

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

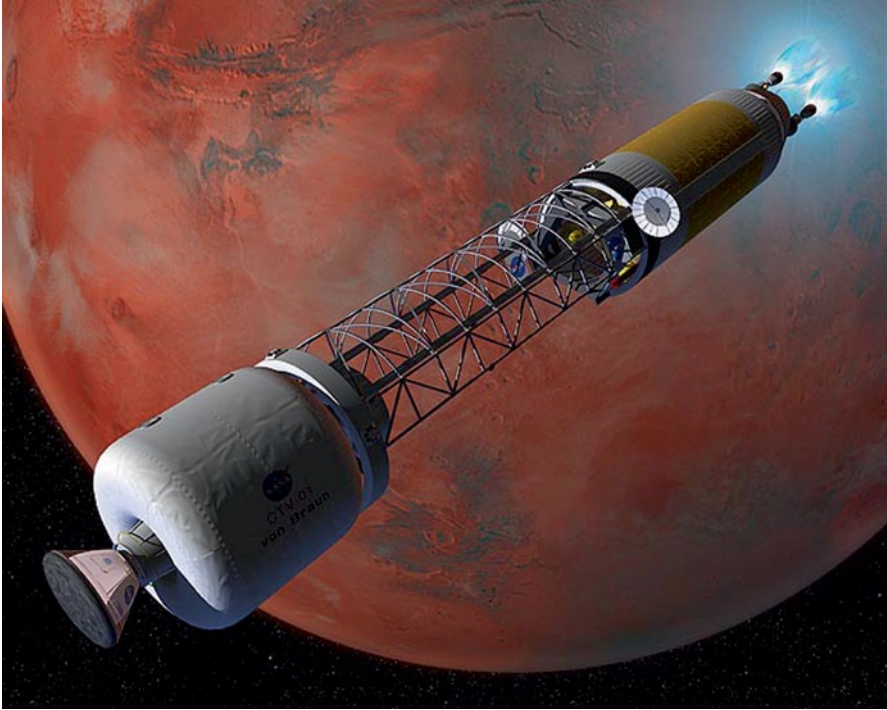


Fig. 1.3 A manned mission to Mars using chemical propulsion will be a three-year affair. It is unlikely any of the crew will be trained ophthalmologists, which is why it's so important that NASA resolve the visual impairment issue. (Illustration courtesy of NASA)

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 cribosa 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 funduscopy 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 CO_2 is a potent vasodilator (which dilates the blood vessels), so it also can increase intracranial pressure. Thus, microgravity and CO_2 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

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