WHITE MATTER HYPERINTENSITIES IN ASTRONAUTS: POSSIBLE IMPLICATIONS FOR FUTURE SPACE OPERATIONS

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INTRODUCTION

White matter hyperintensities (WMH) are lesions in the brain that show up as areas of increased brightness when visualised by T2-weighted or fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI). WMH commonly form in normal aging, increasing in prevalence from 11-21 percent at 64 years of age to 94 percent at 82 years of age.[1,2] They are more common in those with small vessel disease and cardiovascular risk factors, and they display heritability of up to 76 percent.[3]

Pathologically, WMH represent local oedema, often secondary to demyelination and axonal loss. Based on aetiology and region, they can be subdivided into two distinct types: deep (DWMH) and periventricular (PWMH). DWMH occur in subcortical areas and are typically associated with small vessel disease.[4] PWMH occur in ependymal areas and are believed to be caused by ventricular cerebrospinal fluid (CSF) pulsations leading to microtears in the ependymal lining.[5] In normal aging, WMH predominantly affect the frontal lobe, whereas diffuse WMH tend to indicate other aetiologies.[6,7]

WMH are important markers of loss of cerebral integrity. They are significantly associated with increased stroke risk, cognitive decline (globally as well as in the domains of executive function and processing speed), dementia, and mortality.[8] Thus, as a non-invasive clinical test, they may be useful in prompting detailed screening for cardiovascular risk factors. In research, they may be a useful intermediate marker to test the efficacy of novel preventative therapies.

Recently, WMH have been found at a greater incidence in high-altitude U-2 pilots. Here we discuss these findings and hypothesise that, given the similarities between U-2 flight and extravehicular activities (EVAs) operating conditions, WMH is a phenomenon that may be relevant to the future astronauts of exploration missions that are currently being planned.

WMH IN HIGH-ALTITUDE PILOTS

In 2013, McGuire et al. discovered a greater incidence of DWMH in high-altitude U-2 pilots compared to healthy controls.[9] This finding was present even in U-2 pilots who had not suffered from clinical neurological decompression sickness (DCS). A subsequent study confirmed the same finding in hypobaric chamber personnel, providing strong evidence that the WMH are related to hypobaric exposure, rather than other potentially confounding aviation-related factors like hypoxia, high sustained positive acceleration, radiation, or use of stimulant drugs.[10]

The volume of WMH lesions was greater in U-2 pilots who had experienced neurological DCS, suggesting that the two may be pathologically related.[11] In contrast to the predominantly frontal WMH in healthy controls, the WMH in pilots were uniformly distributed throughout the brain in subcortical areas. This is consistent with the aetiological hypothesis of a diffuse process such as thrombosis, coagulation, and/or inflammation, secondary to microembolic nitrogen gas bubbles formed during hypobaric exposure. A study of fractional anisotropy in this cohort demonstrated diffuse white matter damage beyond the punctate damage implied by WMH, adding weight to this hypothesis.[12]

WMH in U-2 pilots were found to be associated with subclinical neurocognitive decline, specifically in the domains of reasoning/calculation, memory, information processing accuracy, and general cognitive functioning.[13] The natural history (i.e. reversibility versus progression) and long-term consequences of hypobaria-induced WMH remain unknown, so further follow-up of this cohort is strongly recommended. Given their distinct underlying pathological process, it is difficult to predict if hypobaria-induced WMH display the familiar associations of stroke, progressive cognitive decline, and mortality present for age-induced WMH.

U-2 OPERATING CONDITIONS

The U-2 high-altitude reconnaissance aircraft is operated by the United States Air Force above 21,000 m (70,000 ft).[14] Prior to 2014, cabin altitude was maintained at approximately 9,000 m (30,000 ft), equivalent to 30.3 kPa (4.4 psia). The cohort of pilots studied by McGuire et al. were exposed to these hypobaric conditions for up to nine hours at a time, no more often than every third day.[10] Hypobaric chamber technicians were exposed to similar altitudes at similar frequencies, but with durations of only 30 to 60 minutes.

In order to mitigate DCS risk, U-2 pilots undergo a pre-breathe (PB) of 100% O_2 for one hour prior to take-off. U-2 pilots may also exercise during oxygen prebreathing to increase the efficiency of nitrogen washout.[15] The pilots are maintained on 100% O_2 for the duration of the flight, which ensures normal arterial oxygenation and ongoing protection from DCS.[16]

In 2014 the Cockpit Altitude Reduction Effort (CARE) drove aircraft modifications to increase cabin pressure to 57.9 kPa (8.4 psia), a 4,450 m (14,600 ft) altitude equivalent.[17,18] This was deemed necessary due to increasing DCS incidence in the preceding decade, presumed to be secondary to increasing mission frequency and duration. Since the implementation of Project CARE, there have been no further cases of DCS in U-2 pilots reported publicly. WMH have not been investigated in newer U-2 pilots who have only been exposed to these higher pressures.

WMH IN ASTRONAUTS

EVA Operating Conditions

Astronauts performing an EVA are exposed to hypobaric conditions similar to those for U-2 pilots (Table 1). An EVA is undertaken in a gas-pressure suit, of which two models are currently in use: the NASA Extravehicular Mobility Unit (EMU) and the Russian Orlan spacesuit. These suits operate at 29.6 kPa (4.3 psia) and 40 kPa (5.8 psia) respectively, subjecting astronauts to significant decompression from the 101.4 kPa (14.7 psia) Earth-normal atmosphere on the International Space Station (ISS) (pressure delta 71.7 kPa [10.4 psia] and 61.4 kPa [8.9 psia] respectively).[19] Such low operating pressures are used in EVA suits because with current suit design, higher pressures cause fatigue, reduced mobility and dexterity, and increased risk of injury. Hypobaria duration is similar to U-2 pilots, with an EVA typically lasting for around 4 to 8 hours. The longest EVA on record is 8 hours and 56 minutes.[20]

These operating conditions result in a high risk of DCS. Like for U-2 pilots, this risk is mitigated with PB techniques that aim to achieve adequate denitrogenation prior to decompression. The primary protocol in use on the ISS is the in-suit light exercise (ISLE) protocol, which involves a 190-minute PB of 100% O_2, including 50 minutes of mild in-suit exercise.[19] Other available protocols include a simple in-suit 4-hour PB of 100% O_2, and the campout protocol, in which the two EVA crewmembers sleep in the ISS airlock at reduced pressure during the night prior to EVA in order to reduce the in-suit PB duration.

DCS Incidence in Astronauts

No DCS has been reported in astronauts undertaking EVAs using any of these PB protocols.[19] However, a discrepancy exists between operational and research reports, in that research subjects evaluating the same PB protocols in hypobaric chambers report about 20% DCS.[21] Various reporting factors may be responsible for this disagreement, including DCS symptom under-reporting, masking by spacesuit-related symptoms, premedication with anti-inflammatories, and mild symptom severity and progression unconducive to reporting. Additionally, factors related to the spaceflight environment may truly reduce the incidence of DCS in orbit. The most prominent of these is the lack of lower limb motion during EVA which likely limits DCS and venous gas embolism (VGE) from the lower body. More conservative PB performed in space may also contribute. Anatomical and physiological changes in microgravity may result in more efficient denitrogenation, and various other operational factors related to the in-suit atmosphere composition and temperature may be significant.

Ultimately, the effect of the spaceflight environment on denitrogenation efficacy and DCS incidence is unknown.

WMH Incidence in Astronauts

Given the aforementioned similarities between the parameters of EVA and U-2 operations (pressure delta and hypobaria duration), it is reasonable to wonder whether WMH may also be occurring in astronauts. Indeed, an initial study found an increased incidence of WMH in twenty-one astronauts at even greater levels than in U-2 pilots.[22] However, there was no significant difference between WMH burden in EVA and non-EVA astronauts, suggesting that hypobaria is not the primary driver of WMH in this population. A subsequent study clarified that astronauts tend to have increased PWMH but no increased DWMH.[23] This is likely related to unique characteristics of the spaceflight environment such as cephalad fluid shift in microgravity increasing hydrostatic pressure from CSF into brain parenchyma, and shear forces from launch vibration disrupting the CSF-brain interface.

The PWMH were associated with increased ventricular CSF volume and demonstrated partial reversibility at one month. In contrast, the absence of increased DWMH in EVA astronauts, despite the exposure similarities with U-2 pilots, suggests the presence of protective factors.

One possible explanation for the lack of DWMH findings in astronauts could be the significantly reduced frequency at which EVAs are undertaken,

compared to that of flying in the U-2 pilot cohort. Historically, any individual astronaut will perform an EVA at most four times per year, usually with weeks or months elapsing between each occasion (though some astronauts have performed multiple EVAs within the space of a week).[20] While McGuire et al. found no correlation between the DWMH burden and number of flight hours in the U-2 pilot cohort, it could be that there is a minimum threshold of hypobaric exposure frequency that is required for DWMH to develop in the first instance, which current astronauts have not exceeded.[9]

Furthermore, the same factors which are hypothesized to be responsible for the lack of DCS in astronauts could also play a role in reducing DWMH incidence. More extensive PB protocols and the various factors related to the spaceflight environment discussed previously could be resulting in less stressful hypobaric exposures than in the U-2 pilot cohort, protecting astronauts from DWMH development.

Implications for Future Space Operations

Future space operations will introduce largely different operating conditions for astronauts, so that despite the absence of DWMH found in the current astronaut population, the relevance of DWMH must still be considered. Most notably, future surface exploration missions (i.e. to the Moon and Mars) will likely require significantly increased EVA frequency, up to multiple times per person per day. In order for this to be logistically feasible while meeting acceptable DCS risk, significantly altered spacecraft, habitat, in-suit atmospheres, and PB protocols will be required.

The basis of future EVA architecture development is an 56.5 kPa (8.2 psia) / 34% O_2 Exploration Atmosphere, which has been selected as a compromise to reduce the pressure delta for EVA, while maintaining astronaut oxygenation status and acceptable fire risk.[24] This would be combined with the use of a variable pressure EVA suit and suitports to allow for highly efficient donning and doffing procedures.[25] The suit would be decompressed to 29.6 kPa (4.3 psia) for most of the EVA duration, although more work is being done to quantify the human health and performance impacts of using higher suit pressures. Model predictions suggest that a 15-minute O_2 PB protocol would be sufficient to maintain DCS risk below currently acceptable levels.[25] Furthermore, performing multiple EVAs per day would result in intermittent recompression, which has been shown to reduce decompression stress under some circumstances.[26]

While the use of the Exploration Atmosphere does significantly reduce pressure delta (26.9 kPa [3.9 psia]), all other factors make these operating conditions more comparable with U-2 flying than are ISS EVAs (see Table 1). EVA duration will likely remain equivalent, but EVA frequency and cumulative hours could exceed those of U-2 pilots. Furthermore, unlike ISS EVAs, exploration EVAs will involve gravity and lower limb movement. Taken together, these operational similarities warrant concern about the relevance of DWMH to future astronauts.

Table 1: Comparison of operating conditions for U-2 aircraft, ISS EVA, and proposed exploration EVA.

	U-2 Aircraft	ISS EVA	Exploration EVA
Baseline pressure	14.7 psia	14.7 psia[19]	8.2 psia[24]
Operating Pressure	*Before CARE:* 4.4 psia *After CARE:* 8.4 psia	4.3 psia / 5.8 psia[19]	4.3 psia[25]
Pressure delta	*Before CARE:* 10.3 psia *After CARE:* 6.3 psia	10.4 psia	3.9 psia
Pre-breathe	100% O_2 for one hour[15]	Various	100% O_2 for 15 mins[25]
Operating FiO_2	100% O_2[16]	100% O_2[19]	100% O_2[25]
Gravity	Minimal	0 G	Moon: 0.16 G Mars: 0.38 G
Lower limb movement	Minimal	Minimal	Significant
Exposure frequency	Frequent, no more often than every third day[10]	Up to four times per year, usually weeks/months apart[20]	Frequent, up to multiple times per day
Exposure duration	Up to 9 hours[10]	4-8 hours[20]	4-8 hours with intermittent recompression[26]

Mechanical Counterpressure (MCP) Suits

MCP suits are an emerging alternative to traditional gas-pressure suits. They work by application of mechanical pressure directly to the skin, rather the maintenance of an atmosphere surrounding the skin. The technology is in development at MIT, called the BioSuit, but it is considered to be a long-term project with no foreseeable completion date. The BioSuit aims to uniformly apply 30.3 kPa (4.4 psia) to all body surfaces, except for the head and the hands which will be contained within gas-pressure enclosures.[27] While this does seem to be a promising solution for mobility and aesthetics, there is no obvious benefit in terms of the pressure delta to which astronauts will be subjected. Furthermore, the technology may be imperfect, resulting in localized areas of under- or over-pressure. The effects that this may have on DCS

and WMH risk are unknown. Speculatively it seems that even small areas of under-pressure could precipitate local nitrogen bubble formation, and areas of over-pressure could perhaps impair nitrogen washout. Therefore, even with MCP suits on the distant horizon, it seems that further work regarding DWMH is justified.

Knowledge Gaps

In order to confidently understand the relevance of DWMH to the current and future astronaut population, more knowledge about their pathophysiology, incidence, and long-term consequences is required.

More understanding of the pathophysiology behind DWMH is necessary to model risk for future EVA architectures. McGuire et al. suggest that an animal model could be developed to better understand the responsible mechanisms.[10] In humans, the link between VGE and DCS has been well studied, and although the exact nature of the relationship remains unclear, VGE appears to have high negative predictive value (i.e. the absence of VGE predicts that DCS will not occur).[28] However, this relationship does not appear to hold for neurological DCS, and the link between VGE and WMH has not been studied.[29] Therefore, prospectively monitoring VGE incidence in U-2 pilots or hypobaric chamber technicians with respect to the development of WMH could enhance pathophysiological understanding. If an association was to be found, then VGE may have potential as an intermediate marker for further DWMH research, especially on astronauts.

Learning more details about the incidence of DWMH in different groups exposed to hypobaria may also shed some light on its pathophysiology. For example, patent foramen ovale (PFO) is present in about 25% of the general population and can result in cerebral arterial gas embolism, but has not been analysed for its effect on DWMH incidence.[30] Further studies on U-2 pilots that only started training after the implementation of CARE in 2014 would be of interest to understand the effect of a smaller pressure delta, closer to those being proposed for future EVA architectures. If DWMH incidence remains elevated, prospectively following a cohort of new U-2 pilots, or new hypobaric chamber technicians, could reveal how much hypobaric exposure is required before DWMH develop.

Long-term MRI surveillance should be performed on the current and future astronaut population to see if DWMH or other imaging changes develop exclusively to those who have undertaken EVA. Long-term clinical monitoring of U-2 pilots with and without DWMH will be essential to understand the potential implications for future astronauts. If the disease associations did turn out to be similar to those of WMH in the general population (stroke, cognitive decline, death), the consequences for a long-term space colony could be potentially devastating.

Conclusion

WMH are important markers of loss of cerebral integrity and have significant disease associations in the general population. Hypobaria-induced WMH likely indicate subclinical decompression stress although the mechanisms of their formation are still unclear. While they have not been observed in astronauts under current EVA operating conditions, they should be considered in the context of future mission planning. More work is required to understand why they occur, their relevance to astronauts, and what the long-term implications may be.

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