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Acute and Chronic Effects of Hypobaric Exposure upon the Brain

Paul Sherman and John Sladky

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Abstract

Exposure to the hypobaric environment presents numerous physiological challenges to both aviators/pilots, mountain climbers and astronauts. Decompression sickness (DCS) is one of the most commonly experienced maladies and may present variably in protean fashion from mild symptoms such as the bends to severe neurological or pulmonary (i.e. chokes) symptomatology. Furthermore, exposure to extreme non-hypoxic hypobaric environments such as those experienced by our U-2 pilots, irrespective of clinical history of decompression sickness, incites development of white matter hyperintensity lesions that are diffuse in nature. Additionally, non-hypoxic hypobaric exposure also impacts white matter integrity independent of presence of white matter hyperintensities as measured by fractional anisotropy. Functionally, this translated into subtle but significantly lower neurocognitive test performance in U-2 pilots exposed to extreme non-hypoxic hypobaric conditions when compared to pilots without repeated exposure and correlated with degree of white matter lesion burden. In this chapter, we discuss results of our U-2 pilot studies along with published research on high-altitude climbers. We also review ongoing and future directional research and discuss operational implications due to our findings of non-hypoxic hypobaric exposure. Lastly, we examine the incidence of DCS in our astronaut population as well as the risks of performing extravehicular activity (EVA).

Keywords: decompression sickness, hypobaria, MRI, U-2 pilots, astronauts, extravehicular activity, white matter hyperintensities, fractional anisotropy, acute mountain sickness, military free fall operations

1. Introduction

Normoxic hypobaric (low atmospheric pressure) exposure, such as experienced by U.S. Air Force (USAF) U-2 pilots, and inside safety personnel operating altitude chambers (low pressure chambers), is associated with increased subcortical white matter hyperintensity (WMH) burden [1, 2]. Astronauts conducting extravehicular activity (EVA), also known as “space walks,” are exposed to a hypobaric environment similar to U-2 pilots. WMHs are regions of accumulation of extra-cellular water due to focal degradation of the myelin sheath [3], and the volume of WMHs is a non-specific marker of cerebral integrity sensitive to multiple etiologies [4]. Repetitive normoxic hypobaric exposure is associated with a decrease in axonal integrity as quantified by global decrease in Fractional Anisotropy (FA) using diffusion tensor imaging (DTI) technique in magnetic resonance imaging (MRI) [5]. Further, this decrease in axonal integrity and increased subcortical WMH burden are associated with a decrement in neurocognitive function [6]. A small convenience sample of astronaut brain MRI data suggests similar WMH change to U2 pilots [7], although the astronaut group was an average of 9 years older. The neuropathophysiological mechanism for decreased axonal integrity and formation of WMHs related to decompressive stress is poorly understood and ongoing human and animal studies are addressing this operational concern. The long-term ramifications of repeated hypobaric exposure are uncertain, but are relevant to current United States Air Force (USAF) military operations and deep space mission plans with frequent EVAs.

WMHs have also been demonstrated in high-altitude mountain climbers [8, 9]. Extreme mountain climbers have demonstrated transient white matter volume change and diffusion tensor imaging (DTI) changes [10, 11]. WMHs have also been demonstrated in other dysbaric environments such as occupational and recreational diving [12, 13]. Results of a meta-analysis of experienced, healthy divers, without a history of neurological DCS, suggest that repeated hyperbaric exposure increases the prevalence of WMHs [14]. Divers included military, commercial and recreational divers, caisson workers, and hyperbaric chamber attendants. It is unknown if WMHs associated with diving or altitude exposure behave in a similar fashion.

2. Background

The U-2S Dragon Lady is a high-altitude military reconnaissance aircraft capable of flying at altitudes over 70,000 feet (21,336 m) for up to 15 h. The U-2 has performed high altitude reconnaissance operations for nearly 60 years and remains heavily utilized by the USAF today. The cabin pressurization system exposes U-2 pilots to cabin pressures equivalent to 29,500 feet (8992 m), approximately the altitude on the summit of Mount Everest. The aircraft was designed with a partially pressurized cabin to save weight and thereby increase attainable altitude. Pilots are required to wear a full pressure suit in case of unexpected cabin

decompression. The current pressure suit is designed to automatically inflate in the event of any cabin decompression or bailout to maintain a physiological pressure equivalent of 35,000 feet (10,668 m) or less. U-2 pilots routinely fly operational sorties lasting 8–11 h every 3–4 days. This prolonged hypobaric exposure subjects U-2 pilots to high risk for decompression sickness (DCS). Altitude DCS generally occurs in individuals exposed to a cabin pressure equivalent to 18,000 feet (5486 m) or higher [15]. Pilots can voluntarily inflate the suit during flight to lower DCS risk or to reduce any DCS symptoms they are experiencing. To mitigate risk of DCS, U-2 pilots also undergo a standard denitrogenation (“prebreathing”) procedure by breathing 100% oxygen for 60 min before flight. Prebreathing establishes an oxygen gradient to offload nitrogen from tissues to the blood, thereby decreasing nitrogen stored in the body. This prebreathe has been proven highly beneficial in reducing the incidence and delaying the onset of DCS [16]. In 2010 a 10-min exercise-enhanced pre-breathing (EEP) period was added to the standard 60-min resting prebreathe prior to any high-altitude sortie. This further enhances the denitrogenation process and, therefore, may further lower the risk of DCS for the U-2 pilot population [17]. During flight, the pilots breathe 100% oxygen provided by a separate dedicated life support system.

Low-pressure chamber inside safety monitors undergo routine exposure to 25,000 feet (7620 m) for approximately 30 min per training flight, with total time above 18,000 feet (5246 m) not exceeding 60 min. Exposure frequency is variable but generally not more often than every third day, although occasionally mission demands require every other day exposure. The flight profile includes a 30-min denitrogenation period on 100% oxygen and the monitor remains on oxygen (never experiences hypoxia) for the duration of the flight (see **Figure 1** below, Air Force Instruction [AFI] 11-403).

Altitude chamber inside observers experience a similar hypobaric environment to U-2 pilots at a much shorter duration and without increased radiation exposure risk.

2.1. DCS physiology

Following the creation of the first vacuum pump circa 1670, Robert Boyle first noted the formation of numerous gas bubbles in his animals exposed to the reduced atmospheric pressures of the pump [18]. However, it was not until 1862 when the first human episode of DCS was recorded by Paul Bert in his hot air balloon. Bert documented his experience of transient left arm flaccid paralysis that occurred following rapid ascent (305 m/min) to 29,000 feet (8838 m) which resolved following his return to surface [19]. Both hypobaric and hyperbaric exposures can result in decompression sickness (DCS) and neurologic DCS (NDCS). Each of these dysbaric environmental exposures share similar clinical and pathophysiological features, but there are inherent differences to both. One of the fundamental differences is the time of onset; in a hypobaric environment (aviators and astronauts), the symptoms occur during the exposure to a low atmospheric pressure. Conversely, following hyperbaric exposure (divers), the symptoms typically occur after the exposure with majority occurring within 24 h. Furthermore, the pathophysiology is felt to be different as arterial gas embolism occurs primarily during hyperbaric exposure and rarely during hypobaric exposure. Furthermore, the spinal cord is more

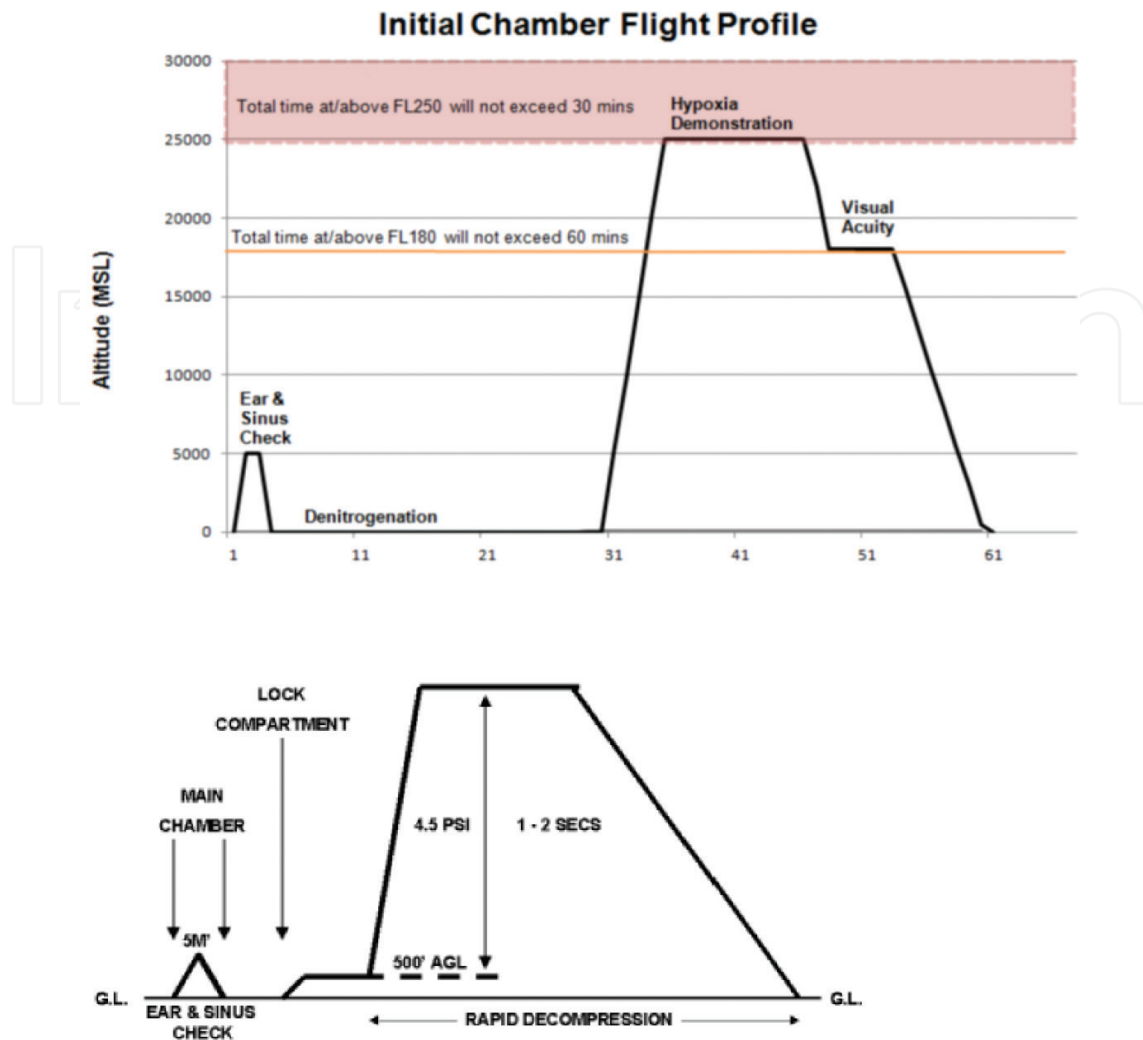


Figure 1. AFI 11-403; Nov 30, 2012. Initial altitude chamber flight profile with rapid decompression.

preferentially affected and vulnerable during hyperbaric exposure [20]. Arterial gas embolism (AGE) arises as expanding gas ruptures alveolar capillaries allowing the entry of alveolar gas into the arterial circulation. Venous gas emboli (VGE) in small quantities are common in diving but are typically asymptomatic as they are effectively filtered by the lung. However, VGE is not a desired condition and in large quantities can cause cough, dyspnea, substernal chest pain, pulmonary edema (referred to as the “chokes”) and further cardiorespiratory distress. The presence of a patent foramen ovale (PFO) or other right-to-left shunt can cause the VGE to enter the arterial circulation. The incidence of PFO is approximately 25% in the general population [21].

There are two conditions requisite for development of DCS. The first requires the supersaturation of an inert gas in the surrounding tissue. Supersaturation is defined simply as the partial pressure of the inert gas is greater than the surrounding ambient pressure. The

second condition is the development of a gas bubble from the presence of bubble nuclei from the supersaturated tissue. This typically occurs when the decompression rate of the ambient pressure exceeds the rate of inert gas wash-out from the tissues. During diving, caisson work or operation in a compressed air tunnel, supersaturation results due to increase in inert gas partial pressure in the tissues as a direct result of inspiring the air at high pressures. Hypobaric conditions such as aviation or extravehicular activity (EVA) in space predispose to supersaturation of pre-existing dissolved nitrogen at sea level (~570 mm Hg) which can then form bubbles when exposed to reduced barometric pressure. Gas supersaturation in the tissue can be mitigated with phase transition. The issue with DCS is when a gas space arises due to partial or complete desaturation of a pocket of supersaturated tissue. This sets up a pressure difference or “deformation pressure” within the tissue [22]. It is the pressure difference and not necessarily the volume of gas involved which causes the pain observed in pain-only DCS.

Formation of bubbles can result in direct mechanical, embolic and even biochemical effects and the results can range from trivial to fatal. The bubbles can result in mechanical distortion of tissues resulting in pain or may occlude vascular structures resulting in stroke-like signs and symptoms. There are three potential sources of microemboli: (1) micro-bubbles of gas; presumably nitrogen; (2) small thrombi secondary to platelet activation and deposition; (3) microparticles. Other effects also include endothelial injury resulting in leakage of plasma and increased leukocyte endothelial adhesion. The classic symptoms of DCS including joint pain, paresthesias and skin changes are thought to be secondary to either direct pressure of the gas bubble on the tissue itself, blockage of small arteriolar vessels, and/or interaction with serological proteins [20]. While echo imaging has shown the presence of venous gas emboli in tissues [23], the presence of arterial gas emboli is quite uncommon, reported in only 6 of more than 1500 altitude chamber exposure cases [24]. Occlusion of small cerebral vessels by activated platelets due to accelerated coagulation in the presence of venous nitrogen gas bubbles was demonstrated in both medium and large-sized arteries in mice after DCS and therefore remains another possibility for the development of WMH [25].

2.2. Signs and symptoms of DCS

Signs and symptoms of decompression (DCS) are protean and range from mild to severe including death. Historically DCS has classically been divided into arterial embolism, Type I, Type II and skin bends. However, due to inconsistencies in applying this classification system, it has largely been replaced by the all-inclusive term decompression illness (DCI) and based on system involvement. For consistency, we will keep with the prior classification system. Type 1 is typically referred to as “pain only” DCS symptoms or the “bends” with localized pain in the joints (lower extremities; particularly knee involvement) and may be accompanied by cutaneous manifestations (pruritus and mottling) and constitutional symptoms. Type II symptoms are systemic and more severe and generally involve both the central nervous

system and cardiopulmonary systems (see **Table 1** below). Skin bends refer to the marbled appearance of the skin whereas the characteristic rash of livedo reticularis (cutis marmorata) is a more severe form of skin bends and is nearly pathognomonic for decompression sickness in the appropriate clinical context [26]. In one prospective study that looked at 447 cases of DCS over an 11 year period at the Armstrong Laboratory, the most collective symptom was musculoskeletal in 83% of the cases of which knee pain was the most common. This was followed

DCS classification	Signs and symptoms	Location of bubbles
Type I: “Pain-only”		
“Bends”	<ul style="list-style-type: none">Localized deep joint painPain may often occur at altitude but may occur during descent or even hours later	Large joints: <ul style="list-style-type: none">ElbowsHipsWristsShoulders
Mild skin changes	<ul style="list-style-type: none">PruritusMottling (mild)Formication (feeling of ants crawling on skin)	Skin
Type II: More severe systemic involvement		
Neurological	<ul style="list-style-type: none">Confusion/memory lossVisual changes: diplopia, scotomasHeadacheSeizures, vertigo, unconsciousness	Brain
	<ul style="list-style-type: none">Dysthesias and paresthesias around lower chestConstriction pain/pressure around chest or abdomen	Spinal cord
	<ul style="list-style-type: none">Ascending paralysisBowel/bladder incontinenceFasciculations or muscle twitchingParesthesias/numbness	Peripheral nerves
Cardiopulmonary: aka “Chokes”	<ul style="list-style-type: none">Dyspnea (shortness of breath)Dry coughPain worsened with breathingDeep burning chest pain	Lungs
Skin bends: cutis marmorata	<ul style="list-style-type: none">Livedo reticularis rashPitting edema	Skin

Table 1. DCS signs and symptoms.

by paresthesias in 10.8%, chokes in 2.7%, cutaneous lesions in 2.2% and neurological deficits in 0.5% [27]. Neurological decompression sickness (NDCS) resulting from hypobaric exposure typically involves the brain more than spinal cord and may range from mild symptoms such as slowed thought processes to severe including confusion, aphasia, unresponsiveness and even permanent cognitive decline [28].

2.3. Incidence of DCS in U-2 pilots

The USAF U-2 pilots are at considerable risk of development of DCS due to the extreme altitudes and long duration sorties. The risk of DCS is dependent on both the rapidity of ascent as well as the duration of exposure to altitude (typically defined as >18,000 feet) in a hypobaric environment. In a 1996 survey of 416 active/retired U-2 pilots (60% response rate), more than 75% of the pilots attested to DCS symptoms such as joint pain or skin manifestations. 12% of those surveyed cited at least one episode that was severe enough to abort or alter the profile of their mission [29]. The risk of DCS per flight increased from 0.076% pre-2006 to 0.23% during the 2006–2010 operation years [30]. Furthermore, 44% of episodes were diagnosed as NDCS including 5 life-threatening cases with symptoms ranging from mild, such as complaints of slowed thought processes to severe, including anomia, confusion, unresponsiveness, and cognitive decline. Neuropsychiatric symptoms persisted in 6 pilots which may represent permanent injury. This upsurge in NDCS was felt to be a consequence of more frequent and longer periods of flight/hypobaric exposure for the pilots [28].

2.4. Incidence of DCS in astronauts

Astronauts are also at risk for the development of DCS. Before the very first EVA (extravehicular activity) occurred, NASA realized that DCS was a risk to be mitigated. Earth-normal atmospheric pressure at sea level is 760 mm Hg (14.7 psia or 1ATA). The current NASA space-suit referred to as the EMU (extravehicular mobility unit) operates at 4.3 psia or 222 mm Hg above the vacuum of space whereas the Russian Orlan space-suit operates at 5.8 psia. Increasing the space-suit pressure or reducing cabin inert pressure are the two ways to reduce the pressure gradient differential between environments to help minimize risk of DCS. However, increasing suit pressure typically results in reduced operational capacity by the astronaut due to increased fatigue, reduced dexterity and mobility [26]. DCS is a known risk during EVA but complete elimination of DCS is practically impossible. Therefore, mitigation plans between USAF, United States Navy (USN), NASA and the academic research community were undertaken to define “acceptable risk.” The current definition implemented by the International Space Station (ISS) protocols is the following: (1) DCS < 15%; (2) Grade IV VGE < 20%; (3) No type II DCS.

However, despite the above concerns of DCS, there have been no recorded cases of DCS among astronauts and cosmonauts during EVA's working in pressurized space-suits between 3.7 and 5.8 psia. This is in stark contrast to both Russian and American altitude chamber technicians who report symptoms or signs of DCS ~ 20–40% of the time [26, 31]. There are three possible explanations for this disparity: (1) Potential bias not to report symptoms; (2)

Masked DCS symptoms; (3) Potential operational and gravitational benefits of the spaceflight environment.

Regarding the bias not to report, an EVA is considered the pinnacle of any astronaut's career and the willingness to divulge mild DCS symptoms such as pain that was not operationally limiting would be nominal. It is important to note that NASA's current policy states that any DCS symptom incurred by a crewmember or test subject who participate in hypobaric or hyperbaric operations needs to be reported [26]. It is known that under-reporting of DCS symptoms occurred in the U-2 pilot population as reporting of DCS symptoms during hypobaric operational training could lead to disqualification. This was discussed earlier in Bendrick's article on 275 U-2 pilots of whom 75% reported DCS symptoms via an anonymous questionnaire at least once in their career but rarely reported it to their Flight Surgeon [29]. Interestingly, Webb et al. in 1996 published an article citing an incidence of DCS in 77% of test-subjects undergoing the 60 min U-2 pre-breathing protocol [32]. This again highlights the disparity between operational vs. research reports of DCS and underscores that for numerous reasons, astronauts and pilots are not inclined to report every slight discomfort they experience.

However, in addition to under-reporting bias, there are valid reasons why mild symptoms of DCS may be masked during an EVA. Astronauts frequently take aspirin prior to any EVA to pre-emptively mitigate any aches or pain. In addition, the actual operation of the EMU spacesuit that the astronaut dons can be painful. It would be near difficult for an astronaut to discern pain from "pain-only" DCS vs. the natural discomfort incurred from working within the confines of the EMU. Furthermore, as most "pain-only" DCS symptoms resolve following re-pressurization after completion of the EVA, there is no driving force for astronauts to report [26].

Furthermore, it is distinctly possible that DCS has not occurred during an EVA. There is a stark contrast between a test subject wearing an O₂ mask in a shirt-sleeve training environment at 1-G and an astronaut maneuvering in an uncomfortable spacesuit in micro-G environment, surrounded by 100% O₂. One aspect to reduced incidence of DCS is simply due to limited motion in the both the Orlan (Russian) and EMU (American) spacesuits. Another possible explanation is the longer pre-breathing exposure during EVA's compared to those tested in a chamber along with exposure to a micro-gravity (μ G) environment. The latter situation is unique in that during adaptation to a μ G condition, there are substantial fluid shifts from the legs to the torso and head with a net reduction in total body water. As a response to these fluid shifts, denitrogenation may be more efficient and accelerate nitrogen wash-out from the tissues [33]. Furthermore, astronauts are physically active during their prebreathe protocols and it is well documented that exercise during prebreathe enhances N₂ washout from the tissues [34].

2.5. Acute mountain sickness

A review of clinical and MRI findings in acute mountain sickness (AMS) and high altitude cerebral edema (HACE) demonstrates parallels to recent findings in our U-2 pilots and low-pressure chamber inside safety monitors, with the hypobaric environment as the common

element. The primary difference is the presence of hypoxia in AMS and HACE. AMS generally occurs above 2500 m and has been defined by the Lake Louise Consensus Group as the presence of a headache with one or more of the following: gastrointestinal symptoms (nausea, vomiting, anorexia), insomnia, dizziness and lassitude or fatigue [35]. Determining factors include the rate of ascent, altitude reached, altitude at which a person sleeps and individual physiology. Most consider HACE to be a clinical and pathophysiologic extension of AMS. HACE is an encephalopathy, characterized by disturbances of consciousness that may progress to coma, ataxic gait, increased intracranial pressure and retinal hemorrhages.

A growing body of evidence suggests that is not only hypoxia, but hypobaria that contributes to the development of AMS [36–40]. The underlying pathophysiology of AMS remains poorly understood. Hypoxia-induced cerebral vasodilatation or its effectors, such as nitric oxide, may produce the headache, possibly via the trigeminovascular system or by causing mild cerebral edema [41–43]. Whether this edema is cytotoxic (intracellular), vasogenic (extracellular), or both remains controversial. However, MRI has demonstrated reversible abnormalities in HACE, such as areas of increased T2 and fluid-attenuated inversion recovery signal intensity within the splenium of the corpus callosum (white matter structure), with associated increased apparent diffusion coefficient (ADC) values consistent with increased water diffusivity. These findings are indicative of vasogenic edema. Hemodynamic factors such as sustained vasodilation, impaired cerebral autoregulation and elevated capillary pressure may contribute to vasogenic edema [44–47]. Hypoxia-induced biochemical alteration of the blood brain barrier may also be important. Current high altitude human research demonstrates increased cerebral blood flow after a single hypoxic hypobaric exposure to 7620 m for occupational training which persists at 72 h. These findings will be described in detail later in this chapter.

Central nervous system MRI changes demonstrated in AMS have similarity with recently published astronaut data. These include intracranial fluid redistribution, increased intracranial pressure in microgravity, and brain structural plasticity changes from pre-to-post space-flight [48–50].

2.6. Brain magnetic resonance imaging (MRI) techniques

Our original U-2 pilot brain MRI evaluations were performed on a Siemens (Siemens AG, Erlangen, Germany) Magnetom Tim Trio 3-Tesla scanner at the Research Imaging Institute (RII), University of Texas Health Science Center San Antonio (UTHSCSA), with a 12-channel phased array coil. All subsequent human and animal MRI data has been acquired on the same Siemens Magnetom Verio 3-Tesla scanner at Wilford Hall Ambulatory Surgical Center (WHASC), Joint Base San Antonio, Texas using a 32-channel phased array coil. This includes all imaging on control/normal subjects and low-pressure chamber inside safety monitors. Both scanners are operated under quality control and assurance guidelines in accordance with recommendations by the American College of Radiology.

Three-dimensional imaging parameters were for T1 magnetization prepared rapid acquisition gradient echo (MPRAGE), repetition time (TR) = 2200 ms, echo time (TE) = 2.85 ms, isotropic resolution = 0.80 mm, and for fluid-attenuated inversion recovery (FLAIR), TR = 4500 ms,

TE = 11 ms, isotropic resolution = 1.00 mm. FLAIR image processing was previously reported [2, 51–54]. WMH regions were coded as periventricular regions, contiguous with CSF structures, and as subcortical regions as previously described [57]. WMHs were quantified in number (count) and total volume.

Calibration MRI data was performed in 46 patients (CAL) on both the RII and WHASC scanners for the cross comparison and analysis of advanced imaging sequences such as diffusion imaging [5]. The calibration for the average FA values in subjects imaged on both scanners showed excellent correlation ($r = 0.85$), with coefficients of variation were similar to what has been previously reported [56, 57].

High angular resolution diffusion imaging (HARDI) was utilized for diffusion tensor imaging (DTI) and fractional anisotropy (FA) assessment as previously reported [51, 58]. Briefly, DTI data were collected using a single-shot echo-planar, single refocusing spin-echo, T2-weighted sequence with a spatial resolution of $1.7 \times 1.7 \times 3.0$ mm with sequence parameters of TE/TR = 87/8000 ms. We chose the ENIGMA-DTI analysis protocol [59] because it can effectively overcome the impact of the punctate WMH lesions on FA values compared to simple averaging of FA values within a region of interest, effectively limiting analysis of FA values to that of the normal-appearing WM. DTI is a quantitative MRI technique that has an advantage over T2-weighted fluid attenuated inversion recovery (FLAIR) imaging because it can ascertain subtle WM damage in normal-appearing WM prior to development of WMH lesions [60]. FA is a widely used quantitative measure of WM microstructure, extracted from DTI [61]. FA is an important biomarker in clinical studies as it can sensitively track WM changes in neurological and psychiatric diseases [57, 62, 63] and in normal development and aging [64].

Two additional advanced sequence techniques were used in our current hypobaric research: pseudo-continuous arterial spin labeling (pCASL) and proton magnetic resonance spectroscopy (MRS). pCASL technique is a noninvasive method for calculation of estimate cerebral blood flow which does not require intravenous contrast injection. MRS demonstrates quantifiable neurometabolite concentrations regions of interest, both gray and white matter. pCASL imaging data for gray and white matter were collected using gradient-echo echo-planar imaging with TE/TR = 16/4000 ms as previously reported [51]. Further, pCASL data were processed using the pipeline described elsewhere [65]. Perfusion-weighted images were calculated based on the methods described by others [67, 68].

Proton magnetic resonance spectroscopy (MRS) data were acquired from voxels placed in frontal white matter (FWM) and the anterior cingulate cortex (ACC). For the frontal white matter region, short TE and long TE data were acquired using point resolved spectroscopy localization (TR = 1500 ms, short TE = 30, long TE = 135 ms, number of signals averaged (NEX) = 256, volume of interest (VOI) ~ 3.4 cm³). Data were acquired in both hemispheres and averaged together. For the anterior cingulate, the same short TE point resolved spectroscopy localization parameters were used with a voxel size of 6 cm³. Standard neurometabolites were evaluated using available software and methods as previously reported [69, 70]. We have demonstrated a high degree of consistency across structural and physiological measurements with brain MRI [51].

2.7. White matter integrity in high altitude pilots exposed to hypobaria

The number and volume of WMH regions are sensitive markers of cerebral health, commonly used to study the extent of the cerebral injury [71]. Healthy cerebral white matter tracts are myelinated with compounds containing long-chain fatty acids with very short T2-relaxation time and thus appear dark on T2-weighted images. Local edema, often associated with degradation of the myelin sheath, results in localized accumulation of extracellular water, which leads to an increased signal intensity on a T2-weighted image. HWM lesions also form in normal aging, where they begin to occur during mid adulthood (fourth-fifth decade of life). In both normal subjects and patients who suffered brain injury, the number and volume of HWM lesions are correlated with a decline in cerebral integrity [72], reduction in cerebral white matter and gray matter volumes [73, 74], cerebral blood flow [75], and cerebral glucose metabolism [76]. Increasing numbers and volumes of HWM regions have also been linked to cognitive declines, particularly in executive functioning [77], processing speed [78], and general cognitive status [79], and were correlated with the severity of neurocognitive deficits in neuropsychiatric and neurological disorders [80].

The etiology of HWM is nonspecific and is commonly associated with cerebral ischemia and disruptions of cerebral circulation [81]. Histopathological findings indicate there are two distinct types of HWM lesions: subcortical and ependymal. Subcortical HWM regions are more closely associated with ischemic factors [3]. In contrast, periventricular ependymal HWM lesions are thought to be of non-ischemic origin and potentially produced by pulse-wave encephalopathy [55, 82, 83]. This condition refers to the microtears in the ependymal lining caused by the pulsatile movements of ventricular cerebrospinal fluid (CSF) [83–85].

Our initial study evaluated 50 U-2 pilots (avg. age 37.4 ± 5.2 year), 12 (avg. age 38.9 ± 6.1 year) of whom had suffered neurological decompression sickness (NDCS) [86]. The NDCS pilots demonstrated a significantly higher total WMH lesion volume ($p = 0.026$) compared to the non-NDCS pilots, but not a significant increase in total lesion count ($p = 0.120$). Analysis of the lesion by type (subcortical vs. ependymal) did not demonstrate a significant difference between NDCS pilots and non-NDCS pilots ($p = 0.059$). Examination of regional measurements revealed pilots who experienced NDCS had significantly higher number and volume of insular subcortical lesions ($p = 0.020$ and $p = 0.018$, respectively). No difference was noted in the presence of mild hypertension or mild hyperlipidemia. No difference was noted with total flight hours or average high-flight hours per month between the two groups. No pilot had a history of significant head injury, significant scuba diving history, episode of decompression illness associated with diving, or high-altitude exposure other than that associated with USAF flight duties. The initial hypothesis for the elevation of WMH volume in pilots that suffered NDCS was hypobaric-related gas microemboli ($<30 \mu\text{m}$) which may have led to loss of permeability or occlusion of small cerebral vessels and subsequent immune mediated gliosis (**Figure 2**).

What was noteworthy was the prevalence of WMHs in high altitude pilots that had not suffered NDCS, mandating comparison of high altitude pilots to a normal control group.

Subsequent MRI evaluation was performed on 105 total high-altitude U-2 pilots (U2P; mean age 37.7), 83 low pressure chamber aerospace physiology inside observers (AOP; mean age

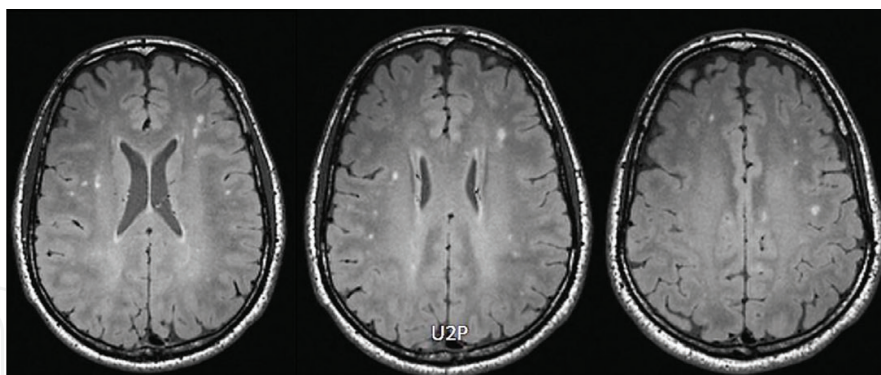


Figure 2. Axial FLAIR images demonstrating multiple subcortical WMHs in a U-2 pilot, without NDCS.

36.5) and 148 age and health matched advanced/doctorate degree control subjects (CTRL; mean age 34.6) [1, 2, 5, 6]. All study subjects were active duty members of the US Armed Forces. All participants were between the ages of 26 and 50 years, were healthy at time of study without any history of central neurologic or psychiatric disease, and had undergone a routine annual medical examination within 12 months prior to study. All participants at the time of testing met USAF Flying Class II neurological standards [87]. Briefly, exclusionary criteria for Flying Class II include a history of any of the following: head trauma with any loss of consciousness or amnesia; migraine headache; psychiatric or psychological disease requiring any medication or hospitalization; hypertension (HTN) requiring more than a single angiotensin-converting enzyme inhibitor (ACE-I) for control; hyperlipidemia (HLD) requiring more than a single statin for control; diabetes or glucose intolerance; ischemic cardiac disease; any neurological disease including infection, seizure, or stroke; any medical condition associated with neurological injury; or substance or drug abuse or dependence. All AOP had experienced >50 occupational exposures to >25,000 feet altitude. Two (2.4%) of AOP and 16 (15%) of U2P reported mission-related symptoms of NDCS. All U2P and AOP undergo standardized hypoxic hypobaric chamber exposure as part of routine aircrew qualification training every 5 years; these exposures are of 30- to 60-min duration with hypoxia relieved via 100% oxygen aviator mask with the onset of physiological symptoms. Fourteen CTRL had experienced a single episode of aircrew hypoxic hypobaric chamber exposure as part of initial flight surgeon qualification training. No subject experienced NDCS related to this periodic aircrew chamber training.

Group-wise analysis demonstrated that both AOP and U2P, two groups occupationally exposed to nonhypoxic hypobaria, had significantly elevated WMH volume/count compared to CTRL. Although the WMH volume/count were higher in U2P than in AOP, neither was statistically significant. Comparable results were obtained in group-wise analysis after excluding any subject with HTN or HLD (14 CTRL, 10 AOP and 20 U2P) and after excluding AOP or U2P who had experienced NDCS. Equivalency of U2P to AOP WMH volume was noted on the Kolmogorov–Smirnov test ($p=0.388$). The Jonckheere–Terpstra test demonstrated CTRL < PHY_U2P on WMH volume ($p=0.024$) and count ($p=0.012$); AOP < U2P was not significant ($p > 0.10$). The Spearman correlation coefficients between WMH volume/count and age and hours of hypobaric exposure were positive but not significant. Linear regression of combined

AOP and U2P total hours of hypobaric exposure versus WMH volume/count was not significant (WMH volume/count, $r_{250.002}/r_{250.009}$, respectively). The total hours of exposure were not significantly associated with WMH presence in either group. Likewise, the Spearman correlation coefficient between 2 measures of WMH burden and age were positive but not significant (all $r^2 < 0.03$; all $p > 0.10$).

Regional analysis revealed that frontal lobe lesions constituted the largest fraction of both volume and number of WMH loci in both U-2 pilots (50 and 56% for volume and number, respectively) and normative controls (69 and 70% for volume and number, respectively). This is presumably because higher metabolic demand and cerebral blood flow. Pilots had a higher volume ($p < 0.03$) of WMH in the frontal, insula, limbic, sublobar, and temporal regions and a higher number ($p < 0.01$) of WMH in the insula, limbic, temporal, and sublobar regions. WMH were normally uniformly distributed throughout the brain in U2P than in controls and did not increase with age.

The relationship between hypobaric exposure and WMH is complex. We observed no significant correlations between WMH measurements and the total number or hours of hypobaric exposure. This suggests that other factors may modulate the hypobaria-related WMH change, including hyperoxemic pre-exposure nitrogen degassing, exposure duration, level of physical and mental activity during exposure, frequency of exposure episodes, and amount of rest between exposures, as well as other yet unknown environmental and genetic susceptibility risk factors. Injury secondary to microemboli, of nitrogen gas, platelet-based thrombi or microparticles, remain a potential source of this injury.

Diffusion tensor imaging (DTI) and FA findings in U2P were noteworthy for demonstrating effects suggesting a global process, affecting normal appearing white matter, not just subcortical white matter damage, presumably secondary to repetitive hypobaric exposure. Whole-brain average FA values for all pilots were significantly lower than in controls (KS $p < 0.001$; GLM $p < 0.001$). After Bonferroni correction of p -values, we observed two regional findings: pilots had significantly decreased FA values for the sagittal striatum ($p < 0.001$), while pilots had significantly higher FA values for fronto-occipital fibers ($p = 0.003$). Functionally, the striatum coordinates multiple aspects of cognition, including motor and action-planning, decision-making, motivation, reinforcement, and reward perception. The fronto-occipital tract integrates auditory and visual association cortices with the prefrontal cortex. Other FA tracts were not significantly different.

We separated the pilots into lower two-thirds (U2PL)/upper one-third (U2P-U) based on WMH burden (U2P-L/U2P-H). There was no significant difference in WMH burden between U2P-L and controls (CTRL) (WMH volume/count $p = 0.17/0.52$, respectively), while there was a significant difference between U2P-H/U2P-L ($p < 0.001/0.001$) and U2P-H/CTRL ($p < 0.001/0.001$). Comparing FA values of U2P-H and U2P-L to CTRL demonstrated significantly lower FA values in both pilot groups for whole brain average FA ($p < 0.001/p < 0.001$, respectively, U2P-H/U2P-L) and sagittal stratum ($p = 0.005/p = 0.01$). Comparing mean values of U2P-H to U2P-L demonstrated a nonsignificant trend toward lower FA values in U2P-H than U2P-L for whole-brain average FA and all tracts except fronto-occipital where U2P-H = U2P-L).

Lower average FA findings are consistent with a diffuse disruption in white matter integrity. This finding trended with higher WMH burden previously described. Reduced sagittal striatum FA has been shown to be genetically associated with processing speed deficits in two independent cohorts [88]. We observed a decrease in processing speed in U2P compared to a USAF pilot cohort control [11] and this may suggest the reduced sagittal stratum FA in U-2 pilots may explain this decrease in processing speed. Additionally, USAF pilots are uniquely high-functioning individuals with exceptional visual-spatial abilities [89], which may account for the higher FA values in the fronto-occipital fibers in U-2 pilots, reflecting this associative cognitive ability, and provide an anatomical basis for the superior spatial performance noted in all USAF pilots. Historically, the pathophysiological theory of hypobaric related brain damage has been arterial gas emboli, but there are other recent studies which also suggest a more diffuse process [23, 90]. It is improbable that gas emboli alone could produce the diffuse disruption of axonal integrity demonstrated by our MRI findings. Our studies provide support for other potential pathophysiological explanations, including neuroinflammation and microparticle damage [91, 92].

2.8. Neurocognitive changes

WMH are also relevant surrogates for cerebral activity in neurological disorders and also normal aging. As stated earlier, these WMH have also been linked to cortical and subcortical functions particularly executive function, processing speed, overall cognition along with motor/gait function [76–78]. Therefore, we compared neurocognitive performance in U-2 pilots with repeated hypobaric exposure to pilots without repeated hypobaric exposure and also assessed whether cognitive performance correlated with severity of WMH burden. All participants were between the ages of 26–47 years old and had to meet Flying Class II standards and could not have any prior history of neurological or psychiatric disease. 106 U-2 pilots were compared against 83 active duty (AD) pilots who were also matched for age at time of cognitive testing. Computer-based Multi-Dimension Aptitude Battery-II (MAB-II) and Assessment of Cognitive Function (MicroCog) assessments were utilized. MAB-II yields an overall evaluation of neurocognitive ability based on the Wechsler Adult Intelligence Scale and generates three intelligence quotient (IQ) scores: full-scale IQ, verbal IQ and performance IQ. The MicroCog is a separate computer-based cognitive assessment that comprises 18 subsets resulting in 9 index scores. The MicroCog was specifically chosen to provide more accurate information regarding reaction time and processing speed, both critical functions to any active aviator. While there were no significant differences between U-2 and AF pilots on the MAB-II testing, there were subtle but significant differences on the Micro-Cog assessment. Specifically, U-2 pilots scored significantly in the following domains (see **Table 2**): reasoning/calculation ($p < 0.001$), memory ($p = 0.007$), information processing accuracy ($p = 0.016$), and general cognitive functioning ($p = 0.002$). Furthermore, within the U-2 pilot population, significantly lower scores on reasoning/calculation, memory, general cognitive functioning and proficiency were observed in those pilots with higher WMH burden [6]. However, it is relevant to note that despite the differences in the U-2 pilots, their overall neurocognitive performance continues to remain commensurate with age and cohort-specific normative data tempering concerns for any immediate clinical significance. The long-term sequela is unknown.

MicroCog category	U-2 pilots (n = 93)	Air Force pilots (n = 80)	p-Value, t-test (2-tailed)
Attention/mental control	104.4 ± 9.3	103.8 ± 10.8	0.696
Reasoning Calculation	99.4 ± 12.5	106.5 ± 10.9	<0.001
Memory	105.5 ± 12.5	110.9 ± 13.7	0.007
Spatial Processing	109.1 ± 9.4	109.1 ± 9.4	0.989
Reaction Time	107.3 ± 6.7	104.8 ± 9.2	0.047
IPS	103.6 ± 12.5	106.5 ± 10.5	0.100
IPA	102.1 ± 9.8	105.8 ± 10.0	0.016
GCF	103.5 ± 10.0	108.5 ± 10.6	0.002
GCP	105.4 ± 9.4	108.6 ± 10.2	0.037

IPS: information processing speed; IPA: information processing accuracy; GCF: general cognitive function; GCA: general cognitive proficiency.

Table 2. Microcognitive testing results in U-2 pilots compared to Air Force pilot controls.

2.9. Current research and future directions

Current human research is focused upon occupational exposure in military environments, specifically the serologic, neurometabolite and brain MRI changes after a single exposure to low pressure chamber altitude training (training profile as per AFI 11–403 above). Study volunteers are active duty members who have recently completed basic military training and are completing an aircrew fundamentals course prior to additional training for aircrew duties (AFC). AFC students experience hypoxia symptoms for 3–5 min to meet the training objective. An additional active duty age-matched control group (CTRL) group was also recruited. Brain MRI technique is similar to technique previously described; all performed on the same WHASC Siemens 3-Tesla scanner, with discussion of pCASL and MRS.

Preliminary evaluation of pCASL and MRS techniques has been performed on 96 AFC trainees and 68 healthy CTRL subjects. MRI evaluation was obtained 24 h before, 24 h after, and 72 h after low pressure chamber exposure and at the same time intervals for CTRL without the hypobaric exposure. A GAM which controlled for age and gender differences was used to compare the two groups. There is a statistically significant increase in cerebral blood flow (CBF) in white matter in the AFC group ($p < 0.001$). The difference is dependent upon age as a covariable, although there is no significant difference in age between the two groups ($p > 0.10$). It is possible that this might reflect a difference in central nervous system maturation. Increased CBF persists on the 72-h post exposure MRI and it is unknown how long CBF remains elevated. Findings reflect an increased metabolic demand upon the brain and suggest a transient injury from a single exposure to hypobaria. There was a significant difference in most neurometabolites within the ACC and in GSH within the FWM in aircrew personnel with hypobaric exposure as compared to controls. These differences may be representative of changes at a cellular level in response to,

or preceding, changes in blood flow to these regions versus age-related differences or differing WMH between the two groups. This remains a subject of ongoing evaluation.

2.10. Military free fall operations

U-2 pilots are not the only group at risk of DCS during operational movements or exercises. This would include our high-altitude high-opening (HAHO) and high-altitude low opening (HALO) parachutists. Due to improvements in both parachutes and life-support systems, military parachutists are now able to drop from altitudes in excess of 25,000 feet. These higher altitudes carry an increased risk of DCS. Furthermore, slow descent (HAHO operations), colder temperatures (ambient temperature at 35,000 feet is approximately -56°C), and even moderate exercise at altitude [93] increase the risk of VGE. Another practical issue is that the presence of any facial hair can impair the seal of the oxygen mask over the parachutist’s face rendering prebreathing ineffective. All parachutists engaged in military free fall (MFF) must undergo strict prebreathing protocol as outlined by Air Force Instruction (AFI) 11-409 (See Table 3 below) [94].

Furthermore, in an effort to reduce the physical demands and risk of DCS on MFF parachutists, the following military protocol was issued: (1) MFF parachutists may not conduct more than two jumps between 13,000 and 17,999 feet in a 24-h period; (2) Conduct no more than one oxygen jump above 18,000 feet in a 24-h period; (3) not conduct MFF operations within 24 h of making a non-oxygen dive and (4) not wear dark goggles on MFF operations that require prebreathing to facilitate viewing of the eyes of the jumpers by the jumpmaster to ensure they are not experiencing physiological difficulties [95]. Despite such extensive and potentially mitigating protocols there is little information in the literature regarding the actual incidence of DCS affecting parachutists engaged in HAHO or HALO operations. One small study of 10 experienced parachutists underwent blinded exposure in a hypobaric chamber to both 17,500 and 35,000 feet respectively separated by 48 h. Participants underwent 60 min 100% O_2 prebreathe, and then decompressed to respective altitude over 7 min where they remained for 15 min followed by slow descent over 35 min. They were suspended to reduplicate the effects of the harnesses on blood flow in the lower limbs. VGE detection was accomplished by precordial

Altitude	Oxygen requirement	Pre-breathe time	Maximum
10,000–12,999 feet	Aircrew: supplemental jumpers: see below ^a	N/A	Unlimited
13,000–19,999 feet	Supplemental	N/A	Unlimited
20,000–24,999 feet	100% O_2	30 min	110 min
25,000–29,999 feet	100% O_2	30 min	60 min
30,000–34,999 feet	100% O_2	45 min	30 min
35,000 feet or greater	100% O_2	75 min	30 min

^aSupplemental oxygen: parachutists/jumpers may perform unpressurized operations between 10,000 and 13,000 feet without supplemental oxygen not exceed 30 min. For unpressurized flight above 13,000 feet or exceeding the 30-min envelope between 10,000 and 13,000 feet, a continuous supply of supplemental oxygen will be used.

Table 3. AFI 11-109.

2D and Doppler echocardiography. Following exposure, the 10 parachutists then engaged in ground level moderate exercise consisting of a 4 km/h. march on a treadmill while carrying a Bergen weighing 40 lbs. While the study sample was small, there was no evidence of VGE or DCS during the altitude profile of the study and no evidence for resurgence of VGE or exercise intolerance during the ground profile of the study [96]. These findings corroborated Webb's work in 2002 that indicated that exercise at ground level would not trigger a resurgence of VGE or DCS symptoms following a 2-h exposure at an altitude of 35,000 feet [97].

2.11. Extravehicular activity (EVA)

As discussed earlier in the chapter under DCS subsection, there have been no reported cases of DCS during EVA. This concern has been mitigated using various strategies such as implementation of a lower pressure high oxygen environment utilized in the Gemini, Apollo space missions and Skylab space station coupled with single 4-h pre-launch oxygen prebreathe. This resting 4 h-in-suit prebreathe protocol [98] has been utilized six times during space-flight without reported incidents of DCS. Other protocols included the "Camp-Out" protocol (last used on May 6, 2011) which involved exposure to a mildly hypoxic environment requiring a single 40–75 min in-suit prebreathe, along with several exercise-enhanced protocols. The two most common of the exercise prebreathe protocols include the "cycle ergometer with vibration isolation and stabilization" (CEVIS) and "in-suit light exercise (ISLE) protocols. These were developed to help minimize scheduling constraints of EVA's following delivery of the International Space Station (ISS) *Quest* airlock in 2001. The theory behind these protocols is that since denitrogenation is a perfusion-limited process, the implementation of exercise into the prebreathe protocol may facilitate denitrogenation. The CEVIS protocol uses a short but intense prebreathe exercise protocol (10 min duration) utilizing cycle ergometry with escalating workload peaking at 75% $\text{VO}_{2\text{ max}}$. After completion of exercise, the astronaut then pre-breathes 100% oxygen for the next 50 min followed by depressurization to 10.2 psia in the ISS airlock over 30 min. It is during this depressurization that the spacesuit is donned. As of May 6, 2016, the CEVIS protocol has been utilized 52 times with no reported signs or symptoms of DCS. In contrast to the CEVIS protocol, ISLE prebreathe protocol replaces the bouts of short, intense exercise with longer period of mild exercise in the EMU (spacesuit). While it shares many steps with the CEVIS exercise protocol it does differ in that only 40 min are spent prebreathing followed by 20 min depressurization to 10.2 psia. Once the suit is donned, mild exercise consisting of arm and leg circular motions are performed over 4 min followed by 1-min rest period. This cycle continues for total duration of 50 min achieving a $\text{VO}_{2\text{ max}}$ of 6.8% (compared to 75% in the CEVIS protocol). This is followed by an additional 50 min prebreathe of 100% oxygen culminating in a final depressurization of the airlock to vacuum. The ISLE protocol has been used over 40 times since May 6, 2016 without any occurrences of DCS is currently the prime protocol used by the ISS [26].

These complex prebreathing protocols were designed to meet operational demands but in doing so have left knowledge gaps regarding DCS risk factors particularly in space. These include risk of bubble formation in space, micronuclei generation, implications of tissue saturation across different gas and pressure environments, and nitrogen elimination in space. Furthermore, there are numerous physiological factors to consider such as age, body habitus,

aerobic conditioning, presence of PFO, gender, hydration status and even timing of menstrual cycle that can influence the development of DCS in a hypobaric environment or vacuum such as space. The relative risk and importance of these physiologic risk factors in the genesis of DCS is unknown until a multivariate analysis such as logistic regression or survival analysis is undertaken. Lastly, these DCS risk-mitigation protocols will not likely be sufficient or applicable to future space exploration missions that utilize suitports, variable pressure suits, and require the ability to rapidly deorbit for medical therapy. Historically EVA has been a single event in a flight day. However, the standard operational concept for future exploration missions is the possibility of multiple EVA's in 1 day or performing a single EVA several days in a row. Development of the Exploration Atmosphere coupled with use of suitports is going to push the boundaries of EVA operations and the subsequent potential risk of DCS is unknown [26].

3. Conclusion

Over the past 50–60 years, we have seen rapid developments in our aeronautics and space capabilities with planes such as the U-2S operating in the stratosphere along with the launch of the International Space Station in 1998. As we push the technical boundaries to attain various strategic and tactical advantages, we need to remain wary of the physiological effects that extreme and austere environments can impose on our military personnel and astronauts. While the effects of hypobaria and decompression sickness have been known for decades (brought to the forefront by Fulton's seminal work in 1951 [22]), the increase in NCDS experienced by our U-2 pilots from 2006 to 2010 has brought increased scrutiny. Furthermore, the findings of increased WMH coupled with subtle but significantly lower neurocognitive profiles (even among those that did not experience a clinical event of NCDS) heightens the concerns regarding the short and long-term effects that recurrent exposure to hypobaria carries. While the physiology has classically been thought to be secondary to VGE, other inflammatory factors may likely play a role which are being actively investigated. If elucidated, this allows the development for other therapeutic interventions in addition to the numerous prebreathing protocols to mitigate the risk of DCS. This has major significance for both military operations and further space exploration as we continue to press both the technological boundaries as well as our equipment and physiological limits of our personnel.

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Conflict of interest

Neither Dr. Sherman nor Dr. Sladky report any conflicts of interest.

Author details

Paul Sherman* and John Sladky

*Address all correspondence to: paul.m.sherman3.civ@mail.mil

711th Human Performance Wing, United States Air Force School of Aerospace Medicine,
Dayton, Ohio, United States

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