴ Adapted from The Visual Impairment Intracranial Pressure Summit Report NASA/TP-2011-216160, October 2011.



Fig. 1.4 One of the many imaging modalities used to resolve the VIIP issue. (Illustration courtesy of NASA)

Many of the symptoms presenting in an astronaut suffering from VIIP are similar to those of a patient suffering from papilledema. In an effort to better understand how papilledema may help us understand VIIP, Chapter 4 describes the pathology of this condition and explains how it is diagnosed on Earth. Also described are the imaging (Fig. 1.4) modalities used to diagnose this condition and how microstructural abnormalities may determine severity of symptoms.

One of the classic physiological changes experienced on arriving in orbit is a two-liter headward fluid shift. This often causes headaches as a result of the increased pressure, and it is one of the theories that has been offered to explain VIIP. In Chapter 5, the role of microgravity-induced fluid shift is described as it pertains to the development of VIIP symptoms. Also examined are the various Earth-bound analogs (Fig. 1.5) such as head-down tilt (HDT) that are used to simulate microgravity.

In microgravity, blood does not drain from the head as well as what we're used to in 1 G, and this in itself causes an increase in intracranial pressure. We know that CO₂ is a potent vasodilator (which dilates the blood vessels), so it also can increase intracranial pressure. Thus, microgravity and CO₂ may be working in synergy to cause headaches.

NASA flight surgeon Jennifer Law, Journal of Occupational & Environmental Medicine. May 2014. Vol 56. Issue 5. P 477–483.

One of the challenges on board the ISS is ensuring the life support system (LSS) continues to function. More often than not, carbon dioxide levels are much higher than they should be because the LSS just cannot scrub all the carbon dioxide from the

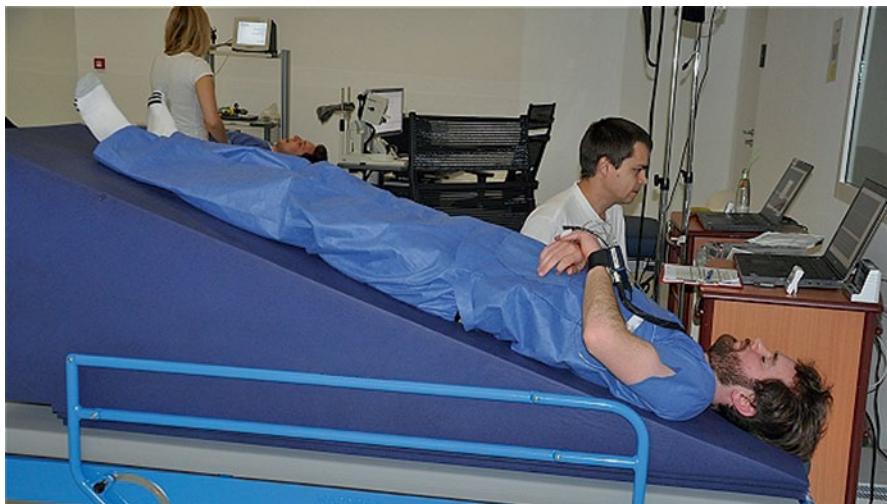


Fig. 1.5 Head-down tilt is one of several analogs used to simulate weightlessness here on Earth in an attempt to better characterize VIIP related signs and symptoms. (Illustration courtesy of DLR/ESA)

atmosphere. On Earth, the carbon dioxide concentration is 0.3 mmHg, but on board the ISS levels are typically between 2.3 and 5.3 mmHg. Such high concentrations cause headaches and may be implicated in the development of VIIP, which is why the role of carbon dioxide is discussed in Chapter 6.

After carbon dioxide we turn our attention to exercise. Astronauts have to exercise for two or three hours a day, and much of this exercise is resistive exercise that drives up blood pressure, which in turn may cause VIIP symptoms. That's the theory, which is why Chapter 7 examines the link between resistive exercise and intraocular pressure and ICP.

Chapter 8 addresses the link between ICP and altered sodium intake. Astronauts on board the ISS have excess intake of sodium in their diet and excess sodium has been implicated in peripheral edema with retention of water, which in turn can lead to VIIP symptoms. Also examined in this chapter is the subject of polymorphisms with particular reference to the one-carbon pathway, since research has suggested that features of this may influence individual susceptibility to VIIP.

Leading on from the subject of polymorphisms is the concept of personalized medicine—Omics—which is the subject of Chapter 9. One of the core threads of this book is the effect of genetics and intra-individual differences and how these may cause an astronaut to be more or less susceptible to VIIP. If this is the case, then perhaps personalized medicine and genotyping is the answer? Finally, in Chapter 10, we look over the horizon at the directions NASA is taking to resolve the VIIP issue by examining VIIP risks 1, 12, 13, and 3.

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Chapter 2

Long Duration Flight Data

Astronaut's bodies suffer in microgravity. Without effective countermeasures, muscles atrophy, bones shed calcium, and eyesight deteriorates. We've known about this for some time, but the problem has only been put under the spotlight recently with several astronauts experiencing severe eyesight deficiencies [1]. Until crew-members began complaining of eyesight-related symptoms researchers had thought the problem to be transient.

However, thanks to anecdotal reports by astronauts and a comparison of pre- and post-flight ocular measures, microgravity-induced visual acuity impairments have now been recognized as a significant risk. And this problem doesn't affect a minority of crewmembers. Retrospective analysis of medical records has revealed that 29 percent of 300 shuttle astronauts and 60 percent of space station astronauts have suffered some form of visual degradation [1]. That's a serious problem for an agency planning on sending its astronauts to asteroids and to Mars (Fig. 2.1).

Theories

The problem has its own acronym—this is NASA after all—and is referred to as the visual impairment/intracranial pressure (VIIP) syndrome. Since VIIP has only recently been identified, there hasn't been much research performed, so scientists are in the dark about what might cause the vision impairments. The data that is available shows that astronauts who suffer VIIP-related symptoms experience varying degrees of visual performance decrements. Some suffer cotton-wool spot formation while others may present with edema of the optic disc. Others may suffer flattening of the posterior globe while some may present with distension of the optic nerve sheath [1, 2]. In short, there is a profusion of signs and symptoms, but the reason for the vision impairment has researchers a little flummoxed.



Fig. 2.1 Canadian Space Agency astronaut, Chris Hadfield, is given an eye examination by Expedition 34/35 Flight Engineer Tom Marshburn. (Illustration courtesy of NASA)

One theory suggests that the changes in ocular structure and impairment to the optic nerve is caused by the cephalothoracic fluid shift that astronauts experience while on board the International Space Station (ISS) [3]. It is theorized that some astronauts are more sensitive to fluid shift due to genetic and anatomical factors. We'll discuss this theory some more later. In the course of conducting studies on the VIIP syndrome, researchers have focused on three systems—ocular, cardiovascular, and central nervous. These studies have revealed a variety of symptoms other than visual decrements, including increased intracranial pressure (ICP) and changes in cerebrospinal fluid (CSF) pressure [2, 3]. But, because the preflight, inflight and post-flight data is so thin on the ground, it is very difficult to define why and how these symptoms occur. Inevitably, since the impact of VIIP is an operational concern, space agencies have increased preflight, inflight, and post-flight monitoring of the syndrome to better characterize the syndrome and the risks.

To date, more than a dozen astronauts have suffered VIIP symptoms [4]. Some of these symptoms persist post-flight and some don't. Some astronauts experience quite severe symptoms, and for others it is just a mild inconvenience. Very little is known about the etiology of symptoms, but researchers believe microgravity-induced cephalothoracic fluid shift and associated physiological changes are implicated.

To better investigate the syndrome, NASA's Human Health and Performance Directorate brought together a VIIP project team in 2011 to investigate the problem using data compilation, analysis, and multi-discipline, cross-cutting collaboration.

To give you an idea of the complexity of the issue facing the VIIP project team, the following is a brief account of the first seven cases of the perplexing syndrome.

History

Case #1

The first VIIP case affecting a NASA astronaut occurred during an ISS mission. The affected crewmember first noted a reduction in his ability to see objects up close. On his return, the crewmember was subjected to fundoscopic examination, which detected choroidal folds behind the optic disc. The examination also revealed a cotton wool spot in the crewmember's right eye, although the left eye was clear. Three years after his mission the choroidal folds were still there [4].

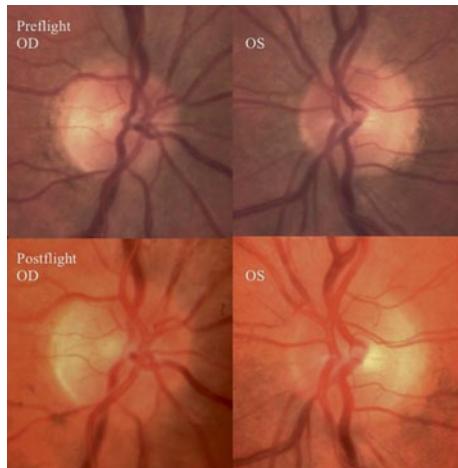
Case #2

The second case occurred three months into an ISS mission when a crewmember informed the ground that he was only able to see Earth clearly if he used his reading glasses. For the remainder of his mission there was no improvement in his condition, but neither did the symptoms get worse. After his return to Earth the astronaut noticed a gradual improvement, but his vision didn't return completely. The astronaut was subjected to fluorescein angiography that revealed choroidal folds. This was also one of the signs in the first case of VIIP. The astronaut was also subjected to magnetic resonance angiography (MRA) and magnetic resonance venogram (MRV) tests, but these were normal [4]. A more sensitive test using optical coherence tomography (OCT) was also performed. OCT is a non-invasive test that uses light waves to take images of the retina. The results of this test showed increased thickening of the astronaut's retinal nerve fiber layer (NFL). It was one more variable in the VIIP puzzle.

Case #3

The third VIIP case was a strange one because the crewmember didn't suffer any vision impairment during his mission—no headaches or diplopia. Nothing. But when he returned to Earth, ophthalmologists discovered that the astronaut had asymmetrical disc edema, which can be seen in Fig. 2.2. Unlike Cases #1 and #2, this astronaut did not have choroidal folds, but his fundoscopic examination did reveal a small hemorrhage behind the optic disc of his right eye. What was especially unusual about Case #3 was the fact that this astronaut had the most serious optic disc edema

Fig. 2.2 VIIP Case #3. The fundoscopic images of the right and left optic disc in the third case of visual impairment observed in spaceflight. Grade 3 edema can be seen in the *right* optic disc and grade 1 edema in the *left* optic disc. (Illustration courtesy of NASA, Mader and Elsevier)



of all the crewmembers tested to date, yet he had reported no visual impairment during his flight [4].

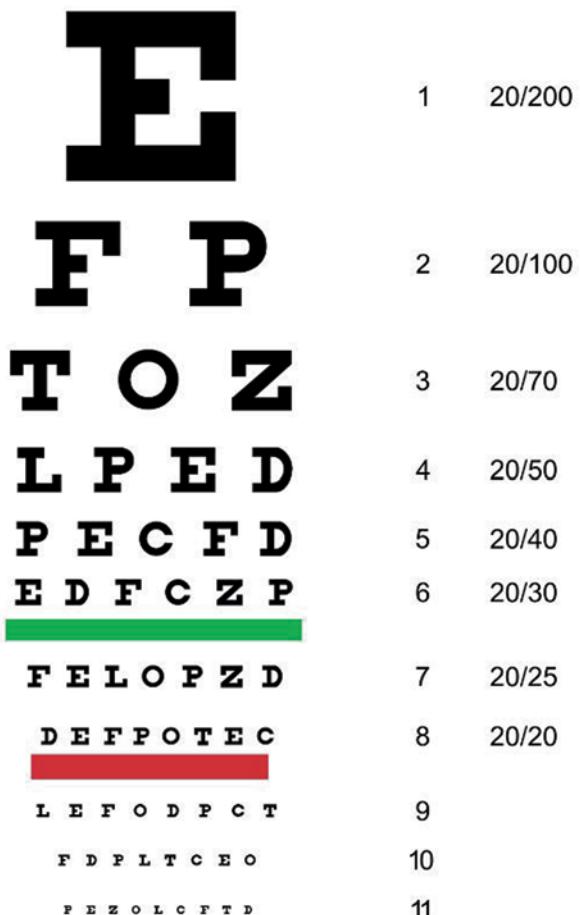
Case #4

The fourth case of VIIP was no less unusual than the first three. This astronaut noticed his vision altering after two months in orbit. His symptoms included a reduction in the near-vision of his right eye and scotoma in his right temporal field. The scotoma affected the crewmember to the extent that he was unable to read 12-point font, which is probably close to what you're reading now. What was strange was that everything about this astronaut was normal: he didn't complain of any symptoms—headache, diplopia—that might normally be associated with such vision impairment [4]. Also, the environment on board the ISS was well within nominal margins during his stay—no excess carbon dioxide concentration or toxic fumes. Furthermore, his pre- and post-flight (correctable) visual acuity were the same, although fundoscopic examination revealed choroidal folds in the astronaut's right eye.

Case #5

Another layer was added to the VIIP enigma with the fifth case, which occurred after only three weeks in orbit. This astronaut's vision was affected so badly that his glasses had to be adjusted by one to two dioptres to enable him to read procedures [4]. By this time NASA was becoming a little concerned with this VIIP issue and decided it would be prudent to perform inflight ocular ultrasound exams to observe

Fig. 2.3 A simple vision test to assess nearsightedness and farsightedness. (Illustration courtesy of NASA)



changes in the ocular health of its crew. To that end, the astronaut who represented Case #5 was subjected to ultrasound examinations, which revealed flattening of the posterior globe and dilated optic nerve sheaths. More tests were conducted after NASA had uploaded near and far acuity charts (Fig. 2.3) together with an Amsler Grid (Fig. 2.4). This case occurred back in the day when the shuttle was flying, so mission managers decided to fly up a video-ophthalmoscope, which also allowed remotely guided fundoscopic exams to be performed (Fig. 2.5).

Once the examinations had been performed, the images were sent to neuro-ophthalmological consultants who decided that no treatment was required, but suggested that fundoscopic and visual acuity exams be conducted once a month for the remainder of the mission. The examinations served a dual purpose. They provided neuro-ophthalmologists with a baseline to compare against other vision issues and they served as a means of monitoring the ocular health of the crewmembers.

Another procedure that was added around this time was the 3-Tesla MRI examination. Before Case #4, astronauts spent three weeks recovering in Star City,

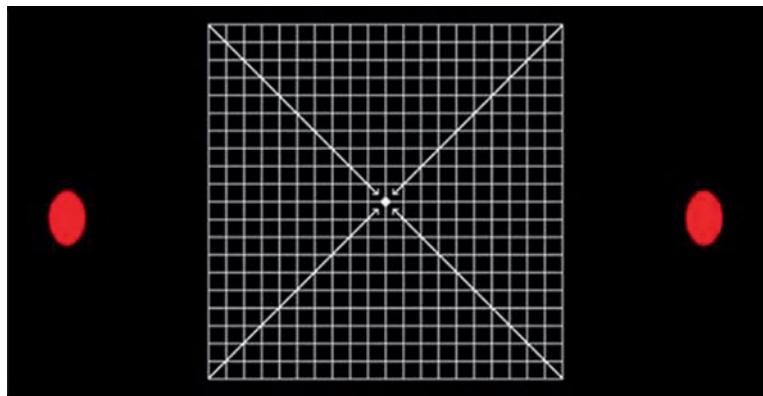


Fig. 2.4 Amsler Grid. (Illustration courtesy of NASA)

Fig. 2.5 ISS Commander Leroy Chiao performs an eye examination on Flight Engineer Salizhan Sharipov using the Advanced Diagnostic Ultrasound equipment. (Illustration courtesy of NASA)



Russia. The problem with this arrangement was that there was no 3-Tesla MRI equipment [4].

Why 3-Tesla MRI? Well, this item of equipment is extremely sensitive and can detect abnormalities that just can't be detected using other imaging equipment—all the way down to the ultra-structural level such as blood vessels just 200 to 300 microns in diameter. 1.5 Tesla MRI's had been performed on all crewmembers pre-flight, so the results of these examinations were compared against the 3-Tesla MRIs taken three days post-flight following Case #4. The comparison revealed that posterior globe flattening had not been present preflight, so researchers could rule out that pre-existing condition as a reason for VIIP—at least as far as this crewmember was concerned.

Case #5 continued to be examined following his flight. Thirty days post-flight another MRI was performed that revealed significantly dilated optic nerve sheaths, flattening of the posterior globe and thickened optic nerves [4]. At this stage the crewmember was still affected by the same vision impairment he had experienced on orbit.

Another examination—a lumbar puncture – performed 57 days post-flight revealed normal CSF pressure. This astronaut, who became aware of visual changes three weeks into his mission, reported that his vision had remained static for the remainder of his stay on board the ISS [4]. He hadn't complained of headaches, visual obscurations, or diplopia, and yet several weeks post-flight he was still suffering vision impairment. More tests were conducted, including cycloplegic refraction and fundus photos, but these were all normal; no sign of choroidal folds or disc edema. Nothing.

Case #6

VIIP Case #6 was identified after the crewmember returned from a six-month mission. This crewmember reported that his distance vision was better when he used his reading glasses. Ophthalmological tests performed three weeks post-flight revealed optic-disc edema (Fig. 2.6) in the astronaut's right eye and—in what was becoming a common sign—choroidal folds. As with Case #5, a brain MRI was conducted, which revealed flattening of the posterior globe and an enlarged optic nerve sheath in the right eye [4]. Nine weeks post-flight, ophthalmological examination—OCT—revealed disc edema and a cotton-wool spot in the crewmember's left eye.

Case #7

The seventh case of VIIP was notable because this astronaut was treated post-flight. After two months in orbit, this astronaut noticed a gradual decrease in his near and distance vision in both eyes [4]. The vision impairment continued for the remainder of his mission and became so much worse that the astronaut could no longer perform close-up tasks even when using his prescription glasses. When this happened

Fig. 2.6 The sixth case of visual impairment during spaceflight. Images on the left are preflight images of the optic disc. Images on the right are post-flight images of the right and left optic disc showing grade 1 edema in the right optic disc. (Illustration courtesy of NASA)

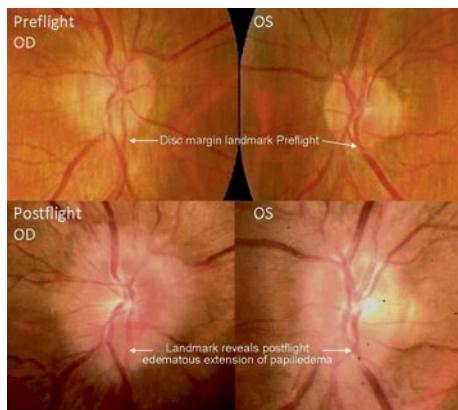


Fig. 2.7 Upper images are preflight images of the right and left optic discs. Lower images show post-flight images of the optic nerve and the superior and inferior nerve fiber layers. (Illustration courtesy of NASA)



he switched to the more powerful Space Anticipation Glasses, which helped him continue his work. In common with Case #5 this crewmember did not complain of visual obscurations, headaches, or diplopia. Also in common with Case #5 the station atmospheric pressure, carbon dioxide and oxygen levels were reported to be at nominal levels during the mission.¹ Following landing a fundus assessment revealed Grade 1 bilateral optic-disc edema and choroidal folds (Fig. 2.7). Case #7, in common with several earlier cases, also had signs of an enlarged optic nerve sheath [4].

Summary

Cases 2, 4, 6, and 7 shared the common signs of disc edema, posterior globe flattening, choroidal folds, and hyperopic shift. These signs closely align with those reported by patients suffering from increased intracranial hypertension, which we will discuss shortly.

¹ As a reminder, the CO₂ levels on the ISS are between 2.3 and 5.3 mmHg, which is 10–20 times the normal terrestrial atmospheric level of 0.23 mmHg.

Table 2.1 Clinical practice guidelines classifications of 36 long-duration U. S. crewmembers [6]

CPG class	Definition	# Of affected astronauts
Non cases	< 0.50 diopter cycloplegic refractive change No evidence of papilledema, nerve sheath distension, choroidal folds, globe flattening, scotoma or cotton wool spots compared to baseline	2
1	(Repeat OCT and visual acuity in 6 weeks) ≥0.50 diopter cycloplegic refractive change and/or cotton wool spot No evidence of papilledema, nerve sheath distension, choroidal folds, globe flattening, scotoma or cotton wool spots compared to baseline CSF opening pressure (if measured) ≤25 cm H ₂ O	2
	(Repeat OCT, cycloplegic refraction, fundus exam and threshold visual field every four to six weeks × six months, repeat MRI in six months)	
	≥0.50 diopter cycloplegic refractive change or cotton wool spot Choroidal folds and/or optic nerve sheath distension and/or globe flattening and/or scotoma No evidence of papilledema	8
	CSF opening pressure (if measured) ≤25 cm H ₂ O	
2	(repeat OCT, cycloplegic refraction, fundus exam and threshold visual field every four to six weeks × six months, repeat MRI in 6 months)	
	≥0.50 diopter cycloplegic refractive change or cotton wool spot Optic nerve sheath distension, and/or globe flattening and/or choroidal folds and/or scotoma Papilledema of Grade 0–2	1
	CSF opening pressure ≤25 cm H ₂ O	
	(Institute treatment protocol as per CPG)	
3	≥0.50 diopter cycloplegic refractive change or cotton wool spot Optic nerve sheath distension, and/or globe flattening and/or choroidal folds and/or scotoma Papilledema of Grade 2 or above Presenting symptoms of new headache, pulsatile tinnitus and/or transient visual obscurations CSF opening pressure > 25 cm H ₂ O	4
	Too little evidence at present for definitive classification	
	Early ISS flyers with no, or limited testing	19

These cases also shared other similarities, including optic nerve sheath distension and posterior globe flattening. These observations were revealed by MRIs performed post-mission. Despite myriad tests (summarized in Tables 2.1 and 2.2) and scans, a definitive etiology for the findings in the seven crewmembers remained elusive. It was suggested that venous congestion in the eye, caused by cephalotho-

Table 2.2 Summary of ophthalmic changes from seven affected long-duration crewmembers [6]

Ophthalmic condition	Total affected
Optic nerve sheath distension	6/7 (86%)
Nerve fiber layer thickening	6/7 (86%)
Optic disc edema	5/7 (71%)
Posterior globe flattening	5/7 (71%)
Hyperopic shift in one eye or both eyes by $\geq +0.50$ dioptres	5/7 (71%)
Choroidal folds	4/7 (57%)
Elevated post-flight CSF pressure (indicative of increased ICP)	4/7 (57%)
Cotton wool spots	3/7 (43%)
Decreased intraocular pressure (IOP) post-flight	3/7 (43%)
Tortuous optic nerve	2/7 (29%)

racic fluid shift, could have been responsible for elevated choroidal volume changes. Given the commonality of that sign, it was also suggested that this could be a unifying mechanism.

A Final Note: Intracranial Hypertension

Intracranial hypertension is a disorder the primary feature of which is persistently elevated intracranial pressure (ICP) [5]. The most pertinent neurologic sign of ICP is papilledema, which is discussed in Chapter 4. Papilledema is a red flag condition because it may lead to progressive optic degeneration and ultimately blindness [5]—that's a big problem if you're en-route to Mars or some other far-flung destination. Typical signs and symptoms are usually related to increased ICP and papilledema and may include the following:

- headaches, often varying in type, location, and frequency
- diplopia
- pulsatile tinnitus
- pain that radiates, usually in the arms

Symptoms of papilledema may include the following:

- transient visual obscurations, often uniformly orthostatic
- gradual loss of peripheral vision in one or both eyes
- blurring and distortion of central vision
- sudden visual loss [5].

The most significant physical finding is bilateral disc edema secondary to the increased ICP. In more severe cases, edema and diminished central vision may be present. Visual function tests for diagnosing and monitoring patients with intracranial hypertension are similar to those used to assess VIIP and include:

- ophthalmoscopy
- visual field assessment
- ocular motility examination
- MRI of the brain [5].

The goal of managing the condition is to preserve optic nerve function while managing increased ICP, which is why common pharmacologic therapy may include acetazolamide, which is the most effective agent for lowering ICP.

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Chapter 3

Earthbound and Microgravity Pathophysiology of Increased Intracranial Pressure

Before we take a look at the mechanisms, symptoms, and potential causes of increased intracranial pressure in weightlessness it is useful to review how the syndrome develops on Earth. Here on Earth, idiopathic intracranial hypertension (IIH) is a syndrome that shares many of the mechanisms observed in space. IIH is caused by an increase in cerebrospinal fluid pressure (CSP), and it is characterized by elevated intracranial pressure (ICP), although there is no neurological explanation for this.

Someone suffering from increased ICP—which is discussed in more detail in the next chapter—is likely to complain of all sorts of symptoms and signs ranging from headache, pulse synchronous tinnitus (pulsatile tinnitus), transient visual obscurations and visual loss [1], to diplopia and papilledema [2]. These symptoms and signs are similar to those reported by astronauts reporting visual impairment/intracranial pressure (VIIP), so it's worth taking a closer look at IIH (Fig. 3.1).

Causes of IIH

The annual incidence of IIH is less than one per 100,000 persons and 3.5 per 100,000 in females aged between 15 and 44 [3]. More than 90 % of those suffering from IIH are obese, and more than 90 % are women of childbearing age [4, 5]. There have been studies that have suggested IIH is associated with a number of medical conditions, but in controlled studies most of these associations have been disproved [6]. In some controlled studies however, strong associations have been found between IIH and obesity.



Fig. 3.1 Karen Nyberg performs a fundoscopy examination during Expedition 36/37. (Illustration courtesy of NASA)

IIH Symptoms

Persons suffering from IIH will report headache (94 %), transient visual obscurations (68 %), pulse synchronous tinnitus (58 %), photopsia¹ (54 %), and retrobulbar² pain (44 %). Diplopia (38 %) and visual loss (30 %) may also be reported [3]. The type of headache reported is one characterized by extreme head pain that may be accompanied by nausea [7]. Two-thirds of IIH sufferers will report visual obscurations, and some may report episodes of transient blurred vision that may last less than 30 s. The cause of the visual obscurations is thought to be increased tissue pressure, which is similar to the mechanism that causes visual impairment in astronauts in orbit.

If you look at your eyes very closely in the mirror you will notice some blood vessels. The degree to which these can be seen is one of the ways ophthalmologists grade IIH. In common with VIIP, one of the classic signs of IIH is papilledema, which is optic disc edema caused by increased ICP. Generally, the higher the grade of the papilledema, the greater the loss of vision. To quantify loss of vision, a grading scale called the Frisén Scale (Fig. 3.2) is used [8]. On this scale, Grade 0 de-

¹ This is when people see flashes of light.

² This is the space behind the eye.

Modified Frisén Scale

Papilledema Grade

0 (Normal Optic Disc)

- Prominence of the retinal nerve fiber layer at the nasal, superior, and inferior poles in inverse proportion to disc diameter
- Radial nerve fiber layer striation, without tortuosity

1 (Minimal Degree of Edema)

- C-shaped halo that is subtle and grayish with a temporal gap: obscures underlying retinal details^a
- Disruption of normal radial nerve fiber layer arrangement striations
- Temporal disc margin normal

2 (Low Degree of Edema)

- Circumferential halo^a
- Elevation (nasal border)
- No major vessel obscuration

3 (Moderate Degree of Edema)

- Obscuration of ≥1 segment of major blood vessels leaving disc^a
- Circumferential halo
- Elevation (all borders)
- Halo (irregular outer fringe with finger-like extensions)

4 (Marked Degree of Edema)

- Total obscuration on the disc of a segment of a major blood vessel on the disc^a
- Elevation (whole nerve head, including the cup)
- Border obscuration (complete)
- Halo (complete)

Grade 5 (Severe Degree of Edema)

- Obscuration of all vessels on the disc and leaving the disc^a

^aKey features (major findings) for each grade

Fig. 3.2 Modified Frisen Scale. (Illustration courtesy of NASA)

scribes a normal optic disc and Grade 1 is when a C-shaped halo of edema obscures the retina adjacent to the optic disc. When Grade 2 is reached, the halo becomes circular, and in Grade 3 at least one major vessel is completely covered.

Grade 4 papilledema is diagnosed when at least one major vessel is covered and a significant amount of edema is observed. When Grade 5 is reached it is almost impossible to see any of the vessels in the eye.

About one-third of IIH patients report double vision (diplopia), and almost all those suffering from the condition report visual field loss of varying degrees. Usually the visual field loss associated with IIH includes an enlargement of the physiological blind spot [9], and in rare cases (less than 5%) the loss of vision may eventually lead to blindness. Although there is some variation in the presentation of symptoms in those suffering from IIH, generally the greater the loss of vision the greater the severity of edema in the eye [3]. But what causes the papilledema? Researchers have identified three factors: CSP, intraocular pressure (IOP), and systemic blood pressure (Fig. 3.3). One reason that vision loss occurs is due to the pressure exerted on the (optic) nerve sheaths that serve the eye. These nerve sheaths are composed of fibrous tissues, and they can only tolerate so much pressure. Once a certain pressure is exceeded vision begins to be degraded.

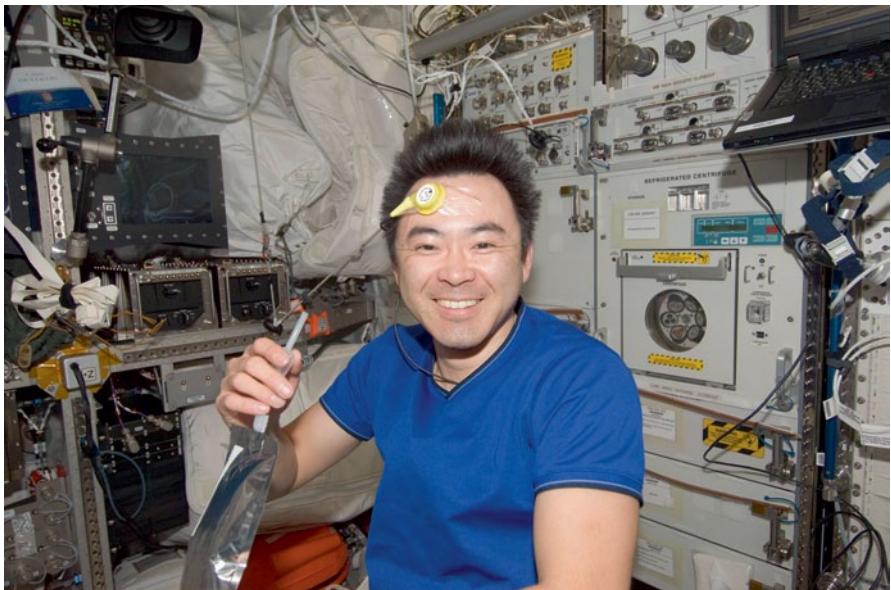


Fig. 3.3 Expedition 33 flight engineer, Akihiko Hoshida, prepares to conduct an ultrasound eye exam in the Columbus laboratory. (Illustration courtesy of NASA)

Another factor is related to that individual variation mentioned earlier. Very simply, some people tolerate greater ICP better than others before suffering visual symptoms. Also, there are individual variations in the structural integrity of each person's optic disc. Some people may have minor damage to their retinas that make them more susceptible to vision loss than those without any retinal damage. Of course, all this uncertainty doesn't help the patients who are mainly interested in being treated for pain and for vision loss, so how is terrestrial IIH treated?

IIH Treatment

There are all sorts of treatments for IIH. Some are pharmacological, some are surgical, and all have been tried with varying degrees of success. Since the most commonly reported symptom of IIH is headache, the first course of pharmacological therapy is to reduce the ICP and the CSF flow [10, 11]. One way to do this is to administer acetazolamide (Diamox®), after which the patient is monitored for pressure reduction [12]. The normal dose is between one and two grams per day. Another treatment is furosemide (Lasix®), which has also been shown to reduce ICP by reducing sodium transport [13–15] to the brain and also by diuresis (increased excretion of urine).

A more radical strategy is surgery, in which a series of slits are made in the optic nerve sheath behind the globe. This procedure is known as optic nerve sheath fenestration [16, 17] and is reserved for patients who suffer progressive loss of vision and headaches. It's a fairly successful therapy, although a small number of patients may lose vision during the procedure.

Whether pharmacological or surgical, the treatment of those with IIH is usually challenging because it is necessary to consider myriad factors, including the severity of symptoms, the extent and severity of vision loss, and to what degree this is affecting their daily activities. Sometimes, even following pharmacological and surgical intervention, there are some patients who don't respond to treatment, which usually requires that they have repeat neuro-imaging. In other cases in which the individual also suffers from migraine, it is sometimes difficult to differentiate between the headache pain caused by IIH and that caused by the migraine.

What It Means for Astronauts

Approximately 2 liters of fluid from the lower limb moves into the thorax towards the head, and we see an equilibration of pressures across the body, not just arterial but also venous. So we think this fluid redistribution results in this ocular pathology resembling terrestrial idiopathic intracranial hypertension, characterized by high intracranial pressure.

Dr. Christian Otto, speaking at the annual meeting of the American Glaucoma Society, 2 March 2015.

In March 2015, at a meeting of the American Glaucoma Society, NASA provided more support for the effect of IIH, as evidenced by the statement above. One of the reasons NASA was able to do this was thanks to the extra diagnostic equipment (such as the Spectralis, which is discussed later in this brief) that had been flown to the ISS since the VIIP problem arose.

Pathophysiology of Increased Intracranial Pressure in Weightlessness

Intracranial Pressure

The reason researchers were interested in examining those who suffered from IIH was because the ophthalmic changes these patients reported were so similar to those reported by astronauts. Researchers reasoned that the increased ICP suffered by terrestrial patients might somehow explain the visual changes observed in astronauts. It was a good hypothesis, but slightly flawed (Fig. 3.4).

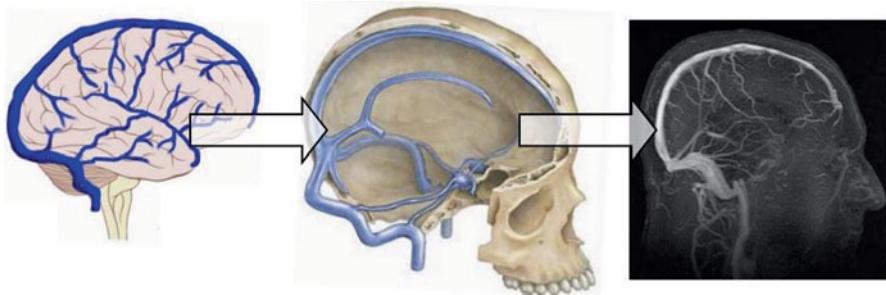


Fig. 3.4 One of the mechanisms contributing to VIIP symptoms is an increase in cerebrospinal fluid pressure. (Illustration courtesy of NASA)

Although ICP is reported by those suffering from IIH and by astronauts suffering from VIIP syndrome, the mechanism of ICP is not the same in both groups. Those complaining of ICP here on Earth typically report much more severe symptoms than those on board the ISS. In addition to the pain of headaches, terrestrial ICP sufferers report cognition impairments, nausea, and vomiting. At this point it is worth emphasizing the numbers of patients we're dealing with. The terrestrial ICP problem has been observed in thousands and thousands of patients, whereas the VIIP syndrome has been reported in only a dozen or so astronauts—given the few ‘patients’ in orbit it’s difficult to make correlations between terrestrial ICP and its space-based equivalent.

Cerebrospinal Fluid

Another complicating factor is that of the very, *very* small number of astronauts who have been studied, only a handful who reported ICP have had ICP measurements taken pre- and post-flight. ICP measurements are usually taken by performing a lumbar puncture (sometimes referred to as a spinal tap). This procedure involves inserting a needle between two lumbar vertebrae to remove cerebrospinal fluid (CSF). When this procedure was performed on astronauts who had reported VIIP symptoms their CSF pressure was only mild to moderately above normal pressure. Although this didn’t significantly strengthen the hypothesis of increased ICP in flight, it did go some way to helping researchers understand the mechanisms implicated in the syndrome (Fig. 3.5).

Optical Nerve Sheath Diameter

Another observation that bolstered the ICP hypothesis were the measurements performed on the astronaut’s optical nerve sheath diameter (ONSD) and optical diameters (OD). These ultrasound post-flight measurements revealed a distension of the

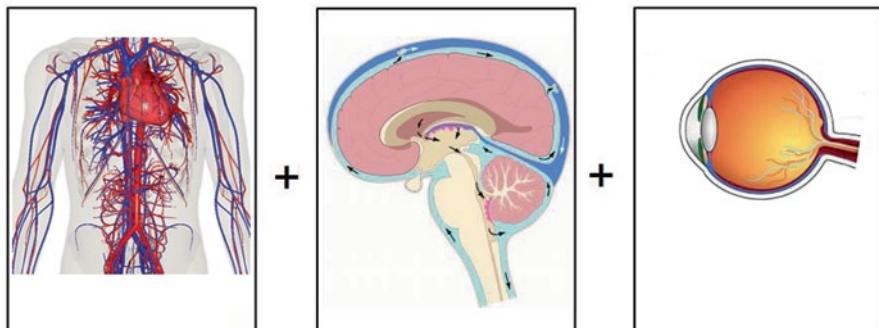


Fig. 3.5 The effects of cerebrospinal fluid are implicated in intracranial pressure. (Illustration courtesy of NASA)

ONSD, and since this is an indication of IIH, the hypothesis of ICP being a symptom of VIIP gained some more traction [18–20]. But only some. That was because the findings were inconclusive [21], since the post-flight images were taken a long time after landing—in some cases months or years!

Another drawback to what had seemed promising evidence of the ICP link was the fact there was no control group to compare the ONSD measurements with. At the time there was a lot of talk about the VIIP problem being similar to IIH, which caused some confusion as to the exact nature of the syndrome. In particular, the term “papilledema” was sometimes used to refer to the swelling of the optic disc observed in those reporting VIIP symptoms. But papilledema is simply swelling of the optic disc caused by an increase in ICP, whereas in space the optic disc swelling could have been caused by ONSD or other effects (damage perhaps) on the optic nerve head.

Although the ONSD link may have supported the rationale for studying IIH for its usefulness in understanding VIIP, it should be noted that while IIH is well-characterized, the causes are poorly understood. The same is true for VIIP. For example, visual changes are not reported by all crewmembers who report VIIP symptoms, and in some crewmembers these symptoms can be quite pronounced, whereas in others the symptoms may barely register. The point is that there seems to be little rhyme or reason or pattern to the symptoms. Part of the reason for this is the fact that so few crewmembers have been evaluated.

To give you an idea of just how confusing the symptom pattern is, consider the case of one crewmember who reported no symptoms during or after his flight but whose post-flight examination revealed the worst case of optic disc edema ever observed! This crewmember not only had Grade 3 edema in his right optic disc and Grade 1 in his left but also had a small hemorrhage inferior to the optic disc of his right eye, nerve fiber thickening, *and* increased CSF pressure! Having said that, this crewmember had no signs of choroidal folds or globe flattening. Still, it was a head-scratching case that left many researchers puzzled.

Posterior Globe Flattening

But back to the ICP issue. Another confounding variable in the link between IIH, ICP, and VIIP is the symptom of posterior globe flattening. On Earth posterior globe flattening can be induced by ICP [18, 22], but after treatment for IIH no one knows if globe flattening persists, because there just haven't been any studies to follow up on the issue. This means that no one knows if pressure behind the optic disc results in permanent posterior globe flattening. It's just another hole of knowledge in the VIIP syndrome.

Microstructural Anatomical Differences

Perhaps ICP—and therefore VIIP—is a function of anatomical differences? After all, there are several structures in the eye that are affected by pressure, and differences in the morphology of these could result in some crewmembers suffering more symptoms than others. Let's take the lamina cribosa sclera as an example. This structure is located between the optic nerve and the intraocular space, and its function is to serve as a pressure barrier between that space and the retrobulbar CSF space that surrounds the retrobulbar part of the optic nerve [23]. On Earth, under normal conditions, the lamina cribosa bulges slightly outwards in the direction of the optic nerve. This is because intraocular pressure (IOP), which is 15 mmHg, is higher than intracranial pressure, which is 10 mmHg. But, if these pressures are changed in any way, the lamina cribosa will respond in a way that may affect vision.

For example, if the structure is displaced excessively, the lamina cribosa can squeeze adjacent nerve fibers, thereby causing nerve damage and vision loss. This is essentially what happens in people with glaucoma. But this mechanism doesn't affect everyone equally. That's because a person's anatomy can make them more or less susceptible to syndromes and ailments. So, if you happen to be an astronaut whose tissue elasticity is greater than most, chances are you may be less affected by pressure changes exerted on your lamina cribosa. That's because the more elastic a tissue is the lower the chances are that a significant pressure change will have a damaging effect on the sensitive tissues in the eye and the brain.

Equally, those who had an unfortunate genetic roll of the dice and who have less elastic tissues, are probably at greater risk of ICP-induced visual changes. Remember that crewmember who reported no symptoms inflight but who was diagnosed with Grade 3 edema on his return? He probably experienced increased ICP, but because his vessels and tissues were more compliant than most, he didn't suffer any visual deficits.

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Chapter 4

Papilledema and Microgravity-Induced Fluid Shift

Papilledema Pathology

One of the features of visually impairment/intracranial pressure (VIIP) is swelling of the optic nerve. The term for this is *papilledema*, and it is instructive to understand how this occurs on Earth, but first some basic anatomy (Fig. 4.1).

The optic nerve (Fig. 4.2), which connects the retina's inner lining to the visual cortex, is made up of axons, which are fibers that carry signals from the retina's light sensitive cells to the visual cortex [1]. In the visual cortex these signals are converted to form images. The optic nerve itself is covered by three membranes, the first and innermost of which is called the *pia mater*.

The second and middle membrane is called the *arachnoid*, and the outer membrane is the *dura mater*. One of the key features when it comes to understanding the significance of papilledema in spaceflight is the subarachnoid space that lies between the arachnoid and the pia mater. In the brain, the subarachnoid space is filled with cerebrospinal fluid (CSF), but this is not the case with the subarachnoid space of the optic nerve.

Normally, the subarachnoid space around the optic nerve is filled with fibrous strands, but when intracranial pressure (ICP) increases, this changes because this space becomes distended. As the subarachnoid space surrounding the optic nerve continues to distend, CSF enters the space, with the result that the optic nerve becomes compressed [2]. Not only that, but the increased ICP will also exert pressure on the central retinal vein that follows the central retinal artery. This is important because the job of the central retinal vein is to drain blood from the inside of the eye. The result of the compression of the central retinal vein and the optic nerve? Papilledema. At least that's what researchers think.

Fig. 4.1 These are fundoscopy images taken as part of NASA's Longitudinal Study of Astronaut Health. The images on the left show preflight optic discs whereas the images on the right show optic disc edema postflight. (Illustration courtesy of NASA)

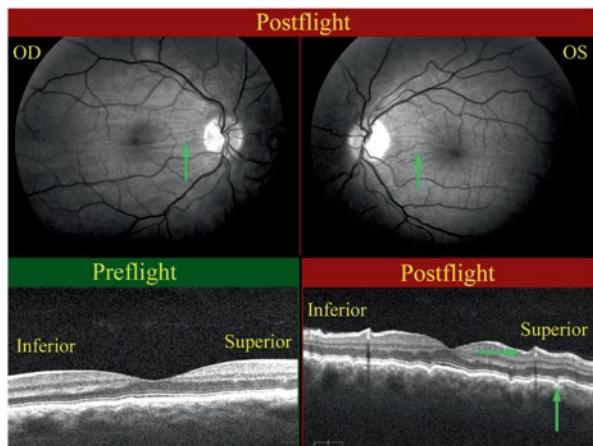
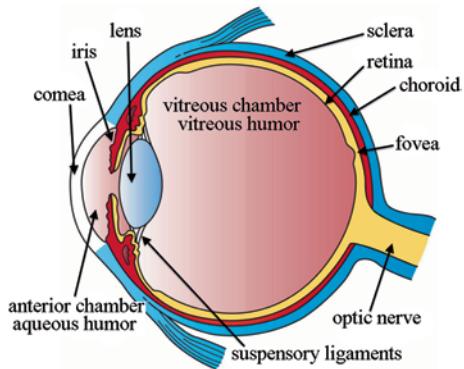


Fig. 4.2 Structures of the eye. (Illustration courtesy of NASA, Holly Fischer, University of Michigan)

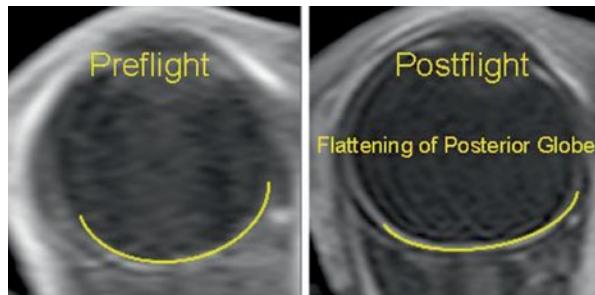


Diagnosing Papilledema

When doctors are diagnosing papilledema, one of the signs they look for is an absence of venous pulsations at the optic nerve because under normal conditions arterial pulsations occur along the central retinal artery. That's because there is no pressure. But, with the increased pressure, these pulsations cease, and a patient is deemed to have intracranial hypertension and hence papilledema. One of the issues over which there is some argument is if it is possible to have intracranial hypertension but not have papilledema. The answer is maybe. That's because there may be occasions that patients suffering from intracranial hypertension may not show all the classic signs of papilledema because of a time lag between the increase in CSF pressure and the development of typical signs and symptoms.

Another issue is anatomy, especially very small anatomical variations in the optic nerve and other ocular structures (see below). For example, some patients may

Fig. 4.3 The image on the *left* is an eye with no flattening (preflight), while the image on the *right* shows flattening of the posterior globe (post-flight). (Illustration courtesy of NASA)



have very narrow optic nerves that are so fine that it's just not possible for much CSF to enter the subarachnoid space. Another possibility is that CSF pressure may be redirected to other anatomical areas: the only way to determine this is via the use of very sensitive imaging techniques.

The Role of Anatomical Variation

We'll talk more broadly about intra-individual differences in later chapters and how this issue may have a significant bearing on why astronauts suffer VIIP and why some don't. For now we'll take just one example of the complexity of the problem by considering the lamina cribrosa sclera (Fig. 4.3). The function of the mesh-like lamina cribrosa sclera (see Chapter 3), which lies between the optic nerve and the intraocular space, is to act as a pressure barrier between the intraocular space and the retrobulbar cerebrospinal fluid space [3].

Under normal conditions, this structure tends to protrude outwards in the direction of the optic nerve. The reason for the slight bulging is because intracranial pressure (10 mmHg) is less than intraocular pressure (15 mmHg). But, if the intracranial and intraocular pressures are altered, the lamina cribrosa will stretch, and the changed pressure gradient will affect how the optic nerve fiber functions [4–8]. In fact, if the lamina cribrosa is stretched excessively, nerve damage can result, and this damage may be manifested as visual impairment. This is what happens in those with glaucoma. But in patients with papilledema the opposite occurs, and the increased ICP forces the lamina cribrosa towards the intraocular space, which in turn causes swelling of the optic disc.

Remember, we mentioned earlier that there may be significant microstructural intra-individual variations, and these can determine to what degree a person may be affected by these various ocular syndromes. For example, elasticity tends to decrease with age, so older individuals may be more susceptible to visual impairment. Elasticity may also be affected by the genetic luck of the draw—some individuals may not have vessels and tissues that are particularly compliant, which is another reason to perform phenotype testing, which is discussed later.

Imaging

The problem even when using sensitive imaging techniques is that the structures being imaged are very small. For example, even when using magnetic resonance imaging (MRI) it is difficult to obtain high soft-tissue contrast because the optic nerve is only between 0.4 cm and 0.6 cm in diameter [9, 10]. This problem also applies when trying to achieve high-fidelity images of the subarachnoid space and the optic nerve sheath. But MRI has been able to provide measures of optic nerve distensions of patients with papilledema and those without. For example, Seitz [11] observed a mean optic nerve sheath diameter of 7.54 millimeters in patients presenting papilledema symptoms compared with 5.52 millimeters in healthy subjects.

Another important measure was the extent to which CSF had surrounded the optic nerve in patients with papilledema and those without. In patients with papilledema, CSF was visible surrounding 12.4 millimeters of optic nerve compared to just 6.3 millimeters in healthy subjects [11]. Similar imaging studies observed other manifestations of papilledema. For example, in those patients diagnosed with severe papilledema it was found that the optic nerve diameter (OND) was much less than in patients with moderate papilledema, a difference suggesting that the increase in subarachnoid pressure might lead to a deterioration of the optic nerve [12].

But it isn't just optic nerve sheath diameter and the subarachnoid space that changes in patients suffering from papilledema. Remember, one of the signs of papilledema is increased ICP, and one of the features researchers have focused on to determine the severity of ICP is flattening of the posterior sclera (Fig. 4.3) and protrusion of the optic disc. The sclera's function is to maintain the shape of the globe. Structurally, it is up to one millimeter thick and is pierced by many nerves and blood vessels, most which are on the surface. What happens in patients with increased ICP is scleral flattening [13–15] which is often accompanied by protrusion of the optic disc [10]. Although scleral flattening usually doesn't result in significant visual impairment, the optic disc is particularly sensitive to increased CSF pressure because of the effects upon the blood vessels [16].

Another papilledema symptom that can be observed using MRI is *kinking* (sometimes referred to as *tortuosity*) of the optic nerve. Once again, the issue of micro-anatomical differences comes into play because a patient with a very thick optic nerve may be less affected by increased ICP than a patient with a very thin optic nerve [6]. On the subject of micro-anatomical differences it is worth noting that there are many anatomical structures in the eye that are affected differently by the increase in CSF pressure. The problem is that this effect is poorly understood because it is very difficult to obtain accurate pressure and pressure-gradient measurements in the very small structures of the eye.

Microstructural Abnormalities and Future Imaging Techniques

All these problems with imaging and measuring not only makes it very difficult to define the pathogenesis of papilledema but also to use signs of papilledema to diagnose increased ICP. Although most ophthalmoscope examinations of the optic nerve abnormalities used to diagnose ICP reveal swelling of the optic nerve head, this is not always the case because optic nerve head swelling is not strongly correlated with ICP [17]. Another abnormality used to diagnose ICP is optic nerve sheath diameter, with five millimeters being normal and nine millimeters abnormal [4].

Again, there is not a strong correlation between optic nerve sheath diameter and ICP because the optic nerve sheath is not a rigid structure and doesn't react as other intracranial structures do [4]. However, although optic nerve abnormalities may not correlate highly with ICP, scleral flattening does, since this has been found in 80% of patients with papilledema [6].

As you can imagine, diagnosing papilledema and ICP is a difficult task terrestrially, even with high resolution imaging equipment. Fortunately for flight surgeons trying to make the diagnosis in astronauts and trying to understand the correlation between ICP and VIIP, the latest imaging techniques offer some promise. For example, the latest (functional) magnetic resonance imaging (fMRI) technology allows ophthalmologists to examine anatomical disruptions and physiological dysfunction much more closely [18–22]. Although fMRI is still developing, the technology has been used on animals, and these tests have shown promising results. For example, it has been possible to tell apart the two retinal layers, and fMRI has also identified retinal damage [17, 23]. Another promising technology is diffusion tensor imaging (DTI), which may be used to identify micro-structural changes in the eye [24].

Microgravity-Induced Cephalad Fluid Shift

One factor researchers are particularly interested in when trying to understand the mechanisms of visual impairment/intracranial pressure (VIIP) is hydrostatic pressure. This is because hydrostatic pressure changes when astronauts arrive in space. On Earth, this pressure is about 70 mmHg at the level of the heart and about 200 mmHg at the feet [25] (Fig. 4.4).

Because we humans are adapted to living in a one-gravity environment it's not surprising that the body has developed physiological mechanisms to maintain blood flow against the pull of gravity. But, when astronauts start feeling the effects of microgravity, hydrostatic pressure is removed, which results in fluid translocating



Fig. 4.4 One of the first things that occur on reaching orbit—apart from smiling like a Cheshire cat—is a headward fluid shift of up to two liters. This causes astronauts to complain of headaches and stuffiness and the fluid shift may also be the cause of some of the VIIP symptoms. The crew-member in the image is Canadian Space Agency astronaut Julie Payette. (Illustration courtesy of NASA)

(Fig. 4.5) from the legs towards the head and upper body [26, 27]. It's all part of the body adapting to life in space.

With all this extra fluid—up to two liters—in the head, it isn't surprising that astronauts complain of head fullness and congestion [28]. In addition to feeling congested, astronauts also appear slightly different because the tissues in their faces swell [29], giving them a slightly 'puffy' appearance. All this fluid redistribution also has an effect on organ shape. For example, in microgravity flights it has been shown that the heart becomes more spherical [30, 31], findings that have also been documented on board the shuttle, Mir, and the International Space Station (ISS) [32]. Several other changes are also brought about by this fluid shift, including a drop in plasma volume [33], an increase in urine volume [34], and dehydration stemming from the first two factors. Another important change is an increase in intraocular pressure (IOP) [35].

Intraocular Pressure in Parabolic Flight

This change in IOP can also be measured on Earth since changes in posture changes are known to produce an effect on ocular tissues. For example, simply changing from being upright to lying down results in an increase in fluid pressure at eye level

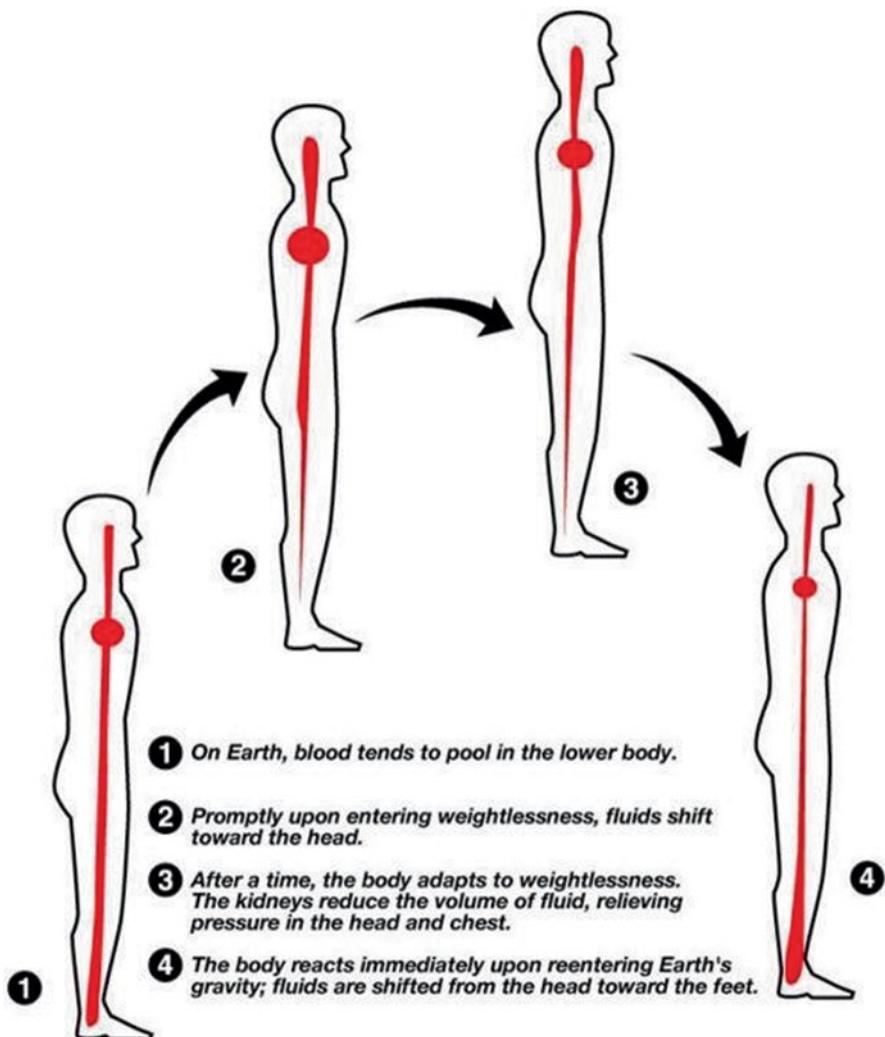


Fig. 4.5 This is what happens when astronauts become weightless—fluid rushes to their head and causes problems, some of which are vision-related. (Illustration courtesy of NASA)

and an increase in IOP [36]. Studies that have experimented with more dramatic changes in posture have found that IOP can double in someone who is inverted [37, 38], so it isn't surprising that astronauts also have higher IOP. But it isn't simply a transthoracic fluid shift that causes an increase in IOP. When that fluid rushes towards the head cerebral blood flow is disrupted, and this also has an effect on the ocular tissues. Unfortunately, the mechanisms by which the ocular tissues are affected are poorly understood [39].

To try and get a better idea of how much IOP increases in microgravity and what the implications of that increased pressure are, researchers have performed studies



Fig. 4.6 Parabolic flight is a useful analog for simulating the conditions of weightlessness. The crewmember curled up in a ball being spun is European Space Agency astronaut Samantha Cristoforetti. (Illustration courtesy of ESA)

in parabolic flight (Fig. 4.6). One of these studies [40] showed that IOP increased 58% above baseline, while the diameter of the central retinal artery decreased. The same research team also studied the mechanism in head down tilt and found that IOP increased rapidly but recovered to normal values within 48 hours [41].

What does all this mean in terms of vision? Well, the structure that researchers focused on mainly was the choroid because it is this structure that supplies a lot of the blood to the eye and ocular tissues. During parabolic flight the velocity of blood entering the choroid increased dramatically and the volume of blood entering the choroid doubled [42]. In the HDT study [43], in which subjects were placed in the HDT position for 30 minutes, the researchers observed an increase in IOP and also an increase in the thickness of the choroid but no change in the thickness of the retina. It was the former change that caught the attention of the researchers because a change in choroid thickness can cause an increase in IOP and therefore a possible degradation in vision (Fig. 4.7).

Intraocular Pressure in Bed Rest

Other studies that investigated the effect of body posture on IOP used bed rest [44] to simulate microgravity. In one such study, in which subjects lay horizontally for 120 days [44], IOP increased from 28 to 30 mmHg. In addition to the increase in

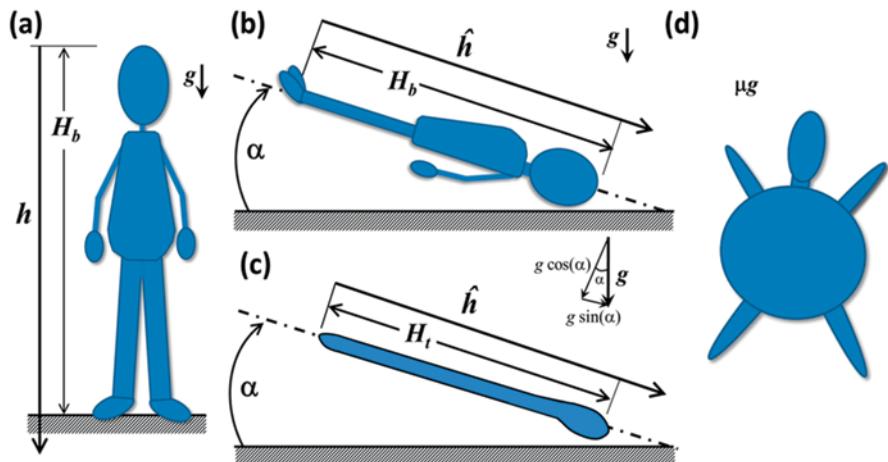


Fig. 4.7 Head-down tilt is another useful analog for simulating weightlessness conditions. After 60 minutes of lying in the 6° head-down tilt position more than 1.5 liters of fluid have relocated to the cephalothoracic region, which is very similar to what happens in space. (Illustration courtesy of NASA)

IOP, two subjects reported clouded vision and a reduction in visual acuity. It was suggested by the lead scientist that the length of the bed rest caused an impairment in the regulation of IOP, but because the study only observed four subjects this hypothesis was inconclusive.

From the few IOP-fluid shift-related studies that have been conducted terrestrially and on orbit, it seems clear that although IOP increases as a result of posture changes such as those in HDT, this increase resolves with time. Although inflight IOP test data is available and there have been a number of posture studies conducted, the problem is that there is insufficient data to say with certainty that the terrestrial observations can be used to better understand what is happening in orbit. In an attempt to remedy this situation NASA's VIIP Task Force has identified analogs such as HDT as a way forward to test more subjects.

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Chapter 5

The Role of Carbon Dioxide and Exercise

Carbon Dioxide Onboard the International Space Station

In addition to studying the mechanisms of fluid loss on the development of the vision impairment/intracranial pressure (VIIP) syndrome, investigators have also examined in-flight risk factors such as carbon dioxide levels and diet. On board the closed system that is the International Space Station (ISS), carbon dioxide is removed by external venting or chemical scrubbing, but all this venting and scrubbing can't keep carbon dioxide levels at the same levels we enjoy on Earth (Fig. 5.1).

The terrestrial ambient concentration of carbon dioxide is about 0.03 % by volume, which equates to 0.23 mmHg [1], whereas the carbon dioxide levels astronauts breathe on board the ISS can be as high as 5.3 mmHg, although no astronaut who reported VIIP symptoms was exposed to levels this high. The high carbon dioxide levels that astronauts are exposed to on board the ISS don't cause long term physiological effects (Table 5.1), but it is hypothesized that prolonged exposure to such high levels could have an effect on intracranial pressure (ICP).

Carbon Dioxide Health Effects

Under resting conditions a normal person will produce about 200 milliliters of carbon dioxide per minute and more than four liters per minute during heavy exercise. A natural product of metabolism, carbon dioxide is important in several physiological processes in the body. For example, when blood carbon dioxide levels rise (a condition known as *hypercapnia*), heart rate and ventilation increase to ensure the body gets rid of that carbon dioxide. Hypercapnia also accelerates cerebral blood flow and increases ICP, which in turn leads to headache and visual impairment.

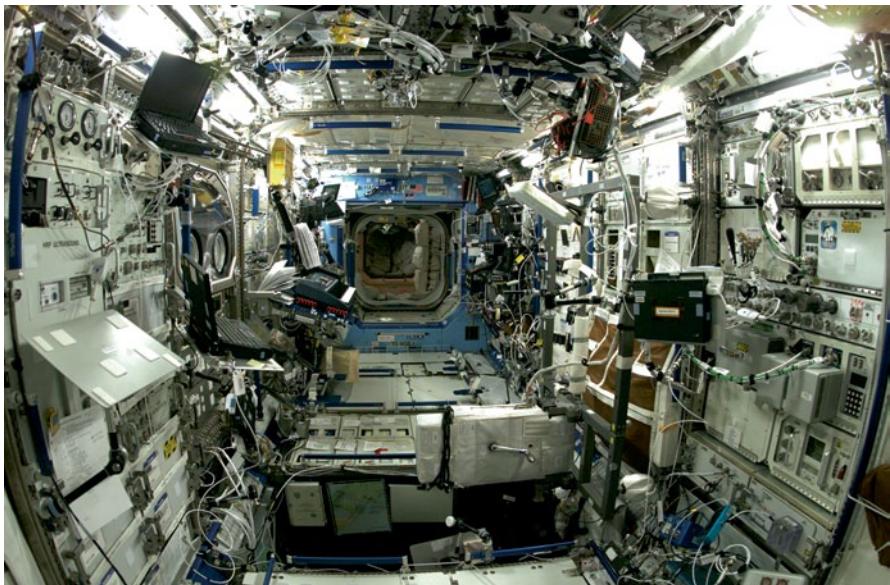


Fig. 5.1 The life support system on board the International Space Station does a good job, but it has a hard time scrubbing carbon dioxide out of the atmosphere which means carbon dioxide levels are much higher than on Earth. (Illustration courtesy of NASA)

As you can see in Table 5.1, a high concentration of carbon dioxide has several adverse effects, but in a closed environment such as a submarine or spacecraft, levels will rise naturally, and there is only so much the atmosphere revitalization system can do to keep levels tolerable. The reason submarine (Fig. 5.2) and spacecraft carbon dioxide levels are higher (20 to 50 times higher) than on Earth is because scrubbing uses up an awful lot of power, so a compromise has been reached that trades crew health for the realities of operating the life support system.

On board the ISS, carbon dioxide is removed by American carbon dioxide removal assemblies (CDRAs, Fig. 5.3) and Russian carbon dioxide removal assembly (Vozdukh). These systems maintain the carbon dioxide level at below the Spacecraft Maximum Allowable Concentrations (SMACs—[3]) for carbon dioxide (these levels depend on the duration of exposure). Unfortunately, the CDRAs and the Vozdukh aren't the most reliable items of equipment on the orbiting outpost, which means carbon dioxide levels sometimes rise above the NASA-mandated threshold. Although breathing carbon dioxide levels that result in a partial pressure of carbon dioxide (ppCO_2) of $\sim 7.5 \text{ mmHg}$ doesn't lead to any short- or long-term effects, once ppCO_2 reaches 12 mmHg^1 , the physiological effects are noticeable [4].

Compounding the carbon dioxide problem is the microgravity environment in which crewmembers work. Astronauts often have to work in tight spaces and behind racks where ventilation isn't as effective as it might be in the larger areas of

¹ NASA's upper limits and emergency levels for carbon dioxide are 15 and 20 mmHg respectively [5].

Table 5.1 Physiological tolerance time for carbon dioxide concentrations and acute health effects of high carbon dioxide concentrations. (Adapted from EPA 2000 [2])

Physiological tolerance			Acute health effects	
ppCO ₂ (mmHg)	%	Max exposure limit (mins)	Duration of exposure	Effects
3.8	0.5	Indefinite		
7.5	1.0	Indefinite		
11	1.5	480		
15	2.0	60	Several hours	Headache, dyspnea upon mild exertion
23	3.0	20	1 hour	Headache, sweating, dyspnea at rest
30	4.0	10	4–5 %	Headache, dizziness, increased blood pressure, uncomfortable dyspnea
45	6.0	5	1–2 mins	Hearing, visual disturbances
45	6.0	5	≤16 min to several hrs	Headache, dyspnea, tremors
53	7.0	<3	7–10 %	Unconsciousness, near-unconsciousness
68	9.0	N/A	Few mins	Headache, increased heart rate, shortness of breath, dizziness, sweating, rapid breathing
75	10	N/A	>10–15 %	Dizziness, drowsiness,
113	15	N/A	1 min to several mins	severe muscle twitching, unconsciousness
128	17	N/A	17–30 % Within 1 min	Loss of controlled and purposeful activity, unconsciousness, convulsions, coma, death

the station. This sometimes means that crewmembers are exposed to even higher concentrations of carbon dioxide that may trigger increased ICP and resulting visual deficits. To better understand this connection it is instructive to discuss the physiological effects that increased carbon dioxide concentration has on the body.

Increased Carbon Dioxide Levels and Intracranial Pressure

Although it is known that exposure to high levels of carbon dioxide can cause changes in cerebral hemodynamics and visual deficits, the data on these effects are limited simply because there aren't many astronauts who have been exposed to high levels of carbon dioxide. Having said that, the mechanism by which altered cerebral blood causes visual effects is well understood. Remember, an increase in carbon



Fig. 5.2 The helm of the Ohio-class guided-missile submarine, USS Florida (SSGN-728), in March 2010. (Illustration courtesy of USN)

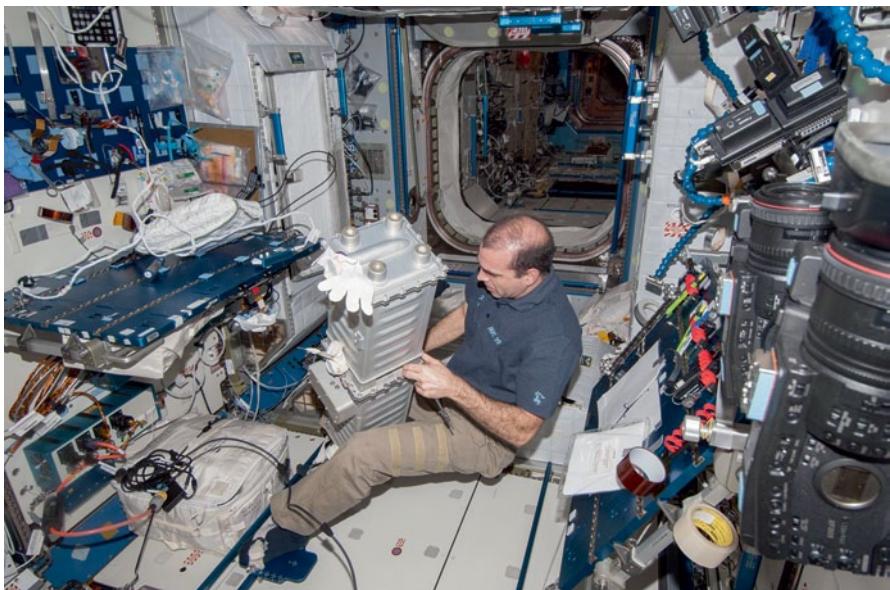


Fig. 5.3 The astronaut working on the carbon dioxide removal assembly in the Harmony node of the International Space Station is flight engineer Rick Mastracchio, a member of Expedition 38/39. (Illustration courtesy of NASA)



Fig. 5.4 Canadian Space Agency astronaut Bob Thirsk enters the International Space Station. (Illustration courtesy of NASA)

dioxide concentration causes vasodilation, and when the cerebral vessels become vasodilated problems occur. This is because cerebral circulation takes place within a finite volume, and there is very little capacity to adjust for increases in blood volume. So, if vasodilation occurs, it stands to reason that cerebral blood vessel diameter will increase, resulting in an increase in cerebral blood flow (CBF) and an increase in cerebral blood volume (CBV).

The outcome of these changes may be an increase in ICP, an outcome that has been confirmed in mathematical modeling. In 1998, researchers Ursino and Lodi [6] used this technique to demonstrate the relationship between carbon dioxide, cerebral autoregulation, and ICP. Using their mathematical model, these researchers confirmed that an increased carbon dioxide concentration caused an increase in CBV and resulted in ICP.

It should be noted that in the reality of spaceflight CBF may be compromised due to the effects of microgravity, which means that even a relatively small increase in CBF might cause a significant increase in ICP. This would be particularly noticeable by the astronauts on reaching orbit (Fig. 5.4) because of the combined effect of the two-liter cephalothoracic fluid shift and the sudden exposure to increased carbon dioxide concentrations. (During the first week blood volume decreases by about 15 to 17%, so this effect would gradually be less pronounced.) For this reason, it would be interesting to measure ICP as soon as astronauts arrive in orbit, which is what NASA has in mind in future research.

One study [7] that investigated the effect of increased carbon dioxide concentrations was conducted via private medical conferences with crewmembers. This study, which examined the incidence of reported headaches and the average carbon dioxide levels inside the ISS, found a correlation between the carbon dioxide concentration and the number of headaches reported.

Fig. 5.5 The absence of gravity on board the ISS causes bones to lose density, especially the load-bearing bones. (Courtesy NASA)



Although headaches could be caused by ICP, and therefore cause visual deficits, this study didn't report this. On Earth, hypercapnia has an effect on vision, but there is no link with ICP. With such little data, it has been difficult for researchers to draw conclusions, a situation compounded by the fact that some individuals/genders may have a naturally higher tolerance to high carbon dioxide concentrations, while others may be very susceptible. Until more data is collated, researchers must rely on informal reports, private medical conferences and open communication.

Exercise and Vision Changes

The Role of Exercise in Orbit

As long as there have been astronauts, researchers have been investigating the effects of spaceflight on the musculoskeletal system. And with good reason. Although this system is very well adapted to a one-G environment, the absence of the constant force of gravity and the lack of impact forces from walking and running causes havoc upon exposure to microgravity. In short, the removal of these forces causes a cascade of biochemical and structural changes in bone, muscles, and the connective tissues (Fig. 5.5).

Worst affected are the load-bearing bones, including the femur, the lumbar spine, tibia, and the hip. On average, astronauts lose up to 2 percent of their average bone



Fig. 5.6 ESA astronaut André Kuipers. (Illustration courtesy of ESA)

density per month while in orbit. One of the countermeasures to these debilitating effects is exercise (Fig. 5.6).

Despite astronauts exercising like marathoners, crewmembers still lose bone density. This is because it is impossible to prevent bone loss—only to slow the process. To that end, the International Space Station (ISS) is furnished like a Gold's gym, featuring treadmills, bike ergometers, bungee-cord devices, and assorted resistive exercise devices. This latter item of equipment has been added following the results of bed-rest studies that indicated astronauts would benefit from performing resistive exercise.

To try to stave off the insidious effects of bone loss, astronauts perform heel raises, squats and dead lifts, using up to 120 kilograms of force. That might sound impressive, but don't forget we're talking about exercising in weightlessness, and on the ISS a large part of that load is used to offset body mass and isn't used in actual loading of the bones. The most advanced item of exercise equipment on board the ISS is the Advanced Resistive Exercise Device (ARED), which was delivered in 2008 (Fig. 5.7).

Resistance Exercise: A Physiology Primer

So what does all this exercise equipment have to do with vision loss? Well, to understand that we need to be somewhat familiar with the physiology of resistance

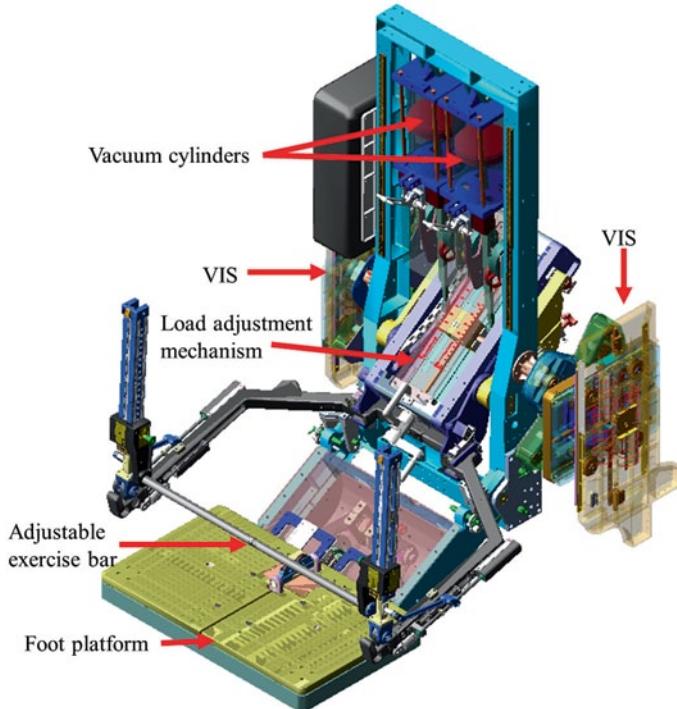


Fig. 5.7 The Advanced Resistive Exercise Device seen here fitted with the Vibration Isolation System to reduce the impact forces through the International Space Station when astronauts are exercising. (Credit NASA)

exercise. One of the mechanisms researchers are interested in when astronauts use the ARED is the regulation of blood through the brain. This regulation of cerebral blood flow (CBF) is a biological mechanism that has evolved to ensure the brain is protected when there are significant blood pressure changes. Under normal circumstances, the body's regulatory mechanisms maintain blood flowing through the brain at a pressure of $\sim 45\text{--}50 \text{ mL}/100 \text{ g/min}$ [8]. This regulatory mechanism is very responsive to variations in mean arterial pressure (MAP) and can adjust pressure within three to five seconds across a pressure range between 50 and 160 mmHg [9].

Once pressure exceeds this range the regulatory mechanism is unable to maintain CBF, and other mechanisms have to kick in. As you can imagine, an astronaut performing dead lifts or squats using 100 kilograms of resistance is forcing his/her body to work very hard to adjust MAP within that pressure range mentioned earlier. What happens when the crewmember performs each repetition is a spike in MAP that may exceed the ability of the regulatory mechanism to cope. Of course, this depends on the fitness of the crewmember and breathing technique, but generally when exercises such as the leg press and squat are performed, researchers have noted that the velocity of blood flow through the middle cerebral artery (MCA) fluctuates in parallel with changes in MAP during the exercise [10]. These changes



Fig. 5.8 Performing high-G maneuvers requires that pilots perform the AGSM, thereby driving hydrostatic pressure and preventing blackout. (Illustration courtesy of the United States Air Force)

in MAP combined with performing the forceful exhalation required to perform the resistance exercise results in a sudden increase in central venous pressure (CVP) which in turn obstructs the blood flowing from the brain via the jugular venous system [11]. This in turn causes an increase in intracranial pressure (ICP) and intraocular pressure (IOP).

This mechanism is well documented in other activities. For example, weightlifters performing forceful exhalations have been known to black out as a consequence of reduced cardiac output caused by a compromised venous return and a reduction in CBF [12, 13]. Another example is when fighter pilots (Fig. 5.8) perform the anti-G straining maneuver (AGSM) in an effort to maintain sufficient CBF when performing high-G turns and evasive maneuvers. Sometimes, when the AGSM is unsuccessful, these pilots suffer almost loss of consciousness (A-LOC) or gravity-induced loss of consciousness (G-LOC) as a direct consequence of the CBF falling below thresholds required to maintain consciousness.

The Link Between Resistance Exercise, IOP, and ICP

Although resistance exercise leads to an increase in MAP and ICP, aerobic exercise, which is also performed on board the ISS, leads to a decrease in these parameters

and also a decrease in IOP [14]. This is in marked contrast with what happens during resistance exercise, in which IOP rises by up to ~ 4.3 mmHg [14].

The mechanism leading to the increase in IOP is the forceful exhalation that in turn causes a rise in intrathoracic venous pressure. This increase in pressure spreads through the vasculature and to the choroid, and it is here where the problems begin because this increase in pressure results in an increase in IOP [15]. How this affects the trans-lamina cribrosa pressure is not known, but it is known that on Earth an increase in IOP will cause the lamina cribrosa to be forced against the optic nerve, which can lead to blindness [16].

Advanced Resistive Exercise Device

Since these mechanisms had the potential to cause visual deficits it wasn't surprising that the effects of exercising on the ARED were keenly studied after the equipment was delivered on shuttle flight STS-126, just in time for the *Expedition 19* crew to start using it. Once again, the small n numbers made it difficult to deduce if the resistance training was causing visual effects or not. Four of the ten astronauts who were studied reported having visual changes before they started exercising using the ARED, so it was difficult to make a connection between resistance exercise and visual impairment.

Equally, it was difficult to exclude the possibility that resistance exercise might be implicated in the vision changes. Having said that, it's worth emphasizing that while the connection between increased MAP and visual changes have been made on Earth, in orbit the situation is rather different. The athletes studied on Earth tended to be weightlifters and bodybuilders who exercised using maximum lifts and few reps because their goal was to build muscle and bulk up (in this group an increase of 15.0 mmHg in IOP from rest has been observed [12]). This is not the case with astronauts, whose objective is very different. The crews on board the ISS are interested in using exercise as a countermeasure against the effects of muscle atrophy and bone loss. That's it. Consequently, astronauts tend to use less weight and therefore less resistance than terrestrially bound weightlifters.

Astronauts also perform many repetitions—up to 10 or 12 per set usually. Since they are using less resistance, the increase in MAP and IOP is not significant: Vieira [14] reported an increased IOP of 4.3 mmHg from rest. Although a definitive connection has not been made between resistance exercise and increased IOP, astronauts are taught not to use the Valsalva maneuver when exercising, since this greatly increases MAP and therefore could increase IOP [17].

Ideally, researchers would like to examine astronauts reporting visual changes and then see how they are lifting and which exercises they are using. Researchers would also like to measure IOP and ICP before, during, and after resistance exercise because this might shed some light on the possible connection between resistance exercise and increased ICP.

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Chapter 6

Diet and Personalized Medicine

Although one of the most likely causes of vision changes is the cephalothoracic fluid shift that occurs when astronauts enter orbit, there is evidence to suggest other factors may be implicated. One of these is diet. Researchers have found that astronauts who suffered vision changes had lower serum folate and higher concentrations of homocysteine, cystathionine, 2-methyl citric acid, and methyl malonic acid than crewmembers who did not report visual deficits [1]. We'll consider the first of these (Fig. 6.1).

Folic Acid Deficient Optic Neuropathy

A condition in which a nutritional deficit causes visual changes is known as *nutritional optic neuropathy*, and this condition is rare. If a patient is folic acid deficient he or she usually complains of gradual loss of vision (LoV), dimness of vision, reduced color vision and possibly scotomas. An ophthalmic exam will reveal swelling of the optic disc. Patients with this condition are often those with a history of alcohol abuse since excessive alcohol consumption often leads to poor nutrition.

Why does a folate deficiency cause vision loss? Well, researchers think the anterior visual pathway is susceptible to folate deficiency, although exactly how a nutritional deficit can damage this pathway is not fully understood. What *is* known is that folic acid is needed to produce *tetrahydrofolate*. Tetrahydrofolate is a derivative of folic acid, and one of its characteristics is that it helps in the detoxification of formate [2]. If someone has low folic acid levels his or her body doesn't produce sufficient quantities of tetrahydrofolate, which in turn means that formate levels increase and formic acidemia results. And since formic acidemia causes a reduction in the production of adenosinetriphosphate (ATP) this means there is less energy for the fibers (such as the long fibers found in the optic nerve) that surround the optic nerve [3].



Fig. 6.1 This image was taken in the days of the Apollo-Soyuz Test project. It shows NASA astronauts enjoying space “vodka.” The containers hold borsch (beet soup) over which vodka labels have been pasted. Space nutrition has evolved a little since then, but it tends to be very high in sodium, which is thought to be a factor in VIIP symptoms. (Illustration courtesy of NASA)

If there is a direct link between folic acid deficiency and vision changes in astronauts the fix is a simple one of vitamin supplementation. But folate isn’t the only nutritional issue implicated in the vision problem.

Sodium

Sodium is added to so many foods that as much as 75 % of a person’s daily intake of sodium may be derived from the salt (40 % sodium, 60 % chloride) added by food manufacturers. Sodium plays a vital role in ensuring water balance inside cells, muscle contraction, and nerve impulses. But too much (the U. S. Department of Agriculture recommends a daily sodium intake of 2,300 mg) sodium can cause many problems, including kidney stones, hypertension, bone loss, and vitamin D metabolism.

The key health issue here is hypertension, since there is plenty of evidence showing a relationship between high sodium intake and high blood pressure [4]. Unfortunately, the astronaut diet has always been very high in sodium. Mission requirements for missions lasting between 30 days and one year recommend a daily sodium intake of less than 3,500 mg. In reality, that figure is much, *much* higher (Fig. 6.2).

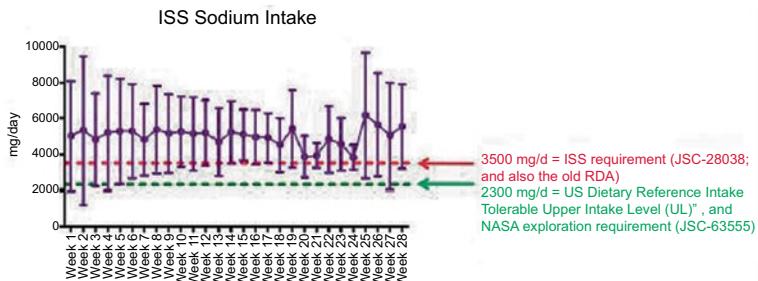


Fig. 6.2 Sodium intake during an International Space Station increment: average ISS sodium intake (in purple), compared to the ISS requirement (red) and recommended U.S. sodium intake (green). (Illustration courtesy of Dr. Scott M. Smith and NASA)

As you can see in Fig. 6.2, the daily intake in many cases was more than double the amount recommended by NASA. Part of the reason for this very high sodium level is that most space food is stuff taken right off the supermarket shelf, which means it has a high sodium content for shelf life. Another problem is that the calorie intake of astronauts has been underestimated, which means astronauts eat more than originally planned with the result that they eat even more sodium. NASA recognized this problem a few years ago and has steadily been reducing the amount of sodium in on-orbit diets. But at the time the vision changes were reported, astronauts were eating a diet very high in sodium.

Effects of High Sodium Intake

A high sodium diet, such as the one enjoyed by astronauts on board the ISS until very recently, can have many adverse physiological effects. A high sodium intake is very bad for those struggling to maintain bone integrity because sodium affects the acid balance of the body and therefore affects bone metabolism. Basically, a high sodium intake increases the rate of bone loss because the body becomes more acidic (see below). And in microgravity the effect is accelerated because the body retains sodium.

However, we're interested in the link between high sodium intake and increased blood pressure. This association has been studied intensively over many, many years, and research study after research study has demonstrated a direct relationship between sodium intake and blood pressure [5]. Studies have also demonstrated that a reduction in sodium intake will lead to decreased blood pressure, but there is significant variation when age is considered. For instance, those most at risk for hypertension are those older than 45 [5], which means the current astronaut corps, whose mean age is 46.7, is in the high risk category.

Solo Research

The problem of sodium intake in an astronaut's diet is being investigated by the European Space Agency (ESA). The agency's SOdium LOading (SOLO) research investigates how fluid and salt is retained by the body in space and in analogs such as bed rest. During expedition increments, astronauts take part in two 5-day phases of the study, following a diet either low or high in sodium. The researchers hope that by reducing sodium intake and by using an alkalizing agent such as bicarbonate, the harmful effects of sodium can be negated.

In healthy adults, serum sodium concentration is the key factor in maintaining the osmotic pressure of the water in the body. This pressure varies by no more than two percent under normal conditions because the body adjusts the body water concentration in response to the serum sodium concentration; the body simply retains or excretes body water.

However, this adjustment only occurs up to certain serum sodium concentrations. For those who have a very high sodium intake this balance is disrupted, because high sodium levels cause a shift of fluids from the interstitial (tissue) space to the intravascular (blood) space. This is a compensatory mechanism that has the effect of increasing blood volume and plasma volume that, combined, cause an increase venous volume. Ultimately, this increased venous volume may cause congestion as a result of obstruction in venous outflow.

Effects of Low Sodium Intake

On Earth, a low sodium diet has been recommended as a means of treating idiopathic intracranial hypertension (IIH). The primary symptom of IIH is visual impairment due to papilledema, but this may be treated by acetazolamide and by reducing sodium in the diet [6–8]. Unfortunately, since IIH is a rare diagnosis, and because its etiology is still unknown, there is limited research about the effects of dietary modification on the syndrome. In fact, you need to go back 40 years to find a study that investigated the effects of a restricted sodium diet on papilledema [7].

So should astronauts modify their diet and reduce their sodium intake? Probably. Reducing sodium intake will decrease the risk of hypertension, and it will also reduce sodium retention. Although studies have demonstrated that sodium retention does not cause an increase in body fluid, an increase in blood volume is still observed. Since increased blood volume may be a cause of increased intracranial pressure it is possible that sodium retention could exacerbate intracranial hypertension in crewmembers. Obviously more research needs to be conducted in this area, but though it isn't possible to say that a low sodium diet will reduce the incidence of visual impairments, it is safe to say that dietary modification will improve an astronaut's health.



Fig. 6.3 A polymorphism is a variation of a gene. (Illustration courtesy of NASA)

Polymorphisms

The link between low levels of folate and high levels of sodium seemed a reasonable one to investigate, but while astronauts' diets may be high in sodium, they do not suffer from vitamin deficiency, which is why researchers were still faced with the same question—why were only one fifth of the crewmembers on board the International Space Station (ISS) affected by vision impairment, and why would one astronaut be affected and not another? Scientists decided to look elsewhere for an explanation (Fig. 6.3).

The next potential cause NASA scientists focused on was enzyme polymorphisms. A polymorphism is a variation in a gene or a chromosome [9]. Natural variations are fairly common and usually have no adverse effects, but when the polymorphism is large—a single nucleotide polymorphism (SNP)—problems occur, especially if enzymes are involved. Enzymes play a vital role in bodily functions, and if any are not working correctly, problems occur. For example, those who lack the lactase enzyme will suffer from lactose intolerance—the inability to digest lactose. This is because dietary lactose can't be processed by the body without it being converted (hydrolyzed) into the monosaccharides galactose and glucose before being digested. Since hydrolysis requires lactase, those without the enzyme can't digest cow's milk. Researchers suspected that enzyme polymorphisms may help to explain vision problems because they knew that some enzyme polymorphisms had been linked to intracranial pressure (ICP).

One-Carbon Metabolism Dysfunction

To evaluate the astronauts' nutritional data, NASA established the Nutritional Status Assessment Supplemental Medical Objective (SMO), which was comprised of three researchers (Scott Smith from Johnson Space Center, Martina Heer from the University of Bonn, and Sara Zwart of the Universities Space Research Association). The primary task of the SMO is to increase nutritional testing of crewmembers on board the ISS and to use this test data to help scientists better understand how nutritional status changes over time. Among the SMO projects are studies investigating the effects of exercise on bone density, how oxidative stress is implicated in bone density, the relationship between fish and bone density, and the link between diet and vision.

One mechanism the group has identified as possibly having a bearing on vision is the one-carbon metabolic pathway [10]. This is because the SMO group has identified variations in certain metabolites of this pathway in astronauts who have also been affected by visual impairment [11]. The one-carbon metabolic pathway is folate-dependent, and biochemical data has revealed elevations in four metabolites of the pathway in those affected crewmembers—the enzyme polymorphism (termed the methylenetetrahydrofolate (MTHFR) polymorphism since it is the MTHFR gene that makes the enzyme). The four metabolites (of folate) in question were cystathionine, methylmalonic acid, homocysteine, and 2-methylcitric acid—all vascular toxins.

The serum concentrations of these four metabolites were found to be significantly higher in those crewmembers with visual impairment than those who reported no vision problems. These concentrations were measured preflight, inflight and post-flight. The researchers found that serum folate decreased in astronauts who reported visual impairment and that the concentration of serum folate levels were linked to changes in refraction when comparing post-flight and preflight data.

The results seemed to indicate a link between changes in the one-carbon metabolic pathway and susceptibility to vision problems in orbit. If this is proved to be the case then astronauts with this particular enzyme polymorphism may be required to increase the amount of folate in their diets. Such a hypothesis made sense when reviewing similar research. For example, some studies have shown that homocysteine is linked to types of glaucoma [12], so it is possible that a similar dysfunction in astronauts could be partly responsible for visual impairment. Having said that, it should be noted that while the homocysteine levels observed in crewmembers with vision impairment were higher than crewmembers with no vision impairment, these levels ($9.5 \mu\text{mol/L}$ —[11]) were still within nominal levels between $6\text{--}12 \mu\text{mol/L}$.

Polymorphisms and Vision Changes

The problem with all this research is that scientists are dealing with *very* small sample sizes. Also, the vision impairment problem is the result of several mechanisms, of which genetic polymorphism may be just one. As with all the potential

contributing and secondary effects, whether it be increased carbon dioxide levels, cephalothoracic fluid shift, or resistance exercise, the extent of the effect of genetic polymorphism on visual impairment has yet to be resolved because there are so many physiological effects to consider.

For example, what are the effects of resistance exercise and headward fluid shift on this polymorphism? Remember, each of the metabolites in question is a vascular toxin, so perhaps an increase in homocysteine could cause different vascular effects in a crewmember adapting to weightlessness than would be observed in that crewmember on Earth. After all, we know that adapting to weightlessness affects the body in all sorts of ways, so it stands to reason that genetic polymorphisms may be affected differently in orbit than on Earth.

As always, more research is needed, but what tests need to be done? Well, since the variation we are discussing is genetic, it makes sense to conduct genotyping on the crewmembers who have experienced vision impairment and those who did not. More studies also need to be conducted on how the one-carbon cycle affects vision and how the mechanisms are affected by weightlessness. Once those studies have been performed, further investigation could look into other factors such as exercise and increased carbon dioxide to see if these exacerbate enzymatic function.

Personalized Medicine

Omics

By now it is evident that the vision impairment problem is a multi-faceted issue that is characterized by significant intra-individual variation. Assuming researchers can identify the causes, how will the problem be treated? Perhaps the answer lies in personalized medicine, or Omics [13]. Omics is a trans-disciplinary and inter-disciplinary study of genomics, metabolomics, proteomics, and transcriptomics, that has revealed that many differences exist between people (Fig. 6.4).

Those involved in the field are interested in all clinical aspects of predictive, preventive, and personalized medicine: everything from molecular diagnostics and molecular biomarkers to nanotechnology and oncology. Recently, the field has gained the attention of those working in the space medicine arena, and Astro-



Fig. 6.4 Personalized medicine may hold the key to treating VIIP symptoms. (Illustration courtesy of NASA)

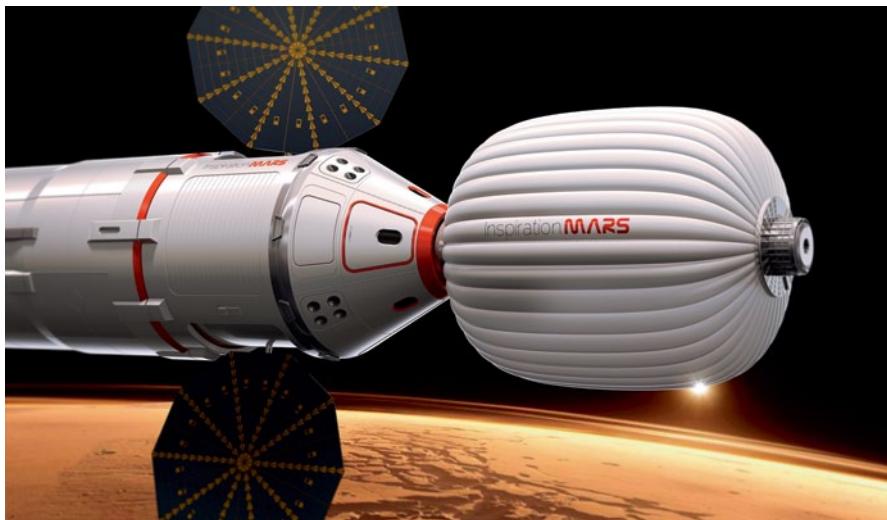


Fig. 6.5 The Inspiration Mars project plans to send two astronauts on a round trip (no landing) sometime in the 2021 timeframe—assuming the VIIP problem has been solved by then. (Illustration courtesy of Inspiration Mars)

Omics¹ was born. It's a very new specialization but one that shows great promise for space medicine and for those seeking to treat visual impairment/intracranial pressure (VIIP). Using genomics, proteomics and metabolomics to acquire personal medical data, Astro-Omics will be able to tailor an astronauts ocular health care, thereby ensuring the most effective treatment for each crewmember suffering from the syndrome [14].

Astro-Omics

As has been mentioned so many times in this brief, one of the most common problems faced by space medical experts trying to identify the cause of a particular space-related malady is the number of people who have flown in space—less than 600 all told. Ever. Although there are ambitious plans by the commercial sector to revise that number dramatically, we are still a few years away from routine public access to space, so that number won't be increasing much any time soon. And with-

¹ An early adopter of the field is Inspiration Mars (Fig. 6.5), which is using the approach to optimize the safety and health of the crew. When Inspiration Mars conducts their crew selection, they will do so using Astro-Omics to find out which candidates are best suited to the 500+ day round-trip. Once the most genetically suitable candidates have been selected, the crew will be monitored using omics-based analysis, and individually-tailored countermeasures will be designed to keep the crew healthy en-route.

out large numbers there is limited heterogeneity, which makes it difficult to study syndromes such as VIIP.

Still, if we are going to get to Mars without our crews going blind, we have to try to solve the problem, and the results have been promising to date. We know that unique susceptibilities exist, and this is why Astro-Omics can help. For example, in the previous chapter the subject of altered one-carbon metabolism was discussed, and it is exactly this type of specific genetic attribute that Astro-Omics was designed to deal with. Using information about an astronaut's genetic code, lifestyle, environment, and nutrition, this revolutionary field will be able to optimize countermeasures and pharmacological intervention specific to the crewmember. But first some background.

Applied Systems Biology

Systems biology is a term describing how the various components of biological systems interact and how these components work together to influence the behavior and function of each system. As far as space medicine is concerned, systems biology incorporates the disciplines of transcriptomics, metabolomics, proteomics, and genomics. In theory, data obtained from each of these disciplines can be pooled with data about the crewmember's diet, environment, lifestyle, medical history, and phenotype.

This data-driven approach, which is one of the hallmarks of Astro-Omics, should, in theory, detect unique pathways and mechanisms, and generate countermeasures specific to the crewmember. By adopting this approach, the assessment of a specific condition or syndrome such as VIIP is fast-tracked, and each astronaut can be prescribed their own countermeasure protocol and/or pharmacological prescription. Astro-Omics can do this because it focuses on five key concepts of systems biology that have immediate application for space medicine:

- a. Genetic variation (Fig. 6.6) in crewmembers (see later) that may increase their susceptibility to space-based syndromes. For example, those crewmembers with low folate levels may be more predisposed to VIIP symptoms.
- b. Genetic variation in crewmembers' susceptibility to pharmacological intervention strategies. For example, some crewmembers may respond better to certain drugs than other crewmembers.
- c. Metabolic profiles of crewmembers may indicate susceptibility to certain aspects of adapting to weightlessness.
- d. Molecular variation in crewmembers may indicate higher or lower susceptibility to radiation and/or bone demineralization.
- e. Aggregation of these factors may provide an accurate risk profile of each crewmember.



Fig. 6.6 Twins Mark and Scott Kelly. (Illustration courtesy of NASA)

NASA's Doppelgänger Study

One study that may shed some light on the issue of genetic variation is the one-year mission that will fly on the ISS between 2015 and 2016. In March 2015, Scott Kelly and Mikhail Kornienko (Fig. 6.7) launched to the ISS, where they will spend a year. Nothing special about that you might think. After all, there have been a few spacefarers who have spent a year or more in space. A unique feature of this mission, though, is the fact that Scott Kelly happens to have a twin—Mark—who also happens to be an astronaut.

Since Mark retired from NASA he has remained on the ground so that researchers could study differences between the in-orbit Kelly and the terrestrial-bound Kelly. By conducting this mission NASA stepped into the field of omics research. As a reminder, omics research includes fields of study such as metabolomics, genomics, nutrigenomics, pharmacogenomics, pharmacoproteomics, transcriptomics...well you get the idea. Of particular interest is the field of genomics because this has never been on the agency's radar, partly because astronauts are terrified that a scientist will find something wrong with them. Which is probably why the Kelly-Kornienko mission has some astronauts a little twitchy; if NASA starts genetically testing astronauts, chances are they may find some aren't so well suited to spending time in space.

For example, a genetic test could reveal an increased susceptibility to kidney stones or identify an astronaut as having a high susceptibility to radiation sickness.



Fig. 6.7 Russian cosmonaut Mikhail Kornienko. (Illustration courtesy of NASA)

Then again, when NASA eventually embarks on a Mars mission (sometime in the 2050's perhaps?), genetic testing will probably be unavoidable due to the extraordinary cost of such a mission.

So what will this twin study reveal? Well, the unique aspect of such a mission is that it will allow scientists to separate the impact of the environment against the influence of genes. One of the issues researchers will be focusing on will be the VIIP problem, so scientists will be tracking biochemical markers that may provide some clues as to why some astronauts experience a vision shift and others don't. For example, scientists will be monitoring levels of homocysteine, which is an amino acid that is a marker of cardiovascular disease. For some reason, astronauts who experience VIIP tend to have elevated levels of homocysteine. Could some astronauts have a predisposition to the syndrome? Perhaps the twin study will shed some light on the issue?

Another focus of the study will be telomeres. These are caps at the end of our chromosomes that prevent the chromosomes from fraying. Telomeres get shorter as we get older, and factors such as stress can accelerate the process, as can illnesses and health issues. The problem is that no one really knows how telomeres react to space and what this might tell us about problems such as VIIP. Gradually, as the mission progresses, NASA scientists will generate an omics profile of Kelly that may establish a template by which the agency customizes countermeasures, including those for VIIP. Of course, that's providing genetic testing is accepted by NASA as a means of identifying healthy and not-so healthy astronauts.

Functional Genomics

We'll return to the vision impairment syndrome shortly, but before we do it's worth highlighting that the popularity of personalized medicine has been gaining traction largely due to the undeniable advances in genomics applied to diagnostics in oncology. For example, there are many examples of molecular diagnostic assessments and biomarkers that are used to identify which patients will benefit most from receiving specific drugs. These tests are invaluable to doctors who, thanks to these tests, can place patients into risk categories: those needing hormone therapy versus those requiring more aggressive treatment, for instance.

This personalized approach can also be applied to the realm of space medicine by examining the voluminous literature that exists on molecular variants specific to spaceflight. For instance, space researchers will be particularly interested in the genetic variations in the metabolism of various pharmaceuticals. They will also be interested in the genetic variation associated with the one-carbon metabolic pathway because this may provide insight into which crewmembers might be more susceptible to VIIP. And they will surely be interested in the genetic variation associated with oxidative stress, DNA repair, and energy regulation.

Genetic Variation and Drug Metabolism

In a typical four- to six-month mission to the ISS, astronauts take all sorts of drugs. Some drugs are taken to help adapt to weightlessness while others are taken based on clinical need. Until very recently, the issue of adverse drug reactions based on genetic variation had been given very little consideration. Thanks to Astro-Omics, that may change in the near future. Very soon, the reality of personalized drug responses based on genotype may help reduce adverse outcomes and enhance astronaut performance on orbit. This characterization of variation in astronauts when it comes to responses to drugs may be especially important to those crewmembers suffering from VIIP if a pharmaceutical solution is developed.

Of course we still don't know if any of the drugs that astronauts take on board ISS today are implicated in the development of VIIP. It could be that some astronauts are particularly sensitive to some drugs and suffer vision impairment as a result. We just don't know, but Astro-Omics could change that thanks to identifying the biochemical uniqueness (sidebar) of each crewmember.

Cytochrome 450

We know there are significant differences in how effectively people process drugs. Some people metabolize drugs well while others suffer adverse reactions. This is because there is significant genetic variation in the enzymes that process these medications, and this is one of the reasons why the cytochrome P450 test was developed. The P450 (CYP450) test can inform doctors how effectively a person will metabolize certain drugs, which is

why it will be a useful test to determine the biotransformation capacity of ISS-bound crewmembers. An example: the CYP450 comprises a family of enzymes that includes specific genes such as debrisoquine hydroxylase, also known as CYP 2D6. CYP 2D6 is very important in clinical practice because it catalyzes the oxidation of many commonly used drugs. It metabolizes codeine to morphine, for example. Then there is CYP3A4, which metabolizes more than 120 drugs, including acetaminophen, lidocaine, and warfarin.

Since there is significant variance in each person's drug-metabolizing capacity, the need for a biochemical uniqueness profile is obvious. Some people are normal metabolizers while others are poor metabolizers and some are ultra rapid metabolizers. It really depends on the genetic luck of the draw. Compounding the problem of drug efficacy is the effect of weightlessness on metabolism, the mechanisms of which are poorly understood. But, by applying Astro-Omics—pharmacogenomics and metabolomics specifically—it will be possible to identify an astronaut's genetic variation to CYP450 enzymes, and this information can then be cross-referenced to the ISS drug list.

One-Carbon Metabolism

The one-carbon metabolic pathway was described in the previous chapter. To review very briefly, the pathway is governed by specific transfer genes and if there are polymorphisms in any of these genes, adverse effects may result. The one-carbon pathway has been under particular scrutiny recently because there may be a link between ocular health and one-carbon metabolism. Research has revealed that many of the crewmembers who have suffered VIIP also have genetic traits that are related to a disruption of the one-carbon metabolic pathway. As noted at the end of the previous chapter, follow-up studies still need to be conducted and replicated to confirm the link, but the 'one-carbon pathway-ocular health' connection seems plausible in light of evidence to date.

Homocysteine

As an example, let's turn our attention to one specific aspect of this pathway—homocysteine. Remember, this was elevated in those crewmembers who suffered VIIP, but how does this explain visual impairment? Well, let's begin by reviewing some of the symptoms of VIIP. We know the etiology of this syndrome is quite specific—anatomical changes include globe flattening, choroidal folds, optic-disc edema and hyperopic shifts [15]. We also know that 46% of ISS crewmembers suffered decreased near-visual acuity [16, 17], and it is known that homocysteine contributes to retinal ganglion cell death [18].

Hypertension

The genetic link here is one between increased ICP and intraocular pressure (IOP). In studies it has been shown that a mutation in a certain gene increases the risk of hypertension on Earth [19], and this could have a bearing on who suffers visual impairment in orbit. The mutation implicated in the one-carbon pathway is MTHFR C677T [20], and the coenzyme complexes that activate this mutation is riboflavin. As with the other genetic anomalies mentioned in this chapter, the MTHFR C677T mutation is another reason for assessing genotypes.

Countermeasures

As we have seen, there are a number of variations in the one-carbon pathway, but these have yet to be characterized in astronauts. Based on the results of Zwart [21, 22] and his colleagues that identified the influence of one carbon metabolism and visual impairment it seems that this metabolic feature may have a measurable impact on the problem of VIIP. By applying a personalized model to manned space-flight medicine there is a strong case to be made for personalized countermeasures, which would require pre-mission testing of each astronaut's one-carbon metabolic pathways. As more and more astronauts are tested in this way, it may be possible to build up a picture of the variances in this metabolic pathway and thereby identify individual biomarkers.

Omics Technology

We know that there are sizeable molecular networks that act together to affect astronaut susceptibility to the myriad mission stressors and physiological challenges. We also know that some astronauts adapt to some of these better than others, and we also know that one countermeasure strategy may not necessarily be effective for all crewmembers. So why not apply omics as a means of developing individual countermeasure strategies? And if this approach was adopted, how would it work to gain better knowledge of the VIIP issue?

Well, we know there is a need to profile genotypes to identify individual influences and individual susceptibilities, so the omics approach would help achieve this. By implementing a personalized medicine approach to space medicine it may be possible to identify VIIP biomarkers that will in turn enable the development of individual countermeasures. In turn, by applying this approach, mission performance will be increased, and the incidence of vision impairment will be reduced. Of course, adding an omics approach to the space medicine arena may present some technological and methodological challenges, but by being able to identify unique

patterns and enhancing predictive capability, this will enhance individual countermeasures, thereby reducing mission complexity. Fair trade?

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Chapter 7

Future Research

The visual impairment/intracranial pressure (VIIP) syndrome is NASA's primary medical concern in their manned space program. To better characterize the syndrome, the Ocular Health Study has been established to develop pre-mission medical testing of astronauts in the hopes that researchers can define how symptoms and signs develop (Fig. 7.1).

The study also aims to better identify how the length of time on orbit relates to severity of symptoms and also to establish how these symptoms change with mission duration. The main thrust of VIIP-related research is conducted within NASA's Human Research Program (HRP), based at Johnson Space Center (JSC). The objectives of the HRP (Fig. 7.2), as stated on its website, are as follows:

1. Develop capabilities, necessary countermeasures, and technologies in support of human space exploration, focusing on mitigating the highest risks to crew health and performance. Enable the definition and improvement of human spaceflight medical, environmental, and human factors standards.
2. Develop technologies that serve to reduce medical and environmental risks, to reduce human systems resource requirements (mass, volume, power, data) and to ensure effective human-system integration across exploration mission systems.
3. Ensure maintenance of agency core competencies necessary to enable risk reduction in the following areas: space medicine, physiological and behavioral effects of long duration spaceflight on the human body, space environmental effects, including radiation, on human health and performance and human space factors. [1]

The main objectives of the HRP program as listed on NASA's website are:

1. Develop capabilities, necessary countermeasures, and technologies in support of human space exploration, focusing on mitigating the highest risks to crew health and performance. Enable the definition and improvement of human spaceflight medical, environmental, and human factors standards.

Fig. 7.1 Visual impairment is one of the main concerns of the manned spaceflight program. (Illustration courtesy of NASA)

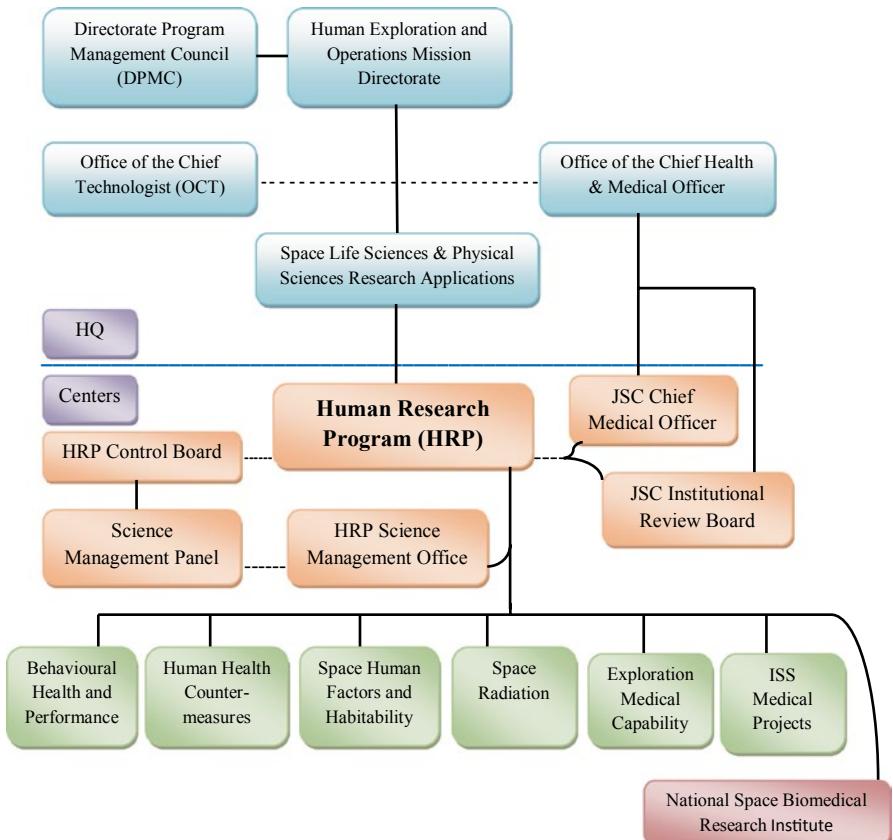
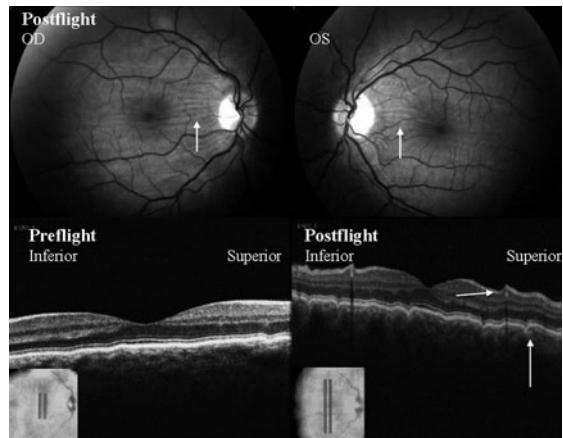


Fig. 7.2 The Human Research Program (HRP) was established in October 2005 at NASA's Johnson Space Center. Its primary goal is to focus research on investigating and mitigating the hig

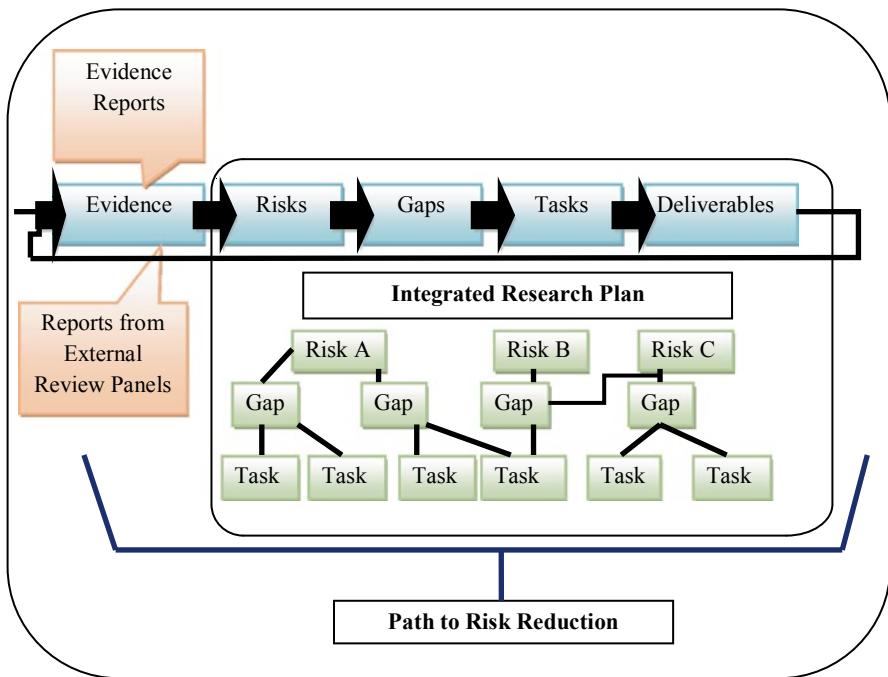


Fig. 7.3 This shows graphically how the Integrated Research Plan documents the research objectives that are needed to fill the gaps associated with each risk listed, while the Human Research Roadmap is the web-based tool that is used to communicate the evidence that supports HRP risks. As you can see, the HRP is integrated and cross-disciplinary in nature and tasks or gaps may be associated with one or more gaps or risks. (Illustration courtesy of NASA. Source: <http://humanresearchroadmapnasa.gov/intro/>.)

2. Develop technologies that serve to reduce medical and environmental risks, to reduce human systems resource requirements (mass, volume, power, data, etc.) and to ensure effective human-system integration across exploration mission systems.
3. Ensure maintenance of Agency core competencies necessary to enable risk reduction in the following areas: space medicine, physiological and behavioral effects of long duration spaceflight on the human body, space environmental effects, including radiation, on human health and performance and space human factors.

Source: <http://humanresearchroadmap.nasa.gov/intro/>

Part of HRP's job is identifying risks to astronauts, risks that must be resolved if astronauts are to embark on longer duration missions. On top of the 'risk list' is VIIP, and the reason that VIIP falls within the purview of HRP is because there exists a knowledge gap about the nature of the syndrome and also how to mitigate the risk. The way HRP works in producing a deliverable that fills this gap is shown in Fig. 7.3. Basically, gaps in the knowledge about VIIP are identified and a risk reduction path is developed that results in a deliverable and new evidence. As new

evidence is generated, the risk is reassessed, and the whole process begins again using what is known as the Path to Risk Reduction (PRR) tool.

The PRR lists all the associated risks—VIIP in this case—and identifies the research tasks that must be conducted to fill the knowledge gaps, which then forms what is called the Integrated Research Plan (IRP). The cross-disciplinary and integrated style of HRP research is then presented in the Human Research Roadmap (HRR) database.

To conduct VIIP research the HRP utilizes a variety of research platforms. Some research is conducted in ground laboratories and microgravity analogs, while other studies are performed on board the International Space Station (ISS). As evidence is generated, it is reviewed, and the results are compiled into HRP Evidence Reports that are then also reviewed.

The seriousness of a risk is color-coded as follows:

Red: Uncontrolled

Yellow: Partially Controlled

Green: Controlled

Grey: Insufficient Data

Blue: Risks that optimize power, mass, and crew time.

These risks are also tracked with regard to NASA's Design Reference Missions (DRMs), which include a one-year stay on board the ISS, a lunar mission, a deep space mission, and a trip to Mars. Throughout the research process, tasks and updates are tracked and monitored until a deliverable and/or product is submitted. The customers for the deliverables tend to be either the Office of the Chief Health and Medical Officer (OCHMO) and/or the Human Exploration and Operations Mission Directorate (HEOMD). As far as VIIP is concerned, deliverables could be a pharmacological intervention measure, clinical practice guidelines, or a specific counter-measure. Once the deliverable is assessed, the results are entered in either the Life Science Data Archive (LSDA) or the Lifetime Surveillance of Astronaut Health (LSAH), two repositories that contain searchable datasets.

VIIP Risks

The VIIP risks are listed on the HRP website. The HRP has identified four risks, each of which is described with respect to a mitigation strategy, knowledge gaps and related risks. We'll deal with each one in this section, but before we do it is worth making a note of the way NASA has categorized the four risks. In the HRP the risks are listed as VIIP1, VIIP12, VIIP13 and VIIP3. These acronyms are related to the HRP database and are simply identifiers of the risks. To make it easier to follow, we will use sequential numbering of risk. Also, each risk identified on the HRP site directs the reader to the areas of research that must be completed to answer the risk statement. For example, for VIIP1 (Risk 1), the first area of research listed is:

Prospective Observational Study of Ocular Health in ISS Crews [OCULAR HEALTH/OTTO/ACTIVE]

Click on this and you are directed to the Task Book, which reads as follows:

Task Book: Entry Unavailable

Principal Investigator: Otto, Christian

Short Title: Ocular Health (Ocular Health Study)

Responsible HRP Element: Human Health Countermeasures

Collaborating Org(s): Space Medicine Medical Operations/NASA JSC

Funding Status: Active—Currently funded and in progress

Procurement Mechanism(s): Directed

Aims: The International Space Station (ISS) Ocular Health Study aims to systematically gather physiological data to characterize the Risk of Spaceflight-Induced Intracranial Hypertension/Vision Alterations on crewmembers assigned to long-duration (6–12 month) ISS increments. The data collected will mirror Medical Requirements Integration Documents (MRID) requirements and testing performed during annual medical exams. The frequency of in-flight and postflight testing will be increased to more accurately assess changes that occur in the visual, vascular, and central nervous systems upon exposure to microgravity and induction of fluid shifting. Monitoring in-flight changes, in addition to postflight recovery, is the main focus of this protocol. A data sharing plan with Medical Operations will reduce redundancy of data acquisition. Preflight, in-flight and postflight measures include: tonometry, ocular ultrasound, fundoscopy, visual acuity, and optical coherence tomography (OCT); while magnetic resonance imaging (MRI), and bio-microscopy will be captured preflight and postflight exclusively. Three additional, non-MRID measures, will be collected preflight, in-flight and postflight, including blood pressure and cardiac output to assess vascular compliance, and transcranial Doppler (TCD) for Pulsatility Index (PI) to assess a surrogate measure of ICP. Data collection will begin one year prior to flight, continue in-flight approximately every 30 days, and continue through to one year postflight. In circumstances where abnormalities may persist beyond one year, postflight data will continue to be collected, but as per the MRID requirements (MedB 1.10) and Visual Impairment/Intracranial Pressure (VIIP) clinical practice guidelines.

At the foot of the ‘Aims’ there is a section listed as resources. Click on this and you are directed to a section outlining the number of subjects required to complete this task—in this case 12. Below the ‘Aims’ is the ‘Deliverables’ section, which provides information about the category and subcategory as follows:

Category: Risk Characterization/Quantification

Subcategory: Evidence

Description: A final report describing the time course of visual changes during long-duration (6–12 month) ISS missions will be delivered. This information will be used to develop future research goals.

Internal Customers: Human Health Countermeasures (HHC)

External Customers: None

Is a Customer-Supplier Agreement (CSA) Required? No

Finally, there is a section devoted to relate tasks. In this case 70 are listed, five of which are presented below as examples:

- Hindlimb suspension (HS) as an analog model of ocular alterations associated with cephalad fluid shifts: resveratrol as a countermeasure
- Spaceflight effects on the mouse retina: Histological, gene expression and epigenetic changes after flight on STS-135

- Pilot study to evaluate a novel non-invasive technology to estimate peripheral and central venous pressure
- Visual Impairment and Intracranial Pressure Project Data Mining
- Combined effects of gamma radiation and high dietary iron on oxidative damage and antioxidant status in rat eyes

(<http://humanresearchroadmap.nasa.gov/Risks/risk.aspx?i=105>)

Because this is a brief, it is not possible to review every risk, task book, deliverable and related task, so what follows is a synopsis of the VIIP risks stated on the HRP.

Risk One

We do not know the etiological mechanisms and contributing risk factors for ocular structural and functional changes seen in-flight and post-flight [2].

As mentioned many times in this brief, one reason there is such limited data is because there are so few astronauts to test. With such limited data it is a challenge to identify the underlying mechanisms that contribute to the VIIP syndrome, and data mining and ocular surveillance can only get you so far. Although the observations to date provide a basic understanding of the syndrome, the individual risk factors are still poorly understood. What this risk identifies is the need to define the continuum along which signs and symptoms develop and the development of countermeasures to reduce the health effects of these symptoms. To that end, NASA has identified its target for closure as follows:

Establish the etiology of VIIP syndrome development and the impact of the hypothesized risk factors (as determined by the RCAP) to direct and focus counter-measure development [2].

To achieve its target for closure for VIIP1 a number of steps are identified. One of these is to establish a timeline for the changes in intracranial pressure from launch to landing, while another step is to see if there is a link between head-ward fluid shift and ocular structure. Alongside these steps, research will be conducted to characterize the timeline of inflight changes to ocular structure and compare these changes to post-flight and pre-flight changes. Another component of the VIIP1 research is establishing the degree to which theoretical risk factors may be implicated in the VIIP syndrome. For example, researchers want to determine to what degree carbon dioxide levels, sodium consumption, anatomical differences, exercise and genetic factors influence the development of VIIP symptoms. Since NASA has determined that the VIIP1 knowledge gap has the highest priority of the four gaps identified, the greatest research emphasis is being channeled towards studies in this area. To that end, more than 30 VIIP1 research studies have been developed or are in the planning stages, five of which are listed here:

1. Risk of visual impairment and intracranial hypertension after space flight: Evaluation of the role of polymorphism of enzymes involved in one-carbon metabolism.

2. Human Cerebral Vascular Autoregulation and Venous Outflow in Response to Microgravity-Induced Cephalad Fluid Redistribution.
3. Association of Diffusion Tensor Imaging Parameters of Optic Tracts and Cerebral White Matter Tracts with Visual Impairment and Structural Changes of the Eyes and Optic Nerves in Long-Duration Microgravity Exposure.
4. CSF Production and Outflow: Cranial Lymphatic Drainage and Study of aquaporins, cellular junction proteins, and cellular permeability in the arachnoid granulations and choroid plexus of an appropriate animal model.
5. Ocular Structure, biomechanics and translaminar pressure gradients in relation to the VIIP syndrome (Flight).

Risk 2

At this time, we do not know whether ground-based analogs and/or models can simulate the spaceflight-associated VIIP syndrome [2].

One of the biggest problems characterizing any space-based malady or syndrome is the numbers game—there just aren't that many astronauts. To get around this problem, researchers have traditionally devised all sorts of analogs to simulate weightlessness, whether this be short periods of microgravity during parabolic flight, or head-down tilt studies designed to induce the headward shift in fluids that occur in weightlessness. One of the big unknowns when it comes to VIIP is that researchers don't know if any of the traditional analogs will produce signs and symptoms similar to space-based VIIP. To fill this knowledge gap, researchers will be conducting various bed-rest and animal models to develop a sensitive ground-based simulation of VIIP. One of the steps towards achieving this will be experimenting with various tilt angles in bed-rest simulations to see if any can reproduce the fluid shift that results in vision impairment.

In addition to evaluating fluid shifts in various analogs, researchers will also be assessing combinations of various factors that may conspire on board the ISS to cause VIIP. For example, they will be looking to see how a high sodium diet, high carbon dioxide environment combined with lots of resistive exercise may affect the development of VIIP symptoms. Since the VIIP12 knowledge gap hasn't been deemed as serious as VIIP1, fewer research studies have been generated, five of which are listed here:

1. Evaluation of hindlimb suspension as a model to study ophthalmic complications in microgravity: ocular structure and function and association with intracranial pressure.
2. Role of the cranial venous circulation in microgravity-associated visual changes
3. Hindlimb suspension as an analog model of ocular alterations associated with cephalad fluid shifts: resveratrol as a countermeasure
4. Combined effects of gamma radiation and high dietary iron on oxidative damage and antioxidant status in rat eyes.
5. Assessment of bed rest plus CO₂, Resistive Exercise and High Sodium as analog for VIIP

Risk 3

We need to identify preventative and treatment countermeasures to mitigate changes in ocular structure and function and intracranial pressure during spaceflight [2].

Astronauts heading up to the ISS today have very few options to relieve the effects of VIIP. Corrective lenses help, but that's about it, because researchers just don't know how effective other countermeasures (such as a reduced sodium diet) are. So, to close this knowledge gap, researchers will be studying countermeasures such as pharmacological intervention strategies and examining other preventive measures such as changing exercise routines and investigating the effect of carbon dioxide concentrations. Examples of some of the studies currently being pursued are listed below.

1. Distribution of body fluids during long-duration space flight and subsequent effects on intraocular pressure and vision disturbance.
2. Fluid distribution before, during and after prolonged space flight.
3. Influence of exercise modality on cerebral-ocular hemodynamics and pressures.
4. Microgravity associated compartmental equilibration.

Risk 4

We need a set of validated and minimally obtrusive diagnostic tools to measure and monitor changes in intracranial pressure, ocular structure, and ocular function.

In addition to characterizing the VIIP syndrome, researchers also need to have diagnostic tools to measure VIIP symptoms. Although the ISS has devices to measure ocular structure and function such as a fundoscope, a tonometer and a Snellen chart, there is no means for astronauts to assess peripheral visual fields nor is there a way of measuring intracranial pressure—thought to play a major role in the development of VIIP symptoms. So the main emphasis of this knowledge gap is to ensure astronauts not only have the necessary equipment to make the measurements but also that the equipment flown is tested (Fig. 7.4) against the gold standards here on Earth so correlations can be made. Listed are a few of the research projects underway to address these issues.

1. Non-invasive ICP device purchase & evaluation
2. Non-invasive monitoring of intracranial pressure (icp) with volumetric ophthalmic ultrasound.
3. Mapping by VESGEN of blood vessels in the human retina for improved understanding of visual impairments and increased intracranial pressure.
4. Validation of in-flight non-invasive ICP as compared to a direct measurement of intracranial pressure.
5. Comparison of continuous non-invasive and invasive intracranial pressure measurement.



Fig. 7.4 An ultrasound eye exam being performed on orbit in the Columbus Laboratory of the International Space Station. The astronaut performing the test is Expedition 37/38 Flight Engineer Michael Hopkins of NASA. Assisting him (L) is European Space Agency astronaut Luca Parmitano. (Illustration courtesy of NASA)

Spectralis

On the subject of equipment, it is important to mention the involvement of Heidelberg Engineering and their Spectralis range of ocular examination instruments. The participation of Heidelberg Engineering began when NASA determined they needed a way to perform screening for choroidal, retinal, and optic nerve defects to ensure flight surgeons had a full picture of an astronaut's eye structure and function. One of the key imaging tests needed to achieve this was optical coherence tomography (OCT), a very advanced scanning technique that generates extremely detailed images of the retina. Think of OCT as an MRI for the eyes. Using OCT on board the ISS meant researchers would be able to detect and monitor changes in the retina with very high accuracy. So, in 2013, NASA phoned Heidelberg Engineering, which manufactures a range of OCT instruments (the Spectralis range), and asked the German company if they would be interested in working with the agency. One thing led to another, and in February 2013, Heidelberg Engineering had its product ready for NASA, which bought a number of the devices.

A couple of months later NASA tested the ruggedness of the Spectralis to ensure space-worthiness by evaluating the device during parabolic flight. Meanwhile, back in Germany, Heidelberg Engineering was performing a 'shake' test to make sure the device could survive the trip to space. Another two months went by, and Spectralis found itself perched on top of an Ariane 5 rocket heading to the orbiting outpost,



Fig. 7.5 Koichi Wakata, a Japan Aerospace Exploration Agency astronaut conducts an OCT examination on board the International Space Station using Heidelberg Engineering's Spectralis system. The Spectralis system arrived on the orbiting outpost on June 15, 2013, and has been put to good use in an effort to try and provide researchers with more vision data. Spectralis is used regularly to perform eye examinations on crewmembers, including the first space-borne OCT exam, which was performed on October 16, 2013. (Illustration courtesy of NASA)

which it reached on June 15. Six days later the first OCP image was taken in space, and four months later the first crew examinations were conducted via streaming video (Fig. 7.5).

One year after Spectralis arrived on the ISS, the Association for Research in Vision and Ophthalmology gathered in Orlando for its annual conference. One of the presenters was Dr. Nimesh Patel (Fig. 7.6), who presented preliminary data from the Spectralis study. Thanks to the accuracy of the Spectralis, Dr. Patel was able to show OCT images of retinal and choroidal folds that had never been seen in terrestrial individuals. He also drew attention to the changes to the optic nerve head, and changes to choroidal thickness that occurred in many ISS crewmembers. He concluded his presentation stating;

With the Spectralis instrument, changes in retinal and optic nerve head anatomy can be monitored in astronauts on the ISS. Although there is inter-individual variability, the trends are similar and will provide important insights into the mechanisms involved.

A video of Dr. Patel's Xtreme Research Lecture can be watched by entering the following link:

<http://www.heidelbergengineering.com/international/xtreme-research-lecture-2014/>

Fig. 7.6 Dr. Nimesh Patel, PhD, from the University of Houston College of Optometry, receives the Xtreme Research Lecture Award from Managing Director of Heidelberg Engineering, Kester Nahen, in Orlando on May 5, 2004. The award was an annual award presented to NASA's Ocular Health Study, which Dr. Patel accepted on behalf of NASA. Following the award, Dr. Patel presented the award lecture, titled 'OCT in Zero G', which outlined details concerning the use of the Spectralis OCT system on board the International Space Station. (Illustration courtesy of NASA)



Next Steps

Although researchers still have a long way to go to fully understand the VIIP problem, the good news is that there is a plan. NASA is active in utilizing myriad research platforms as discussed in this chapter and also as part of the agency's Ocular Health Project. Expedition members arriving at the ISS are now subjected to ultrasound eye imaging tests to compare with the pre-flight and post-flight data. Clinical ophthalmic procedures are performed on all astronauts before, during, and following each flight to determine refractive error, globe geometry, and nerve sheath thickness, and a veritable shopping list of other eye-related metrics. All this data is collated in the LSAH and so, step by step, researchers are increasing our knowledge of the mechanisms of the syndrome and developing countermeasures to ensure those venturing forth may do so safely.

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Glossary

The Language of Ophthalmology

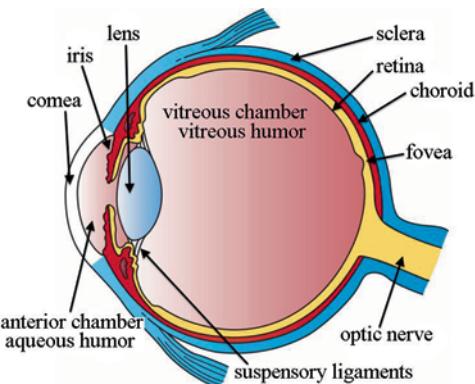
This brief is intended to be accessible to medical personnel and spaceflight enthusiasts alike. To that end, this glossary explains some of the more technical terms used when describing the problem of vision impairment in astronauts, but first some ophthalmology 101.

Overview

The eye is a sense organ and one of its primary functions is reacting to light. This is achieved thanks to an arrangement of rod and cone cells in the retina. These rods and cones enable us to perceive light, to distinguish between colors—about 10 million of them—and to perceive depth. The structures in the eye that receive light signals are the photosensitive ganglion cells, which are located in the retina [1]. When these structures receive light signals the effect is to adjust the size of the pupil. As you can see in Fig. G1 the eye is not a perfect sphere. Instead it can be considered as two parts. The front part, which is the cornea, is connected to the sclera. Connecting the cornea and sclera is a ring called the limbus. Next is the iris, which is the structure that gives color to the eye [1].

Eye Structure

The average adult eye has a front-to-back diameter of 24 millimeters, a volume of 6 cubic centimeters and a mass of 7.5 grams [1].

Fig. G1 Diagram of the eye

Elements

The eye has three layers, the outermost of which is the fibrous tunic, which in turn comprises the cornea and sclera, which can be seen in Figure G1. Inside the fibrous tunic is the vascular tunic, which comprises the choroid, ciliary body, and iris [2]. The third and innermost layer is the retina. The circulation for the retina, which is via the choroid and retinal vessels, can be seen using an ophthalmoscope.

Within these layers is the aqueous humor, which is a clear fluid that comprises the vitreous body and the flexible lens. As you can see in Fig. G1, the aqueous humour is located within the anterior chamber. It is also worth noting the relative locations of the structures enclosing the anterior chamber—the cornea and the iris. As you can see in Fig. G1, the lens is attached to the ciliary body by the suspensory ligament (this is also given the term the *Zonule of Zinn*). Also depicted is the vitreous body, which comprises the vitreous chamber and vitreous humor. As you can see, this structure (which is a clear jelly) is located behind the lens.

The next structure to note is the retina, which lines the eye's inner surface. This is a light-sensitive layer of tissue, and one way to think about how the retina functions is to think of the film in a camera (remember those days?). Basically the image of whatever is being viewed is created through the cornea and lens and is portrayed on the retina. The way this occurs is the result of a complex series of chemical and electrical events that trigger nerve impulses, which then travel to vision centers in the brain via the optic nerve.

Vision

When we talk about the eye's visual range we use the term 'field of view' (FoV). The FoV of the eye is about 95° away from the nose, 75° downward, 60° toward the nose, and 60° upward [2]. This means that our eyes have almost 180° forward-facing horizontal FoV, but since we can rotate our eyes rotation up to 90°, our

horizontal FoV can be as high as 270° if we exclude head rotation and include our peripheral vision.

When our eyes are exposed to either light or dark, an adjustment occurs automatically as the iris, which regulates pupil size, adapts depending on the type of exposure. For example, we adapt quite quickly—about 4 seconds—to the dark, but that is only the initial adaptation. Full adaptation takes about 30 minutes. One wrinkle to this is that any interruption to light means the adaptation process has to start again. It's the reason soldiers are always told to preserve their night vision by keeping one eye closed when flares are launched.

When it comes to focusing, the analogy of the camera can be used again. As you can see in Fig. G1, the eye has a lens that is similar to the lens found in a camera. When you focus a camera you have to consider aperture, refraction, and light and the same principles apply when focusing your eyes: the aperture of the human eye is the pupil, while the iris is the diaphragm that functions as the aperture stop.

Anatomy and Function

Of course there is much more than pointing our eyes and focusing. We also need to be able to process the information we see. This is one of few drawbacks of the visual system because it can only process information at what is a fairly slow speed. Any faster than a few degrees per second and the retina just can't cope. Fortunately, the brain can compensate when we move by turning the eyes.

However, moving the eyes 'doesn't solve all the problems of moving because we also want to see what we're looking at with a degree of clarity, which brings us to the fovea centralis, because it is this structure that is linked to visual acuity. If you want to view an image clearly and with clarity then you must point your eyes so whatever you're looking at falls on the fovea. In short, eye movements are key for visual perception. Eye movements have to be made with sufficient accuracy so that what you're looking at falls on the corresponding points of your two retinas. If this doesn't happen then double vision (diplopia) will likely occur [3].

Extraocular Muscles

So how do you move your eyes and how are these movements controlled? Well, your eye has six muscles—the lateral rectus, the medial rectus, the inferior rectus, the superior rectus, the inferior oblique, and the superior oblique—that control movements. By exerting different tensions these muscles generate a torque, and it is this that causes your eye to turn.

Saccade and Microsaccades

Other terms often used to describe eye movements are *saccades* and *microsaccades*. These jerky type movements, which are controlled by the frontal lobe, occur when focusing on a single location. One purpose of the movements—microsaccades move the eye about 0.2° —is to ensure the eyes don't drift when focusing [4]. By making these rapid movements the eyes ensure the photosensitive cells are constantly stimulated, thereby creating constant input. Without changing input, these cells would stop generating output.

Vestibulo-Ocular Reflex

In addition to focusing and changing input, the eyes also need to be able to stabilize images. This is the function of the vestibulo-ocular reflex (VOR). A reflex movement, the VOR stabilizes images on the retina while the head is moving in one direction by producing eye movement in the opposite direction. This ensures that the image remains in the center of the FoV.

Vergence

When we view an object close up, our eyes rotate inwards. This is known as *convergence*. When we look at an object at distance our eyes rotate outwards. This is known as *divergence*. There is also a term for what is known as *cross eyed viewing*. This happens when you focus on your nose and is termed *exaggerated convergence*. These movements are linked to the eye's accommodation and happen automatically.

Pupil Constriction

Since our lenses can refract light rays closer to the center than at the edges, the images at the periphery tend to be blurry. This is known as *spherical aberration*. The eye can adapt, and to a certain degree overcome this, by constricting while the eye focuses on objects close up.

Accommodation of the Lens

Accommodation is a term used to describe changing the curvature of the lens. This function is one of the jobs of the ciliary muscles, which also relax the fibers of the suspensory ligament, which in turn allows the lens to relax into a convex shape.

Here, now, are some common terms used in this book.

Amsler Grid Testing This tool is used to assess visual impairments that are the result of changes in the retina. The patient being tested simply looks with each eye separately at a small dot in the center of a grid with horizontal and vertical lines. Those with macular disease may see wavy lines or some lines may be missing [3].

Choroid This layer of the eye, which lies between the retina and the sclera (see Fig. G1), comprises four layers: Haller's layer—the outermost layer of the choroid consisting of larger diameter blood vessels; Sattler's layer—the layer of medium diameter blood vessels; Choriocapillaris—layer of capillaries; and Bruch's membrane—the innermost layer of the choroid [3].

Choroidal folds These are parallel grooves that can be observed in fundoscopy. The grooves give the impression of a sheet of cling film that is being pulled centrally around the disc.

Cycloplegic refraction This exam is performed by administering cycloplegic drops, which take away the patient's accommodation and leaves things blurry for a few hours. The drops also dilate the pupil and makes the patient more sensitive to light.

Diopter This is a unit of measurement of the optical power of a lens. As an example, a 3-dioptre lens brings parallel rays of light to focus at 1/3 meter [2].

Diplopia Double vision.

Frisén Scale This scale[5] is used to grade papilledema (the subject of Chapter 4) as follows:

Stage 0—Normal Optic Disc

Blurring of nasal, superior and inferior poles in inverse proportion to disc diameter

Radial nerve fiber layer (NFL) without NFL tortuosity

Rare obscuration of a major blood vessel, usually on the upper pole

Stage 1—Very Early Papilledema

Obscuration of the nasal border of the disc

No elevation of the disc borders

Disruption of the normal radial NFL arrangement with grayish opacity accentuating nerve fiber layer bundles

Normal temporal disc margin

Subtle grayish halo with temporal gap

Concentric or radial retrochoroidal folds

Stage 2—Early Papilledema

Obscuration of all borders

Elevation of the nasal border

Complete peripapillary halo

Stage 3—Moderate Papilledema

Obscurations of all borders

Increased diameter of optic nerve head

Obscuration of one or more segments of major blood vessels leaving the disc

Peripapillary halo—irregular outer fringe with finger-like extensions

Stage 4—Marked Papilledema

Elevation of the entire nerve head

Obscuration of all borders

Peripapillary halo

Total obscuration on the disc of a segment of a major blood vessel

Stage 5—Severe Papilledema

Dome-shaped protrusions representing anterior expansion of the optic nerve head

Peripapillary halo is narrow and smoothly demarcated

Total obscuration of a segment of a major blood vessel may or may not be present

Obliteration of the optic cup

Fundus This is opposite the lens and is the interior surface of the eye. It is an important diagnostic reference point because this is the only place in the body that microcirculation (vessels with diameters as small as 10 µm) can be observed using an ophthalmoscope. Using this device, an ophthalmologist can see signs of hemorrhages, blood vessel abnormalities and pigmentation.

Hyperopia This is the ophthalmological term for farsightedness, which affects about 25% of the population. Someone with hyperopia can see distant objects clearly but can't see objects up close very clearly.

Macular degeneration This condition tends to affect those 50 years or older. It is caused by damage to the retina, which in turn causes loss of vision in the center of the visual field. In advanced stages it can cause blindness [6].

Papilledema This is a term we'll be using a lot in this brief because papilledema may be an indication of intracranial hypertension [7]. The condition affects the optic disc. Under normal circumstances it is possible to see the borders of the optic disc, but in a patient with papilledema these borders are not visible.

Pulsatile Tinnitus This is a rhythmical noise that usually has the same rate as the heart. This can be checked by feeling the pulse at the same time as listening to the tinnitus.

Scotoma Your eye has a scotoma in its FoV. This is your blind spot. But some people have scotomas that are more pronounced, which may lead to objects ‘disappearing’ due to a partial alteration in the FoV. This compromised visual acuity is another commonly reported symptom in astronauts suffering from visual impairment.

Stereopsis This is how you perceive depth and 3-dimensional structure.

Transcranial Doppler (TCD) This is used to measure the velocity of blood flow.

Transient Visual Obscurations (TVOs) This is another symptom that has been reported by astronauts suffering from visual impairment [8]. Those experiencing TVOs often complain of gray spots or a dimming of vision. The condition, which is temporary, may occur in one or both eyes.

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