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Effects of the 8 psia / 32% O_2 Atmosphere on the Human in the Spaceflight Environment

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Acronyms

ADP	adenosine diphosphate
AFT	Advanced Food Technology
AMS	acute mountain sickness
ARED	advanced resistive exercise device
ATP	adenosine triphosphate
CBF	cerebral blood flow
CHeCS	Crew Health Care System
CHI	Crew Health Index
CMS	Countermeasures System
CNS	central nervous system
CO_2	carbon dioxide
CRT	complex reaction time
CSA-CP	compound-specific analyzers for combustion products
CSA-O_2	compound specific analyzers for oxygen
CSF	cerebrospinal fluid
DCS	decompression sickness
DRATS	Desert Research and Technology Studies
DRM	design reference mission
EAA	equivalent air altitude
EAWG	Exploration Atmospheres Working Group
ECLSS	Environmental Control and Life Support Systems
EHS	Environmental Health System
EMU	extravehicular mobility unit
EVA	extravehicular activity
EVAC	evacuation
ExMC	Exploration Medical Capability
HEOMD	Human Exploration and Operations Mission Directorate
HH	hypobaric hypoxia
HHP	Human Health and Performance
HIF-1	hypoxia-inducible factor 1
HMS	Health Maintenance System

HRP	Human Research Program
HUT	hard upper torso
ICP	intracranial pressure
IMM	Integrated Medical Model
ISS	International Space Station
IVA	intravehicular activity
JSC	Johnson Space Center
kPa	kilopascals
LEO	low-Earth orbit
LET	low-linear energy transfer
LLSQ	Lake Louise symptom questionnaire
LOCL	loss of crew life
LSAH	Lifetime Surveillance of Astronaut Health
NEA	near-Earth asteroid
N_2	nitrogen
mmHg	millimeters of Mercury
MMSEV	Multi Mission Space Exploration Vehicle
NEA	near-Earth asteroid
NH	normobaric hypoxia
NSBRI	National Space Biomedical Research Institute
OSaD	oxidative stress and damage
O_2	oxygen
P_AO_2	alveolar O_2 partial pressure
PH_2O	water vapor partial pressure
P_IO_2	inspired O_2 partial pressure
ppO_2	partial pressure of O_2
psia	pounds per square inch absolute
SaO_2	O_2 saturation
SMAC	Spacecraft Maximum Allowable Concentration
SMEMCL	Space Medicine Exploration Condition List
TBDM	Tissue Bubble Dynamics Model
UPR	unpressurized rover

VGE	venous gas emboli
VIIP	visual impairment/intracranial pressure
VO_2max	maximal O_2 consumption

Executive Summary

Extravehicular activity (EVA) is at the core of a manned space exploration program. Some elements of exploration may be safely and effectively performed by robots, but certain critical elements will require the trained, assertive, and reasoning mind of a human crewmember. To effectively use these skills, NASA needs a safe, effective, and efficient EVA component integrated into the human exploration program. The EVA preparation time should be minimized and the suit pressure should be low to accommodate EVA tasks without undue fatigue, physical discomfort, or suit-related trauma. Commissioned in 2005, the Exploration Atmospheres Working Group (EAWG) had the primary goal of recommending to NASA an internal environment that allowed efficient and repetitive EVAs for missions that were to be enabled by the former Constellation Program. At the conclusion of the EAWG meeting, the 8.0 psia and 32% oxygen (O_2) environment were recommended for EVA-intensive phases of missions.

As a result of selecting this internal environment, NASA gains the capability for efficient EVA with low risk of decompression sickness (DCS), but not without incurring additional negative stimulus of hypobaric hypoxia to the already physiologically challenging spaceflight environment. This paper provides a literature review of the human health and performance risks associated with the 8 psia / 32% O_2 environment. Of most concern are the potential effects on the central nervous system including increased intracranial pressure, visual impairment, sensorimotor dysfunction, and oxidative damage. Other areas of focus include validation of the DCS mitigation strategy, incidence and treatment of acute mountain sickness (AMS), development of new exercise countermeasures protocols, effective food preparation at 8 psia, assurance of quality sleep, and prevention of suit-induced injury.

As a first effort, the trade space originally considered in the EAWG was reevaluated in an effort to find ways to decrease the hypoxic dose by further enriching the O_2% or increasing the pressure. After discussion with the NASA engineering and materials community, it was determined that the O_2 could be enriched from 32% to 34% and the pressure increased from 8.0 to 8.2 psia without significant penalty. These two small changes increase alveolar O_2 pressure by 11 mmHg, which is expected to significantly benefit crewmembers. The 8.2/34 environment (inspired O_2 pressure = 128 mmHg) is also physiologically equivalent to the staged decompression atmosphere of 10.2 psia / 26.5% O_2 (inspired O_2 pressure = 127 mmHg) used on 34 different shuttle missions for approximately a week each flight. Once decided, the proposed internal environment, if different than current experience, should be evaluated through appropriately simulated research studies. In many cases, the human physiologic concerns can be investigated effectively through integrated multi-discipline ground-based studies. Although missions proposing to use an 8.2/34 environment are still years away, it is recommended that these studies begin early enough to ensure that the correct decisions pertaining to vehicle design, mission operational concepts, and human health countermeasures are appropriately informed.

Purpose

The purpose of this report is to evaluate the human health and performance implications associated with the proposed exploration environment of 8.0 psia / 32% O_2 through a combination of literature review and analysis.

Background

Over the past several decades, NASA has operated spacecraft habitable elements and spacesuits at a variety of different atmospheres. Early missions during the Gemini and Apollo programs were short duration and relied on low pressure, pure O_2 environments. Skylab missions were longer in duration, but still employed a low pressure (5 psia), high O_2 (70%) environment. NASA's more recent programs, including the Space Shuttle Program and International Space Station (ISS) programs have operated at an Earth equivalent sea level atmosphere of 14.7 psia and 21% O_2. Selection of this atmosphere facilitated international partnerships and allowed in-flight scientific studies to have ground-based controls, with gravity as the primary variable of interest.

In 2005, the EAWG was convened to formulate recommendations on the designs of habitable internal environments to feed requirements for the development of vehicles during the Constellation Program [1]. The process used to select among several candidate environments is detailed in the EAWG final report, which was first published as an internal NASA document [2] and then later as a NASA Technical Paper [1]. The primary trade space applied to the EAWG analysis for the lunar and Mars habitat and surface spacesuit designs were hypoxia, flammability, and DCS.

The EAWG recommendations were as follows:

- Launch and transport vehicle should operate within the existing ISS and shuttle standard environment designs of 14.7 psia / 21% O_2 and 10.2 psia / 26.5% O_2
- Lunar and Mars landers should operate at both 10.2 psia / 26.5% O_2 and 8.0 psia / 32% O_2
- Surface spacesuits should operate at 100% O_2 and at a pressure range of 3.5 to 8.0 psia
- Long-duration lunar and Mars habitats should operate at 8.0 psia / 32% O_2 nominally with an option to depress further to 7.6 psia / 32% O_2
- Atmospheric recommendations assumed a control box of ± 0.2 psia total pressure and ± 2.0% O_2 concentration

The consensuses coming out of the EAWG were the recommendations for a lower pressure surface habitat and a surface spacesuit with a variable operating pressure range. The 8 psia / 32% O_2 (henceforth referred to as 8/32) environment was selected because it was considered to be a mildly hypoxic dose with acceptable flammability risk and low O_2 prebreathe overhead to maintain acceptable DCS risk [1]. The proposed forward work related to human physiology was almost solely related to DCS, with no mention of hypoxia research.

The EAWG recommendations were developed through a multi-discipline working group and concurred upon by the heads of the Johnson Space Center (JSC) Engineering, Space and Life Sciences, and Flight Crew Operations Directorates as well as the manager of the JSC Extravehicular Activity Office. However,

attempts to move forward with vehicle designs based on the EAWG report were met with mixed approval because the recommendations were not captured anywhere outside of the Constellation Program documentation. Mixed approvals were the case until the recent memorandum by NASA Human Exploration and Operations Mission Directorate (HEOMD) Associate Administrator, which directed programs under HEOMD to begin the work to enable the updated Exploration Atmosphere of 8.2 psia and 34% O_2 [3]. Although forward work will focus on the 8.2/34 environment, the purpose of this paper is still to document the human health and performance impacts of the 8/32 environment. Understanding these potential impacts led to the less-hypoxic 8.2/34 environment and highlights the remaining human performance concerns that still need to be addressed to enable an Exploration Atmosphere for long-term human habitation.

Why and When 8/32

Multiple reasons were proposed for the use of the 8/32 environment. A primary benefit of this atmosphere is a reduction in O_2 prebreathe requirements for EVA. With the 8/32 option, it is expected that a 15-minute prebreathe may be all that is necessary to achieve acceptable risk of DCS during EVA. An 8 psia cabin pressure also allows operational use of a suitport, which greatly reduces the complexity and overhead associated with EVA suit donning. The current expectation is that an astronaut could don the EVA suit through a suitport and complete all necessary checkout procedures and EVA prep during this 15-minute prebreathe window. Also, suitport-compatible suits are proposed to be variable-pressure suits capable of operating from the 8 psia cabin pressure down to the expected EVA-operating suit pressure of 4.3 psia. A variable-pressure suit also provides immediate treatment capability for DCS, because the suit could be repressurized to 8 psia in the field without requiring reentry into the cabin. Furthermore, the short transition times between suit and cabin allow for intermittent recompressions, further reducing the risk of DCS.

Beyond control of DCS to acceptable risk levels, the 8/32 environment coupled with suitport operations is a paradigm shift from NASA's ISS and shuttle EVA protocols. Unlike the ISS construction and maintenance EVAs, which were well understood and very specific, exploration EVAs will be driven by choices made at the destination. Exploration crews need a robust and flexible EVA capability, which is provided by coupling the 8/32 environment with suitport operations. This combination provides an on-demand EVA capability including short-duration EVA, multiple EVAs per day, and single-person EVA.

Application of the 8/32 environment is only needed during high EVA-frequency phases of a mission. The 8/32 environment is not needed for launch or transit to the destination, although the capability should be considered for all habitable elements to ensure transitions between different elements can be accomplished during contingency situations. Currently, any element expected to operate at the 8/32 environment (other than the EVA suit) will also be capable of repressurizing and operating at 14.7 psia and 21% O_2.

Important Changes since the 2006 EAWG Final Report

Much has changed at NASA since the 2006 EAWG recommendations, including cancellation of the Constellation Program, development of the Multi Mission Space Exploration Vehicle (MMSEV) concept,

movement toward a Capability-Driven Framework for space exploration, advances in our understanding of human adaptation to the spaceflight environment, and the identification of new human risks and hazards.

Constellation Program Cancellation

One of the largest changes since the EAWSG was the cancellation of the Constellation Program. This program featured a clear target at the moon with rapidly evolving operational concept development. The requirement for an Exploration Atmosphere of 8/32 was kept in the Constellation Architecture Requirements Document. It is difficult to quantify how much this affected implementation of the EAWG recommendations for vehicle requirements, research, and development. It could be that discontinuity with personnel in the intervening years coupled with a change from a well-defined lunar target to a Capability-Driven Framework contributed to some of the concerns about using the EAWG report as an approved baseline.

MMSEV and Suitport Development

Over this same time period, new space exploration vehicles and spacesuits were designed and developed in accordance with the recommendations from the EAWG. One of these vehicles is the MMSEV, which initially started out as a small pressurized rover for the lunar environment. It has since developed additional capability beyond lunar and Mars surface operations to now include variants with operating capacity in the microgravity environment as well, either as a way-station habitat or as a near-Earth asteroid (NEA) exploration vehicle. The MMSEV assumed the 8/32 environment as the NASA baseline and has developed both the suitport and a variable pressure rear-entry suitport compatible EVA suit. Use of a variable pressure EVA suit with suitport enabled by the 8/32 internal environment yields several benefits. From an operational standpoint, NASA gains the capability for single-person EVA, short EVA, multiple EVAs in a single day, enhanced waste removal using a suitport transfer module, reduced consumables, and high work efficiency index. In terms of safety, there is reduced overhead for meeting acceptable DCS risk, multiple vehicle reentry points, and immediate capability for DCS treatment through repressurization of the EVA suit.

Corrected EAWG Equivalent Air Altitudes

One reason for the general agreement in the 2005 to 2006 timeframe was that the 8/32 environment represented a mild hypoxic exposure because the assigned equivalent air altitude (EAA) was thought to be 1,524 m (5,000 ft) [1] [2]. However, the EAA was based on ambient dry-gas partial pressure of O_2 (ppO_2) instead of inspired O_2 partial pressure (P_IO_2) under conditions where the fraction of inspired O_2 (F_IO_2) was ≠ 0.209. In other words, the breathing gas was not air but enriched O_2 at low ambient pressure (P_B). Simply referencing an air altitude table with the correct hypoxic ppO_2 [4] did not completely account for the contribution of water vapor partial pressure (PH_2O) found to reduce ppO_2 at higher altitude. The error was recently discovered, long after completing the in-house and external reviews of recommendations from the EAWG.

The EAA for the 8/32 environment is actually slightly more than 1,830 m (6,000 ft), which properly accounts for a water vapor pressure (PH_2O) of 47 mmHg at 37°C (98.6°F) to reduce ppO_2 at 8.0 psia while breathing 32% O_2. The computed P_IO_2 for this condition is 117 mmHg through the equation: $P_IO_2 = (P_B – 47) * F_IO_2$, where P_B is ambient pressure of 414 mmHg (8.0 psia), 47 mmHg is PH_20, and F_IO_2 is 0.32,

the dry-gas fraction of inspired O_2. A P_IO_2 of 117 mmHg is equivalent to breathing air at an altitude of 1,880 m (6,170 ft), as indicated in the air altitude table (Figure 1) [5]. Most experts would still consider this exposure mild hypoxia.

10.3 ALTITUDE-PRESSURE TABLE

(1) Altitude m	(2) Altitude ft.	(3) P_B mm Hg	(4) (P_B–47) mm Hg	(5) .209 (P_B–47) mm Hg
0	0	760	713	149
610	2000	707	660	138
1220	4000	656	609	127
1830	6000	609	562	118
2440	8000	564	517	108
3050	10000	523	476	100
3660	12000	483	436	91
4270	14000	446	399	83
4880	16000	412	365	76
5490	18000	379	332	69
6100	20000	349	302	63
6710	22000	321	274	57
7320	24000	294	247	52
7930	26000	270	223	47
8540	28000	247	200	42
9150	30000	226	179	37
9760	32000	206	159	33
10370	34000	187	140	29
10980	36000	170	123	26
11590	38000	155	108	23
12200	40000	141	94	20
12810	42000	128	81	17
13420	44000	116	69	14
14030	46000	106	59	12
14640	48000	96	49	10
15250	50000	87	40	8
19215	63000	47	0	0

Footnotes to Altitude-Pressure Table

(1) Altitude in meters.

(2) Altitude in feet.

(3) P_B = Barometric pressure – U.S. Standard Atmosphere.

(4) (P_B–47) = (a) Total pressure of the dry gases after the inspired gas has been saturated with water vapor at 37° C.

= (b) Also equal to the inspired O_2 tension, P_{IO_2}, when pure oxygen is inspired.

(5) .209 (P_B–47) = Inspired O_2 tension, P_{IO_2}, when air is breathed.

Source of data: W. G. Brombacher Nat. Adv. Com. Aer. Report 538, 1935.

Figure 1. Equivalent Air Altitude Table.

In the EAWG report (NASA TP-2010-216134) [1], there are several instances (page 1, page 16 Table 10, page 116) and various places in JSC-63309 [2]), where the assigned EAA was based on ambient dry-gas ppO_2 instead of P_IO_2 under conditions where F_IO_2 was ≠ 0.209. Table 1 lists the atmospheres in Table 10 from NASA-TP-2010-216134 and shows the incorrect EAA based on ppO_2; Table 2 shows the correct EAA based on P_IO_2. The correct values for EAA should be substituted for the incorrect values when one reads References 1 or 2. Both of these tables use the equations where $ppO_2 = P_B * F_IO_2$ and $P_IO_2 = (P_B - 47) * F_IO_2$.

Table 1. Incorrect EAA Based on ppO_2

P_B psia (mmHg)	F_IO_2	ppO_2 psia (mmHg)	Incorrect EAA (m)	Incorrect EAA (ft)
10.2 (527)	0.265	2.70 (140)	1067	3,500
8.0 (414)	0.32	2.56 (132)	1524	5,000
7.6 (393)	0.32	2.43 (126)	1981	6,500

Table 2. Corrected EAA Based on P_IO_2

P_B psia (mmHg)	F_IO_2	P_IO_2 psia (mmHg)	Incorrect EAA (m)	Correct EAA (ft)
10.2 (527)	0.265	2.46 (127)	1268	4,160
8.0 (414)	0.32	2.27 (117)	1880	6,170
7.6 (393)	0.32	2.14 (111)	2286	7,500

Physiologists talk about O_2 partial pressure in terms of "wet" inspired O_2 partial pressure, designated as P_IO_2, or even alveolar O_2 partial pressure (P_AO_2). As evidence, P_IO_2 is how the risk of AMS is discussed in the Conkin and Wessel critique of the equivalent air altitude model [6]. Engineers talk about O_2 partial pressure in terms of dry-gas ambient O_2 partial pressure, designated as ppO_2. Engineers prefer ppO_2 because this is what Environmental Control and Life Support Systems (ECLSS) O_2 sensors provide. This results in potential confusion when interpreting hypoxic ppO_2, especially when an $F_IO_2 \neq 0.209$ is combined at higher altitude while the contribution of saturated tracheal water vapor pressure at reducing P_IO_2 becomes increasingly more significant at lower P_B.

For example, the current NASA STD 3001 Vol. 2 (V2 6003, below) requires a sustained ppO_2 of 155 mmHg (3.0 psia) or higher. At 8.0 psia, an ECLSS sensor would read 155 mmHg and meet this standard, but the P_IO_2 would be slightly hypoxic at 137 mmHg (normoxic P_IO_2 = 149 mmHg). Modification of this NASA standard is required in two ways. First, if the overall goal is to maintain physiologic normoxia, then the standard should be updated into a table that accounts for differences in ppO_2 and P_IO_2 as a function of P_B and the lung PH_20 of 47 mmHg should be included. Second, the use of an alternative exploration environment, such as 8/32, is currently precluded by this standard. Thus, the standard needs to be updated to reflect that for certain high EVA content phases of a mission, a mildly hypoxic environment can be used for a given period of time. Research will be needed to determine the acceptable duration for an alternative exploration environment.

> **"6.2.1.2 O_2 Partial Pressure Range for Crew Exposure [V2 6003]**
>
> The system **shall** maintain ppO_2 to within the physiologic range of 20.7 kPa < ppO_2 ≤ 50.6 kPa (155 mmHg < ppO_2 ≤ 380 mmHg, 3.0 psia < ppO_2 ≤ 7.35 psia). *Rationale: The system needs to maintain ppO_2 to the specified range throughout all non-joint operations, docked operations, and EVA. The range provided is the physiological values for indefinite human exposure without measurable impairments to health or performance."*

Independent Pressure Effect on Hypoxic Dose

Although not a new debate, recently there has been considerable discussion on whether normobaric hypoxia (NH) elicits the same hypoxic symptoms as hypobaric hypoxia (HH) [7] [8] [9]. In many cases, the differences may not reach statistical or clinical significance, but the general trend is one that seems to indicate that almost all measurable changes associated with hypoxic exposures trend worse in the case of HH as compared to NH. Given that the 8/32 environment is an engineered environment and does not exist in nature; a standard EAA may not be fully representative of the hypoxic stress. An 8 psia P_B is associated with an actual altitude of 4,877 m (16,000 ft). It is the enrichment of O_2 from 21% to 32% that reduces the hypoxic stress to an EAA of approximately 1,830 m (6,000 ft). It is unknown whether the increased hypobaric exposure will increase the hypoxic dose, but at least one literature review suggested that the 8/32 environment increased the risk of one known hypoxic symptom, AMS, from the proposed EAA of about 1,830 m (6,000 ft) to 2896 m (9,500 ft) [10]. This hypothesis is based on literature review and a proposed model and has not been validated, but it does point to the need for human exposure research in the 8/32 environment. A more recent review lends further support that NH and HH are not equivalent for acute and subacute exposures and suggests that using NH as a surrogate for HH during chronic exposures is inappropriate [11].

Research is warranted to evaluate a possible P_B effect on hypoxic adaptations. Results from these studies will aid in the understanding of human physiology in the 8/32 environment as well as inform the scientific community on how best to proceed with hypoxia research. In research settings, it is easier to design and operate systems that manipulate P_IO_2 by F_IO_2 rather than P_B. However, in situations where the P_B effect is significant, then human or animal research will require true ascent-to-altitude or hypobaric chamber studies.

Visual Impairment / Intracranial Pressure Syndrome

Because of its prevalence and potential mission impact, visual impairment / intracranial pressure (VIIP) is considered the top human system risk in the ISS Program. Currently, VIIP is a poorly understood syndrome with potential for permanent damage to the ocular and central nervous systems. The changes that have been observed to date are developing in microgravity without additional exposure to HH. While the pathophysiology of VIIP is under active investigation, the addition of HH to the spaceflight environment may exacerbate the problem.

Elevated Carbon Dioxide on ISS

Elevated carbon dioxide (CO_2) is a known problem in a closed system with humans in the loop. On Earth, the ambient CO_2 concentration is about 0.23 mmHg (0.03%). In spacecraft, it is not practical to control CO_2 to such low levels because of power and consumable constraints, and CO_2 levels on the ISS have typically been 2.3 to 5.3 mmHg (0.5 ± 0.2%), a ten-fold increase compared to terrestrial levels [12]. Over the years, ISS crewmembers have been found to develop CO_2-related symptoms such as headache and lethargy at lower-than-expected CO_2 levels, and symptoms tend to resolve when ambient CO_2 is decreased [13]. While work to quantify this association is ongoing, chronic CO_2 exposure appears to be a contributing factor to several in-flight medical issues, including VIIP [13] [14]. The CO_2 elevation will likely complicate the adaptation to a mildly hypoxic environment, potentially making physiologic symptoms worse.

Literature Review and Design Reference Mission Considerations

Representatives from NASA's Human Research Program (HRP), EVA Physiology Laboratory, and Space Medicine Group contributed different points of view and areas of expertise to this report. The focus was to evaluate the expected and possible human impacts related to living in space at the proposed 8/32 environment. To evaluate potential risk, the team reviewed literature from their respective disciplines on the effects of mild hypoxia, primarily from research done at altitudes of 1,830 to 3050 m (6,000 to 10,000 ft). The 8/32 environment does not exist in nature, but approximates to an EAA of about 1,880 m (6,000 ft). Control box (32 ± 2%) uncertainty stretches the possible EAA to 2,438 m (8,000 ft). Finally, the possibility of an independent pressure effect on hypoxia has been proposed, with one model proposed in a review suggesting that the 8/32 environment would present an AMS risk of 2,896 m (9,500 ft) [10]. In some cases, literature from higher altitudes was reviewed if no literature was available at the lower altitude range.

Design Reference Missions

Nine representative design reference missions (DRMs) have been proposed by the Human Spaceflight Architecture Team as a notional program to extend human presence beyond low-Earth orbit (LEO), to the Cis-Lunar space, near-Earth asteroids (NEAs), the Martian moons, and Mars. As Table 3 shows, these exploration missions will have four to six crewmembers, last up to 1,200 days, and baseline many EVAs for surface missions.

Table 3. Representative Design Reference Missions (modified from: "Focused Human Exploration Design Reference Missions," M. Rucker and L. Toups, 3 May 2012)

DRM	Destination	Duration	Crew	EVA?	Year
1	Lunar Orbit	7 to 10 days	0	None	2017
2	Lunar Orbit	10 to 14 days	4	None planned	2021
3	Cis-Lunar	TBD	0	None	<2027
4	LEO	<21 days	4	TBD	<2027
5	Cis-Lunar	30 to 180 day	4	Contingency	<2027
6	Asteroid	<365 days	4	Few	>2025
7	Lunar Surface	<33 days	4	Many	>2025
8	Mars Moon	600 to 1200 days	4-6	TBD	>2035
9	Mars Surface	Up to 1,140 days	4-6	Many	>2035

The principal goal is to maintain the crewmembers' health so they can accomplish their mission objectives. This means a robust health maintenance program that provides countermeasures against the known physiologic changes to both the space environment (hypogravity and hypercapnia) and the proposed spacecraft environment (HH), and medical care capability that is commensurate with the duration of the mission, communication delays, and distance from definitive medical care facilities. Thus, those missions beyond LEO that will last more than 1 to 2 weeks (DRM 5-9) will require increasingly autonomous medical capability with increasing distance from Earth. At the same time, we recognize that some physiologic questions cannot be answered until crews start flying these missions, or

until simulations of certain mission factors are performed on the ISS; therefore, engineering and operational controls should be in place to prevent such known issues as rapid transitions between atmospheres and chronically elevated CO_2 levels.

EVA Frequency and Spaceflight Considerations

The planned scenarios currently being considered for future missions using the 8/32 environment involve a high number of EVAs. Although all of these scenarios will have a heavy EVA phases, this phase may take place at very different points in a mission. Crewmembers can reach the lunar surface or a Cis-Lunar location within a few days. On the other hand, it will take several months to reach a NEA or Mars. Therefore, we have to consider the operational tempo and known physiologic changes as we look to potential impacts of the inclusion of the 8/32 environment.

In the lunar and Cis-Lunar cases, spaceflight data from shuttle missions should be leveraged. In these cases, the transition to the 8/32 environment would superimpose adjustments to the hypobaric hypoxic environment with adjustments associated with adaptation to microgravity. The concern is that the combination of these adjustments in addition to a heavy-EVA mission profile may degrade the health and performance of astronauts who must maintain a high level of proficiency to accomplish mission goals [15]. The first 2 weeks of a spaceflight is a period of dynamic physiologic change in the crewmember. Primarily, physiologic adaptation to the new spaceflight environment includes: cephalad fluid shift, neurovestibular adaptation, susceptibility to space motion sickness, and changes in spatial orientation. These changes result in physical symptoms such as increased fatigue, headaches, reduced sleep, lack of appetite, back pain, etc., all of which can negatively impact mood and behavior. Cognitive processes such as focus and attention, memory recall, problem solving, and executive function may affect mission operations, which include highly technical and complex procedures [16].

Space Shuttle missions, which typically lasted about 2 weeks, were regarded as high workload and fast-paced, with little to no time available for “winding down” [17]. Crewmembers reported forgoing eating and sleeping to complete timeline objectives [18] [17]. Accordingly, objective data from spaceflight indicate that shuttle astronauts slept an average nightly duration of approximately 6 hours [19]. The increase in stress response and sleep deprivation increases the likelihood of errors. Therefore, effects of the slightly hypoxic environment must be considered with these operational data in mind. It could be expected that more severe detriments would result from the inclusion of a hypoxic environment.

In the NEA and Mars cases, spaceflight data from ISS missions will be more appropriate for analysis. It will take up to 6 months to reach these locations, which nicely parallels the current length of an ISS mission. At the end of a 6-month ISS rotation, the crewmembers are going to be acclimatized the spaceflight microgravity environment; therefore, the problem of complicating the adaptation to spaceflight with the 8/32 environment is avoided. But the long-term issues associated with spaceflight will pose different challenges. Crewmembers may have signs or symptoms of the VIIP syndrome. They may have decrements in cardiovascular, muscular, and aerobic capacity if the current ISS countermeasures effectiveness cannot be maintained during transit. Transitioning to the 8/32 environment in the midst of returning to a gravity environment (3/8-g on Mars) and adding a heavy EVA phase to the mission after months in space is a scenario where we have no operational experience.

Expected problems are less likely going to stem from acute overload, but rather the combination of negative chronic spaceflight adaptation that may worsen with exposure to a mildly hypoxic environment coupled with an increased EVA frequency.

Hypoxia-Mediated Physiologic Concerns

This section will discuss the physiologic concerns and impacts related to the expected hypoxic dose of the 8/32 environment. Decreasing the O_2 delivery to all the bodily organs and systems has an impact on all physiologic functions. However, the 8/32 environment only induces a mild hypoxic stimulus, which we would not be concerned about in itself on the surface of the Earth. We know that humans adapt well to altitude with a similar ambient O_2 partial pressure as the 8/32 environment. Such an environment in combination with other spaceflight factors such as microgravity and space radiation is; however, of concern, because the additive and/or synergistic effects might impair human health and performance to an unacceptable risk level. In particular, the effects on brain and ocular physiology are of concern, because we lack knowledge as to how a decrease in ambient O_2 partial pressure – however mildly – in space might affect the pressure in the brain and eyes and thus human performance. In addition, we do not know how the combinatorial effects of a mildly hypoxic atmosphere and mildly hyperoxic EVA suit atmosphere affects cellular pathways, and whether it induces oxidative stress and damage threatening human health to an unacceptable level. Consequently, the addition of mild hypoxia and its effect on the human system will be needed to augment existing NASA human research. Particular emphasis should be placed on brain and ocular function, sensorimotor performance, and cellular oxidative stress and damage.

Vision Impairment / Intracranial Pressure Syndrome

The VIIP syndrome was first described in 2006 with the observation of papilledema, vision changes, and increased intracranial pressure in long-duration astronauts returning from the ISS. However, postflight questionnaires obtained between 1989 and 2011 revealed that 23% of shuttle and 48% ISS long-duration mission astronauts reported a subjective degradation in vision [20], suggesting that spaceflight-induced visual impairment and intracranial hypertension may have been occurring in astronauts although the syndrome was not recognized until the technology advanced sufficiently to evaluate and look for it [21]. Based on a case definition developed by expert consensus, 15 cases have been identified out of 36 long-duration astronauts to date, although not all of these 36 astronauts have been fully evaluated. Although direct in-flight measurements have not been made, in-flight signs of papilledema, and postflight changes in brain imaging have documented evidence of elevated intracranial pressure (ICP). In addition, postflight lumbar puncture in four ISS crewmembers has indicated elevated ICP ranging from 21.0 to 28.5 cmH_2O (normal range: 5 to 15 cmH_2O). Of note, ICP may remain elevated long after flight in some of the returning symptomatic astronauts, over 18 months in one case [20].

Microgravity exposure induces a cephalad fluid shift likely resulting in elevated ICP. It is possible that the cephalad fluid shift accounts for a 50% increase in ICP in the microgravity environment compared to 1-g [22]. In addition, it is known that the average CO_2 level is elevated on the ISS, which may further increase ICP due to its potent vasodilator effects. Up to an additional 12% increase in ICP may be attributed to current CO_2 levels on ISS [23]. Thus, a combination of the microgravity-induced cephalad

fluid shift and high ambient CO_2 levels very likely increases ICP in astronauts leading to known visual acuity problems and possible impact on cognitive brain function.

One concern of HH alone is AMS (to be discussed further), which lies within the spectrum of high-altitude headache to high-altitude cerebral edema. High-altitude cerebral edema is associated with increased ICP [24] [25] [26]. AMS itself appears to be strongly associated with increased optic nerve sheath diameter reflecting increased ICP [27]. Sutherland, et al. found that the optic nerve sheath diameter increased in 13 mountaineers from sea level to exposures at 2000, 3700, 5200, and 6400 m (6562, 12139, 17060, and 20997 ft) [28]. Increasing optic nerve sheath diameter has been found to correlate positively with ICP and is based on the fact that the subarachnoid cerebrospinal fluid (CSF) compartment communicates with the perioptic CSF space. Therefore, increases in intracranial CSF pressure are transmitted to the perioptic CSF space and may be measured as changes in the optic nerve sheath diameter. More directly, Yang, et al. found that upon exposure to an altitude of 4,000 m (13,123 ft) for 2 hours, ICP measured by intraventricular catheter increased by 78% from 15.4 to 27.4 cmH_2O in hypoxic goats compared to nonhypoxic goats [29]. Physiologically, any fall in O_2 delivery results in vasodilation of cerebral vessels to increase brain blood flow and elevate ICP. With the addition of microgravity-induced intracranial hypertension, it is likely that astronauts would develop greater increases in ICP in an 8/32 environment than in 14.7/21. Even limited exposures to 8/32 may exacerbate VIIP in an additive or synergistic manner.

At present, 42% of ISS crewmembers are affected by the VIIP syndrome and 15% of those severely in a normobaric, normoxic (14.7 psi/20.9% O_2) environment. Because of its prevalence and potential mission impact due to visual and central nervous system (CNS) impairment, VIIP is considered the top human system risk in the ISS Program. It should be noted that the changes that have been observed to date are developing in microgravity without additional exposure to HH. The combinatorial effects of the spaceflight environmental factors such as microgravity and high ambient CO_2 levels with an 8/32 environment are unknown and could potentially negatively impact brain blood flow and cognitive abilities based on current knowledge of the VIIP syndrome.

Moreover, in the setting of papilledema, hypoxia is expected to worsen optic nerve ischemia. Hypoxia at altitude is associated with optic disc swelling, hypothesized to be due to a hypoxia-induced increase in cerebral blood flow that disrupts the blood-brain barrier and results in cerebral edema [30] [31]. Altitude-associated optic disc swelling has been described since 1969 [26]; a recent study of 27 high-altitude mountaineers by Bosch, et al. [30] found optic disc swelling in 59% of the climbers. Furthermore, high-altitude retinopathy, typically described as retinal vascular engorgement and tortuosity, can be associated with decreased visual acuity and cotton wool spots [32], two of the diagnostic hallmarks of VIIP [21]. There is enough overlap between spaceflight-induced VIIP and altitude illnesses to warrant precaution about intentionally adding HH to spaceflight. The concern is that an 8/32 environment would worsen visual changes, potentially leading to decreased ability to perform tasks and possible permanent damage.

As a result, we are concerned about an 8/32 environment for durations longer than a week, before we know more about the mechanisms of the VIIP syndrome and how to mitigate this risk. As forward work

relating to the 8/32 environment, we suggest adding an experimental arm to the current VIIP research plan, both regarding animal and human studies, to understand the additive or synergistic effects of the 8/32 environment with known spaceflight factors to the VIIP syndrome.

Sensorimotor Performance

Sensorimotor Performance during Spaceflight

Astronauts experience disturbances in sensorimotor function during periods of adaptive change on initial exposure to microgravity and on return to a gravity environment. These disturbances include spatial disorientation, space motion sickness, alterations in gaze control, and postflight postural instability, and gait ataxia [33] [34] [35] [36] [37] [38]. Importantly, sensorimotor disturbances are more profound as duration of exposure to microgravity increases. These changes can impact in-flight operational activities including spacecraft landing, docking, remote manipulation, and EVA performance. In addition, postflight postural and gait instabilities could prevent or extend the time required to make a nominal or an emergency egress from a spacecraft.

Sensorimotor Performance and Hypoxia

The retina is extremely sensitive to changes in O_2; therefore, acute hypoxia can lead to decrement in visual function. These changes are less profound in the mild hypoxic range; however, performance decrements have been observed [39]. In one study that focused on visual performance specifically in the hypoxic range of 1,830 to 2,438 m (6,000 to 8,000 ft), mesopic vision was impaired [40]. Mesopic vision is visual performance in low-light levels but not quite dark conditions, equivalent to that experienced during twilight. Given potential low-light conditions during planetary operations, this decrease in visual performance may have operational implications.

Mild hypoxia has also shown to have an effect on the postural control system [41] [42] [43]. Postural sway measured on subjects standing on a force plate was shown to increase compared to ground-level controls at simulated altitudes of 1,524, 2,438, and 3,048 m (5,000, 8,000, and 10,000 ft) [41]. The postural control system receives input from several sensory modalities including information from vision, the vestibular system, proprioception from joints, tendons, and muscles, and tactile information. These multiple sensory informational sources are integrated in the central nervous system to aid in the control of postural equilibrium. Therefore, a change in postural equilibrium control can serve as a sensitive indicator of mild hypoxic effects on multiple sensory systems along with the efficacy of their central integration.

In terms of pilot flight control performance, exposure to mild hypoxia does not have a significant impact on manual control ability for tasks such as maintaining assigned altitudes and navigation; however, procedural errors appear to increase at the 3,048-m (10,000-ft) level [44]. These events include misdialing frequency codes and failure to follow air traffic control instructions. In a study using self-report questionnaires to assess hypoxic symptoms of helicopter aircrew operating at altitudes below 3,048 m (10,000 ft), aircrew reported potentially operationally significant symptoms of hypoxia at a mean altitude of 2,590 m (8,497 ft) [45].

During gravitational transitions, sensorimotor systems undergo adaptive changes to match motor output to the prevailing environment. It is currently unknown what the impact of hypoxia is on this essential process of sensorimotor adaptive change. Does hypoxia hinder the adaptive response prolonging the period of sensorimotor disturbance experienced during gravitational transitions? If hypoxia interacts negatively with the nominal sensorimotor adaptive process, performance decrements including changes in dynamic visual acuity, postural and gait instability, and spatial disorientation may be exacerbated, impacting performance and mission success. In addition, there are well known vestibular-evoked responses recorded from respiratory muscle nerves that serve to provide adjustments in breathing and airway patency during movements and changes in posture [46]. It is possible that vestibular adaptation shortly following G-transitions may negatively impact the respiratory compensation to the 8/32 environment. Singh, et al. [47] observed that altered vestibular function such as increased sway at high altitudes may reverse with acclimatization. Therefore, sensorimotor interactions with the 8/32 environment are likely to be more important within the first few days following the transitions between G states.

Sensorimotor Performance Conclusion

From a sensorimotor perspective, mild hypoxia can induce alterations in performance including visual and postural stability decrements and some alterations in piloting ability. These effects are not profound in terms of overall impact on performance; however, in combination with other factors unique to spaceflight, these performance decrements may reach threshold to impact mission capability.

To determine whether sensorimotor adaptive mechanisms are negatively affected by the 8/32 environment, the following studies could be done comparing the normoxic adaptive response with the 8/32 hypoxic environment:

- Gaze control and dynamic visual acuity adaptive responses to vision-distorting lenses (magnifying, minifying, etc.)
- Manual control adaptive responses to modified joystick input
- Gait adaptation to an unstable walking support surface
- Combined effects of multitasking and increased G (entry profile) on adaptive responses

If performance decrements are observed that are related to hypoxic derived reductions in ability to adapt sensorimotor systems, then countermeasures could be developed to mitigate these changes. One potential countermeasure entails hypoxic preconditioning training [48] [49] [50]. This training paradigm engages the endogenous mechanisms by which the brain protects itself against cerebral ischemia by exposing the subject to a noxious stimulus near to but below the threshold for damage. Following the preconditioning training, a tolerance is developed to the same or even different noxious stimulus beyond the usual threshold for effect. This type of training has been used successfully to develop an increased tolerance for ischemic stress. In this context, preconditioning to mild hypoxia could be used as a training countermeasure to reduce the hypoxic performance decrements associated with exposure to mild hypoxia and adaptive sensorimotor responses.

Acute Mountain Sickness

Description

AMS affects individuals that ascend rapidly to altitude, with symptoms such as headache, nausea, vomiting, disturbed sleep, and poor physical performance [15]. The acute change in ppO_2 from normoxic (~160 mmHg) to the ppO_2 of 132 mmHg associated with the 8/32 environment can result in the possibility that some crewmembers may develop symptoms of AMS. Between 7% and 25% of adults may experience mild AMS near 2,000 m (6,562 ft) [15] [51]. The risk of AMS is modified by several factors including the ascent rate to altitude, activity level at altitude, and individual susceptibility [52]. HH appears to induce AMS to a greater extent than does either normobaric hypoxia or normoxic hypobaria [53].

AMS symptoms have been recorded using the Lake Louise symptom questionnaire (LLSQ) and include headache plus nausea, dizziness, fatigue, or sleeplessness that develops over a period of 6 to 24 hours. While expected to be mild and transient, these symptoms could potentially impact crew health and performance on critical mission tasks during lunar surface missions. AMS headaches are reported to be throbbing, bi-temporal or occipital, typically worse during the night and on awakening. This has implications for sleep quality. When combined with nausea, it can be likened to the flu or a hangover. Clinical findings confirm a change in mental status, ataxia, peripheral edema, or changes in performance (reduction in normal activities) [15].

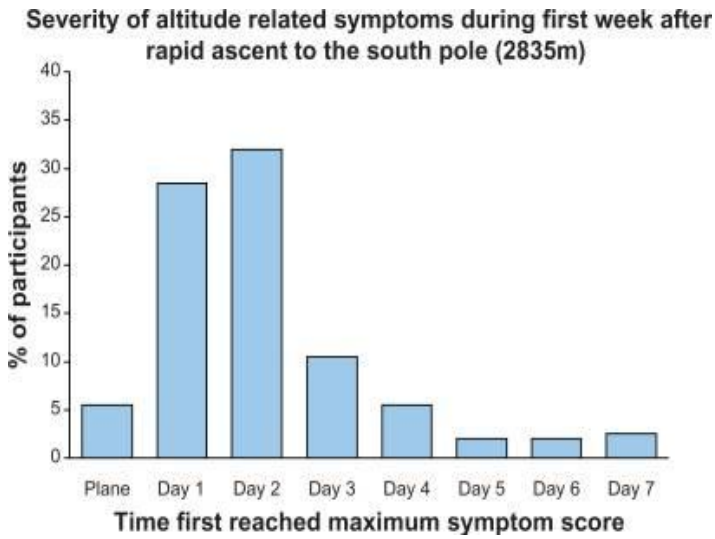

Figure 2. Percentage participants that reached their maximum LLSQ symptoms score during the first 7 days at South Pole Station (2,835 m [9,300 ft]) [54].

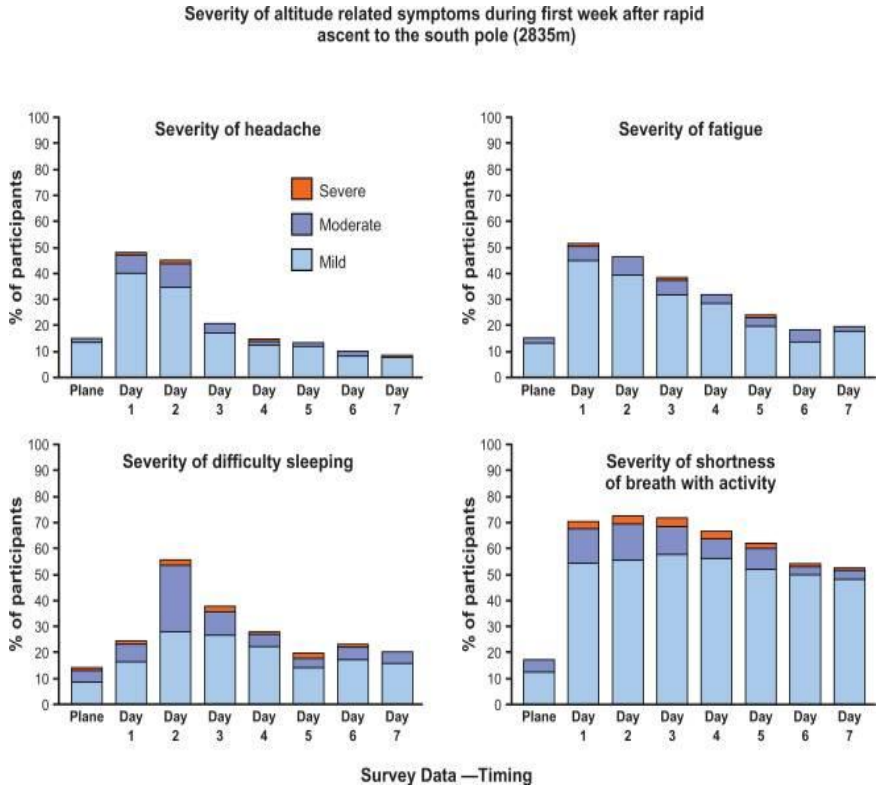

Figure 3. Severity of most commonly reported symptoms over the first week of exposure in personnel rapidly transported to the South Pole (2,835 m [9,300 ft]) [54].

One of the largest studies on AMS was conducted by Anderson, et al. [54] during rapid ascent to Amundsen-Scott South Pole Station (2,835 m [9,300 ft]) in Antarctica. Of 246 subjects, 52% developed LLSQ defined AMS (Figure 2). Anderson et al. are currently working on some follow-up manuscripts that will describe the known physiological differences between the subjects who reported AMS and the subjects who had no AMS symptoms. The most common symptoms were shortness of breath with activity (87%), sleeping difficulty (74%), headache (66%), fatigue (65%), and dizziness/lightheadedness (46%) (Figure 3). Symptom reports at the South Pole were mild to moderate in severity with symptom prevalence peaking on the day after arrival at altitude (day 2, approximately 12 to 18 hours after arrival); yet in greater than 20%, shortness of breath with activity, fatigue and sleep problems persisted through day 7. This reflected conventional knowledge that symptoms appear between 6 to 48 hours after arrival and resolve within the first 3 days [54].

Located on the high-plateau of Antarctica at an elevation of 2,835 m (9,300 ft), the environment of South Pole Station closely reflects the 8/32 environment as well as the operational profile of NASA mission scenarios. Most jobs at South Pole Station require physical activity, with a significant portion of personnel working outdoors. Activities include construction, heavy equipment operation, transport of supplies, science support, research, and fuel delivery [54]. This environment could serve as a high-fidelity, ground-based analog to research hypoxic effects within a true mission-like environment.

AMS Risk Specific to 8/32 Condition

It appears through an extensive literature search [6] and statistical analysis of available data [10] that the 1,830-m (6,000-ft) EAA computed for the proposed 8/32 environment may have more risk of AMS than one would expect at this altitude. This independent pressure effect on true hypoxic dose appears real, and has been suspected since 1946. Ever since the derivation of the alveolar gas equation was published [55] there has been a physiologic foundation to expect different outcomes under normobaric and hypobaric hypoxia given the same hypoxic P_IO_2, termed the nitrogen dilution or the respiratory exchange ratio effect [5]. In the current context, there are two cases: the first is the equivalent air altitude case with assumed exposure to 1,830-m (6,000-ft) breathing air (21% O_2) and the second is the exploration atmosphere case with exposure to 4,877 m (16,000 ft) on 32% O_2. The difference between these two exposures is 3,048 m (10,000 ft) but the P_IO_2 is identical at 117 mmHg, and it appears that the risk of AMS is greater in the exploration atmosphere case due to the lower total pressure [10]. Without considering acclimatization to mild hypoxia from one vehicle to the next, there is about a 25% chance of AMS per crewmember for the proposed 8/32 environment [10]; this also assumes no further negative interactions due to adaptation to microgravity.

Research is justified to measure the acute mild hypoxic response to the 8/32 environment. It seems that the magnitude of the pressure effect on true hypoxic dose is a function of the hypoxic P_IO_2. The pressure difference between 11.8 and 8.0 psia may or may not be sufficient to measure a pressure effect on the onset, intensity, and incidence of AMS, given a reasonable sample of human subjects. If time and money resources are not available, then staged decompression and pharmacologic mitigation strategies should be developed to reduce and manage the predicted risk of AMS.

Mitigations

The most effective mitigation against AMS is prevention by slow ascent to altitude. For exploration missions, transitions between atmospheric pressures should be gradual to allow for acclimatization. However, there is no clear guidance for a transition rate at the lower equivalent altitudes associated with an 8/32 environment. Guidance on conservative ascent rates is usually provided for travel to high altitude after reaching an initial elevation of 2,438 to 3,048 m (8,000 to 10,000 ft). Beyond AMS, there are also DCS mitigation considerations that may have greater influence on the transition rate from 14.7 to 8 psia. Finally, if rapid ascent cannot be avoided, pharmacologic prophylaxis may be considered although all medications are associated with adverse effects and contraindications.

Acetazolamide is considered the first-line medication to prevent AMS on the ground, but it cannot be taken by individuals with a sulfa allergy and commonly causes paresthesias, urinary frequency [56], and decreased intraocular pressure, which may worsen ocular hypotony, a possible etiology of VIIP [20]. Dexamethasone is also recommend by the Wilderness Medical Society for AMS prophylaxis, but its use beyond 10 days is associated with glucocorticoid toxicity (for example, hyperglycemia and delirium) and adrenal suppression [57] [58], and, according to one case report, can lead to altered mental status, gastrointestinal bleeding, skin rash, and avascular necrosis [59]. Given these potential serious adverse effects, dexamethasone is generally considered second line for AMS prophylaxis and reserved for treatment [60]. Ibuprofen is being investigated as a prophylactic agent, but it may increase the risk of gastrointestinal bleeding or renal insufficiency [58]. Regardless of the agent, the potential benefits must

be weighed against the clinical and operational risks. Similarly, treatment options – typically descent to a lower equivalent altitude, O_2, acetazolamide, anti-inflammatories, and steroids – will have to be evaluated in an 8/32 environment.

Decompression Sickness

DCS occurs when nitrogen (N_2) (or an inert gas) comes out of solution when ambient pressure is reduced according to Henry's law and bubbles cause local pressure or ischemia. Type I DCS is milder, generally characterized by joint pain, but can progress to the more serious type II DCS, which involve the cardiopulmonary and/or central nervous system. The treatment of DCS is repressurization to cabin pressure and supplemental O_2 for mild cases and hyperbaric O_2 for more serious cases. The risk of DCS is lowered by effective prebreathe to purge the body of N_2 before EVA. New prebreathe protocols and treatment algorithms will need to be developed and validated for an 8/32 environment.

DCS was a primary trade consideration during the EAWG effort [1]. We expect that the 8/32 environment alone puts the EVA crewmember in a position where DCS risk is mitigated to acceptable levels with even a small amount of O_2 prebreathe. This may even be the case when EVA suits are operated at less than 100% O_2. In one analysis, the NASA Tissue Bubble Dynamics Model (TBDM) [61] was used to calculate the prebreathe duration required from a 10.2 psia / 26.5% O_2 cabin to maintain the current acceptable DCS risk of 15% assuming a 4.3 psia / 95% O_2 EVA suit. From the 10.2/26.5 cabin, a 130 minute prebreathe was required to achieve acceptable risk. In comparison, the expected 15-minute operational prebreathe protocol from the 8/32 cabin assuming a 4.3 psia / 80% O_2 EVA suit, resulted in a predicted DCS risk of 13%. This results in significant improvement in the work efficiency index defined as the total EVA time divided by the overall preparation time for EVA.

Because DCS is expected to be mitigated to acceptable levels through the 8/32 environment in conjunction with a short-operational prebreathe protocol, the use of a variable pressure suit with the suitport on a vehicle like the MMSEV offers additional DCS mitigation capability. These include moving some traditional EVA work to the intravehicular activity (IVA) role, short EVA, single-person EVA, and immediate repress to 8 psia for DCS treatment and intermittent recompression [62] [63] [64] [65] [66]. Although all of these factors look to be reliable strategies for DCS mitigation, they need to be validated in human research studies. Because DCS mitigation is the primary driving factor for the 8/32 environment, it is recommended that the first research efforts conducted by NASA validate that acceptable DCS risk will be achieved using this proposed environment.

Exercise and Cardiovascular Performance

Exercise Performance during Spaceflight

Maintenance of exercise performance is of crucial importance for mobility of astronauts during long-duration missions and upon return to 1-g. Despite crew allocation of about 2.5 hours per day to exercise, current exercise countermeasures are not fully effective in protecting against spaceflight-induced decrements in muscle, cardiovascular function, and bone health. For example, ISS crewmembers (Expeditions 1 through 15, n = 18) demonstrated mean decreases in isokinetic knee extensor and flexor strength of 11% and 17%, respectively [67], 10% reductions in maximal aerobic

capacity [68], and 2% to 7% decreases (depending on site) in bone [69]. Recent analysis, including data from crewmembers with access to the advanced resistive exercise device (ARED), demonstrates that resistive exercise using ARED combined with adequate dietary intake has been even more effective in preserving bone mineral content and lean body mass [70]. It is now generally perceived that the current exercise countermeasures suite is effective at preserving muscle strength and aerobic performance if protocols are adhered to and adequate nutritional intake is maintained. There is a need to prevent spaceflight-related deconditioning to protect the health and mission readiness of current ISS crew as well as to enable NASA to protect fitness of longer-duration astronauts for moon, Mars, and NEO missions.

Exercise Performance and Hypoxia

Exposure to hypoxia is associated with a number of adaptive responses, which could act synergistically with microgravity to further impair muscle and exercise performance. Acutely, acclimatization to a moderate altitude, say 3,048 m (10,000 ft), takes approximately 3 weeks, during which time there is impairment in exercise performance due to decreased cardiac output, increased ventilation, and muscle fatigue [71] [72]. A decrease in the ability to perform exercise countermeasures early in flight may have negative consequences, as a large portion of the strength loss and muscle atrophy observed in ISS crewmembers may occur during the first few weeks in microgravity. Chronic exposure (> 3 weeks) to the 8/32 environment may also magnify microgravity-induced changes in muscle and exercise performance. For example, exposure to moderate altitude accelerates muscle atrophy [73] and the transition from slow-to-fast twitch fiber type [74], decreases mitochondrial function and aerobic metabolism [75], and increases muscle fatigability [76]. Ultimately, there is a 0.5% reduction in aerobic power output per 100 m (328 ft) of elevation [76] [77] [78] [79]. Moreover, similar to microgravity, individuals with higher aerobic capacity are more affected by hypoxic exposure [80], and there are gender differences in performance [81] [82] [83] as well.

Cardiovascular System Performance and Spaceflight

Alterations in cardiovascular function have been reported following both acute and chronic exposure to spaceflight and are thought to be secondary to circulatory unloading mediated by a central redistribution of fluid and an accompanied reduction in plasma volume. It is now accepted that these adjustments contribute to the increased risk of orthostatic intolerance and underlie the reduction in exercise capacity experienced by some astronauts. More recent studies using both ultrasound and cardiac magnetic resonance imaging have elucidated a number of structural and functional changes including left ventricular diastolic dysfunction, cardiac atrophy / remodeling (an average decrease of about 1 gram per week), and vascular / endothelial dysfunction, which is differentially altered between cerebral and peripheral vascular beds.

Cardiovascular System Performance and Hypoxia

The cardiovascular control systems are keenly sensitive to changes in both O_2 and CO_2. While there is no literature on the specific environment in question (8/32) combined with a stressor such as spaceflight, there is a relatively rich literature on the effects of hypoxia (including relatively mild hypoxia) here on Earth. A preliminary review of this literature revealed that chronic exposure to extreme HH such as that experienced at altitudes at or above 3,400 m (11,154 ft) may impart protective adaptive effects on the cardiovascular system. On the other hand, acute or intermittent exposure to such conditions, even at

altitudes that provide only modest hypoxia, may impart maladaptive responses. Specifically, Holloway, et al. demonstrated reduced left ventricular mass (about 11%) and impaired diastolic function in sea level dwelling subjects after only a short and gradual accent to the 5,300-m (17,388-ft) Mt. Everest Base Camp [84]. It was postulated that such changes were due to alterations in myocardial energetics, in particular reduced levels of phosphocreatine and adenosine triphosphate. Such results confirm and provide a mechanistic insight to an earlier finding by Kjaergaard and colleagues, who demonstrated that cardiovascular function was depressed even after only 18 hours of exposure to simulated hypoxia comparable to living at 4,000 m (13,123 ft) [85]. Papers by Nishimura [86] and Iwasaki [87] suggest that a relative altitude as low as 2,000 m (6,562 ft) is sufficient to alter vascular function in the brain in as little as 5 hours.

It is likely that many of these effects are mediated, at least in part, by hypoxia-inducible factor 1 (HIF-1) [88] [89]. There is also evidence that HIF-1 interacts with reactive O_2 species to form a positive feedback loop, thus exacerbating any oxidative stress already present during spaceflight.

Exercise and Cardiovascular Performance Conclusion

Acute and chronic exposure to the 8/32 environment may exacerbate microgravity-induced decrements in muscle and exercise performance. The relative impact of these changes is highly duration dependent. Acute studies are needed to compare muscle and cardiovascular performance at 8/32, probably using NH simulations to determine pre- and in-flight exercise prescriptions. Long-duration 8/32 exposure would prompt need for additional adaptation studies.

Immune System

We know that reactivation of latent herpes viruses occurs during short-duration spaceflights [90]. Recent data from the ISS indicate that in-flight dysregulation persists for the duration of a 6-month mission [91]. Thus, these data strongly suggest that spaceflight is associated with immune dysregulation. Therefore, persistent immune dysregulation leading to increased susceptibility to infections and reactivation of viruses as well as autoimmune manifestations might be a limiting factor for long-duration missions into deep space and constitute an unacceptable clinical risk for the crewmember's health [92].

We also know that T cell function is impaired during hypoxic stress [93] [94], and that hypoxia promotes the accumulation of extracellular adenosine as a result of enhanced purine nucleotide degradation from adenosine tri- and diphosphate (ATP, ADP). Binding of adenosine to the cAMP-elevating G_s protein-coupled A2 receptors results in an inhibition of effector functions of T cells and myeloid cells and includes the inhibition of expansion and secretion of cytotoxic molecules and cytokines [95]. This suppresses the immune system and thus renders the body more susceptible to infections, auto-immune manifestations and viral reactivations.

The combined immune-suppressive effects of spaceflight environmental factors and even a short-term and rather mild hypoxic atmosphere is therefore of much concern. The spaceflight effects per se might be controllable even during long-term missions, but the additive and or synergistic effects of an 8/32 hypoxic environment might render the risk of immune deficiencies less controllable. Thus, forward work investigating to what degree an additive and/or synergistic effect of the well-known spaceflight

environmental factors and 8/32 hypoxia occurs is highly recommended before planning for long-duration deep space missions.

Envisaged forward research for resolving this could constitute estimations of markers for immune function in 1) animal studies combining unloading with hypoxia for various durations, 2) tissue culture studies combining bioreactor rotations with hypoxia, 3) humans during bed rest studies combined with hypoxia, and 4) astronauts on the ISS combined with different levels of short and longer periods of hypoxia.

Oxidative Stress and Damage

There is evidence that spaceflight-induced oxidative stress and damage (OSaD) is a component of immune manifestations, decrease in bone and muscle strength, and development of the VIIP syndrome during spaceflight [96] [97] [98] [99] [100] [101] [102] [103] [104]. OSaD is the result of organic and systemic dysregulation of the free radical normalization and scavenging process, and is also the cause of many different manifestations of disease including atherosclerosis [105] [106] [107]. Therefore, during long-duration missions into deep space, OSaD could likely constitute a mechanism for development of cardiac disease [105] [108] [106] [109].

Changing the environment during spaceflight to an 8/32 environment will lead to hypoxia, which is known to further promote OSaD [110] [111]. The combination of spaceflight (radiation and weightlessness) and hypoxia will be a hazard that most probably will induce augmented synergistic and additive OSaD effects, thereby rendering immune dysfunction, bone demineralization, muscle degradation, and the VIIP syndrome less controllable – even with the use of the current countermeasures. Therefore, OSaD research is warranted before we know whether it is safe for the astronauts to change the vehicle environment to a lower O_2 partial pressure during spaceflight [112] [113] [103]. Such research should be combined with the suggested research scenarios within the immune discipline.

Nutrition and Bone

Nutrition during Spaceflight

In general, nutritional risks increase with duration of exposure to a closed food system and with countermeasure application designed for specific systems [114]. Inadequate nutrition can compromise crew health, leading to loss of bone and muscle mass and strength, altered immune system function, impaired cardiovascular performance, gastrointestinal function, endocrine function, oxidative defenses, ophthalmologic health, and psychological health and performance [114].

Nutrition and Hypoxia

One common effect observed with hypoxia exposure is anorexia. Acute effects of hypoxia at high altitude are anorexia, nausea, and vomiting [115]. Chronic effects are progressive weight loss [116]. Also supportive of this are the findings that low O_2 availability in disease populations at sea level (i.e., respiratory diseases, chronic obstructive pulmonary disease) are associated with reduced energy intake and weight loss, and O_2 supplementation can lead to weight gain in these populations [117].

Several factors have been proposed to explain anorectic effects under hypoxic conditions. Homeostatic pathways dominate when energy stores are low and provide increased motivation to eat. Hedonic, or reward mechanisms, can override homeostatic mechanisms by increasing cravings and desires to eat highly palatable foods [118]. There is evidence that both of these mechanisms may be affected upon exposure to hypoxia [119] [120]. The hormones leptin and ghrelin play a role in the homeostatic pathway by regulating appetite. Leptin suppresses appetite and ghrelin stimulates the appetite. Plasma concentration of leptin and ghrelin were elevated and reduced, respectively, in high altitude acclimatized individuals (acclimatized at 3,675 m [12,057 ft] for 6 months), and the leptin correlated with food intake [120].

There is also evidence that hypoxia can induce bone resorption processes [121] [122] [123] [124]. When bone resorption is increased, there is a potential increased risk for renal stones if bone formation is not concurrently increased. This is a significant concern, given concerns about renal stone risk and bone loss during spaceflight.

Nutrition and Bone Conclusion

If intermittent periods of hyperoxia and hypoxia are proposed for Exploration-class missions, then studies need to be conducted to determine how long anorexic effects would be expected. With intermittent exposures, a “plateau effect” regarding energy intake may not happen; consequently, crewmembers could lose more weight than expected. Maintaining body weight will be crucial for maintaining overall health in an Exploration-class mission. Bone mineral density and lean body mass can be maintained with proper resistive loads and adequate nutrition [125]. Studies also need to be conducted in these proposed environments to investigate renal stone risk and altered calcium metabolism.

Behavioral Health and Human Performance Risks

The following section examines the literature relating to the risk for behavioral health and performance decrements in a mildly hypoxic environment. These risks include behavioral, sleep, and team interaction effects. No studies were found that provided concrete evidence on the effects of a hypoxic environment on team dynamics at the 1,830 to 3,048 m (6,000 to 10,000 ft) range. Commonly reported psychological and behavioral changes resulting from the effects of hypoxia include susceptibility to AMS (discussed separately), loss of appetite (discussed in Nutrition and Bone section), an increase in anxiety, fatigue, psychomotor effects (with an increase in reaction time), and some implications for acclimatization and performance.

Team

Although no studies were found on team dynamics, there is evidence of high-performing teams in this altitude range. One clear example is mountain rescue teams, which regularly perform high-stress, physically demanding and life-saving missions in this altitude range. As noted in conversations with the Rocky Mountain Rescue Group (Boulder, CO) operations director, rescue team members are also well acclimatized to this altitude, physically prepared, and experienced working in high physical and mental stress situations. These traits are most evident in mountain rescue teams with high, sustained mission counts . In addition to mountain rescue teams, Colorado-based professional sports teams show the capability of success in highly physically stressful environments. This includes two Super Bowl victories

for the Denver Broncos (1998 & 1999), two Stanley Cup championships for the Colorado Avalanche (1996 & 2001), and a National League pennant for the Colorado Rockies (2007).

Anxiety

Few studies examined the incidence of anxiety symptoms in the 1,830 to 3,048 m (6,000 to 10,000 ft) range; most studies were conducted at higher altitudes. At a simulated altitude of 3,500 m (11,483 ft), Bushov, et al. evaluated personality factors in mountaineers and nonmountaineers. It was observed that neuroticism levels were lower in mountaineers, moderated by the physical adaptation to altitude [126]. These reduced levels of neuroticism correlated with reduced levels in the symptoms of AMS and may have implications for astronaut selection. Additionally, Bushov, et al. concluded that the influence of anxiety under hypoxia is only exerted on stimulus-response tasks but not on more complex cognitive or psychomotor tasks [126]. Virues-Ortega, et al. [127] proposes a more complex interaction with the effect of personality traits associated with anxiety (emotional stability, anxiety trait, neuroticism) and differences in the hypoxic ventilatory response as individual differences that affect the effects of altitude exposure. Emotional stability is associated with better adaptation to altitude in regard to fatigue and AMS symptoms. However, only limited research is available, and it would be worth looking at this in an operational spaceflight context.

Fatigue

Martin, et al. [128] describe fatigue as any level of exercise at altitude that represents a greater "work intensity" when compared with that at sea level. High and extreme altitude studies have found negative correlations between fatigue and emotional stability [129]. No studies were found for the 1,830 to 3,048-m (6,000 to 10,000-ft) altitudes. Higher levels of fatigue are likely to exacerbate hypoxia symptoms and could potentially lead to long-term effects, though this remains a question for future investigations [127].

Psychomotor

Most psychomotor studies have been conducted at very high altitudes (6,000 to 8,000 m) (19,685 to 26,247 ft), and there is a lack of consensus on the initial cause of psychomotor effects. It has been argued that psychomotor effects could be due to related factors of hypoxia (such as anxiety and fatigue) instead of a direct result of the hypoxic environment. The minimum height that produces motor impairments varies among investigations between 2,500 and 6,000 m (8,202 and 19,685 ft). In addition, consensus for tasks and protocols to detect motor impairments is necessary (e.g., Purdue Pegboard versus the Finger Tapping Task) [127].

The effect that is most accepted in altitude literature is the increase in complex reaction time (CRT). CRT has been found to be a sensitive index of acute altitude exposure both in laboratory conditions [130] [131] and real expeditions [132] both with and without AMS [133], although most effects do not appear before 6,000 m (19,685 ft). After prolonged exposure, significant increase in CRT can be found above 2,500 m (8,202 ft) [134] [135]. Denison, et al. found an increase in CRT in altitude as low as 1,500 m (4,921 ft) [136]. Fowler, et al. demonstrated a significant increase in CRT in subjects at altitude of 2,438 m (8,000 ft) [131]. Abraini, et al. [137] and Bouquet, et al. [138] show that basic motor processes at high altitudes remain unaffected.

Perception

Few studies have been conducted on perception in the 1,830 to 3,048-m (6,000 to 10,000-ft) range; most have mostly been conducted at high and extremely high altitudes. Altitude simulations at 1200, 2400, and 3700 m (3937, 7874, and 12139 ft) by Watson, et al. [139] observed that event-related potentials (the resulting brain response from a sensory, cognitive, or motor event) and increase of reaction time were not associated with a rise in the absolute threshold for auditory stimuli up to 16 kHz. Fowler and Grant obtained similar results [140]. Burkett and Perrin noticed no effects on the discrimination of speech sounds at 6,600 m (21,653 ft) [141]. Finally, in an analogous investigation, Martin, et al. [128] found no effects on the localization of stimuli at an altitude of 3,700 m (12,139 ft). Alterations in perception of brightness and color have been reported at higher altitudes (3,962 m, 4,300 m) (13,000 ft, 14,107 ft) remaining throughout a stay at altitude [142] [143]. Ground-based analog studies could confirm that no effects are expected in auditory perception, discriminations of speech sounds or localization of stimuli and could examine the threshold for changes in brightness and color perception.

Cognition, Memory and Attention

Sensitivity of brain structures to hypoxia indicates that exposure to altitude has the potential to cause dysfunctions to learning and memory. Numerous high altitude and extreme altitude studies have validated this hypothesis. Research supports that memory difficulties depend on a reduced capacity to learn new information rather than its retrieval [144] [145] [146]. At lower altitudes, conflicting evidence is found. Subjects exposed to a simulated altitude of 2,438 m (8,000 ft) performed a card-sorting task faster [147]. At the altitudes in question (1,830 to 3,048 m [6,000 to 10,000 ft]), alterations in long-term memory, specifically episodic memory, have rarely been observed, and always as an acute effect, never as long-term effect [127].

Both animal and human observations conclude the lower threshold of altitude needed to produce spatial memory dysfunction is above 3,500 m (11,483 ft) [148] [149].

Altitude effects on attention capacity are rarely described in altitude literature. Some impairment was found in subjects at 4,200 m (13,780 ft) using the Digit Symbol test from the Wechsler Adult Intelligence Scale [150]. Reductions in cognitive flexibility and resistance to interference have been recorded several times above 2,500 m (8,202 ft) [127]. As previously noted, however, these decrements could be related to anxiety or fatigue.

Neural Structural Changes

Neuropsychological impairment are said to be the result of respiratory, circulatory, and brain detriments in adaptation to hypoxic environments. Some brain structures are more dependent on O_2 supply than others, including the hippocampus, and the parahippocampal region (surrounding temporal lobe region). These structures are involved in conscious recollection and memory, and the temporal lobe is involved in familiarity-based discrimination. These structures would be most affected during acclimatization to the 8/32 environment during spaceflight.

Schulze, et al. observed that exposing his subjects to an O_2 saturation (SaO_2) between 88% and 90% (2,500 m [8,202 ft]) produced a metabolic delay in the hippocampus, hypothalamus, cortex, and

striatum [151]. These effects have implications for multiple brain functions. The hippocampus is important for spatial memory, short- and long-term memory, the hypothalamus controls the endocrine system that regulates body temperature, fatigue, hunger, thirst, sleep, and circadian cycles, the striatum is linked to planning and modulation of movement pathways and executive function, and the cortex is related to memory, attention, perceptual awareness, thought, language, and consciousness [152].

Gozal, et al. used immunohistochemistry to record an increase in programmed cell death (apoptosis) in area CA1 of the hippocampus after 2 days of exposure to intermittent hypoxia (10 psi / 21% O_2, EAA = 3,132 m [10,275 ft]) [153]. After 2 weeks, the alteration reverted. It is important to examine the postflight effects to determine the time necessary to return to baseline.

Behavioral Health and Human Performance Conclusion

The findings showed that the effects of the 8/32 environment will have short-term behavioral and performance impacts. Adaptation can occur within 3 days in most cases [54], and the impacts are not expected to be severe enough to compromise a mission, although further study may be needed. Mitigation strategies can be developed to minimize the increased risk of performance and health decrements.

The degree of decrements in the microgravity environment is unknown, as they are subject to many factors (individual / genetic variations, environmental effects, workload, duration of exposure, etc.). Further studies would be beneficial to establish a baseline for these under high-fidelity mission operational constraints, and to develop and validate mitigation strategies.

Sleep

The introduction of an 8/32 environment may have implications for sleep in microgravity. In particular, difficulties in sleep are anticipated in hypoxic environments during the acclimatization phase.

Sleep during Spaceflight

Sleep deprivation is associated with degraded performance of neurobehavioral tasks, as well as decrements in health and well-being; hence, any stressor that has the potential to affect the quality of sleep during a mission could be detrimental to the astronaut. Studies have shown that sleep is reduced with an average nightly duration of 6 hours in short-duration missions (i.e., Space Shuttle), despite schedule requirements that accommodate 8 hours of sleep per night [19] [154]. Duration may not be the only aspect of sleep that is affected currently in spaceflight. Shuttle astronauts reported poor sleep quality on orbit [17]. Few studies have objectively looked at sleep structure in space, but those that have evaluated sleep stages have found changes, although these studies have included only a small number of participants [154] [155]. Ground research demonstrates that changes in sleep structure are associated with health and performance decrements [154] [155] [156] [157]. Reduced sleep and possibly altered sleep structure already poses implications for cognition, alertness, and performance on critical tasks.

Sleep and Hypoxia

Terrestrial studies indicate that hypoxic environments can yield similar detriments to sleep as what has been seen in the spaceflight environment, particularly field studies that include high workload and increased exertion. Hence, the combination of adding a hypoxic environment to existing stressors of sleep in space could potentially exacerbate negative effects.

The lowest altitude at which sleep and/or post-sleep performance are affected is not definitively known. Decreased quality of sleep has been reported after acute ascent to altitudes of North American ski resorts (2,000 to 3,000 m) (6,561 to 9,843 ft) and higher. Changes in sleep architecture include a shift toward lighter sleep stages, with marked decrements in slow-wave sleep and with variable decreases in rapid-eye movement sleep [158]. Accordingly, sleep at these altitudes was perceived as poor quality with the sensation of occasional awakenings, a sense of suffocation caused by periodic breathing relieved by a few deep breaths, and resumption of sleep.

Weil proposes respiratory periodicity (arousals) at altitude results from alternating respiratory stimulation by hypoxia and subsequent inhibition by hyperventilation-induced hypocapnia [158]. Despite relatively the same sleep duration, upon arising from sleep, subjects reported impressions of greatly abbreviated and restless sleep. Also, during wakefulness, subjects experience drowsiness [158]. This relationship may need further evaluation because CO_2 levels are several times greater on the ISS than on Earth [13].

Studies in simulated environments, however, found less conclusive effects on sleep and related outcomes. Muhm, et al. studied post-sleep neurobehavioral performance decrements at simulated 2,438 m (8,000 ft) on O_2 saturation, heart rate, sleep quantity, sleep quality, post-sleep neurobehavioral performance, and mood [159]. Results showed SaO_2 before sleep was significantly lower at altitude than at sea level. During sleep, SpO_2 decreased further at both altitude and ground. SaO_2 was below 90%, 44.4% of the time at altitude and 0.1% of the time at sea level. Subjects participated in three 18-hour sessions and sleep was more disturbed in the first study session than in subsequent sessions (potentially an argument for pre-adaptation before flight), and older subjects had more disturbed sleep. Despite these findings, objective and subjective measurements of sleep quantity and quality did not differ significantly with altitude, nor post sleep, neurobehavioral performance, or mood.

Thomas, et al. found that sleep at simulated 3,962 m (13,000 ft) was not associated with decrements in working memory or simple reaction time in healthy non-smoking men and women [160]. Weiss, et al. found no difference after hypoxia in sleepiness, encoding, verbal learning, objective vigilance, attention, or working memory at the same altitude with intermittent 9-hour exposures for 28 consecutive nights [161]. While these results were unexpected, they highlight the limitations of simulated studies, possibly because they lack the conditions of high workload and exertion found in field studies and the spaceflight environment.

Space Radiation

The Space Radiation Program is focused on research to accurately define, quantify, and mitigate the health risks associated with exposure to high-charge, high-energy galactic cosmic rays and solar protons that are not found on Earth. Of concern are the risks of radiation carcinogenesis, acute or late central nervous system effects, degenerative tissue effects (including circulatory diseases, stroke, and cataract) and the acute radiation syndrome due to solar particle events. At the cell and molecular level, radiation causes genetic damage by two methods, through direct energy transfer to DNA molecules leading to base damage or strand breakage, and indirectly through free radical mediated pathways that cause chemical damage to the DNA molecule. Low-linear energy transfer (LET) radiation, such as gamma or x-

rays found on Earth, mediate much of their damaging impact through indirect mechanisms, whereas high-LET radiation (galactic cosmic rays) found in the space radiation environment form densely ionizing tracks as they traverse a cell and lead to direct DNA damage [162].

The impact of O_2 in modulating the effectiveness of radiation for inducing cellular damage is well documented and is dependent on the type or quality of radiation, radiation dose, and dose-rate. The level of cellular O_2 present during radiation exposure can amplify the generation of radicals and alter the resolution of chemical damage to cellular biomolecules, including DNA. This is known as O_2 enhancement and is expressed as the O_2 enhancement ratio (radiation dose required to cause effect without O_2/dose required to cause effect with O_2, which stems from the ability of O_2 to promote the biological damage of low-LET radiation caused by free radicals. Tissues are less sensitive to the effects of radiation when in a hypoxic or anoxic state, and in the context of a tumor, this effect is directly associated with radiotherapy failure [163]. O_2 enhancement is diminished at low dose and lower dose-rates of radiation exposure, such as those that may be encountered during space travel, and is greatly diminished or lacking for high-LET radiation where the direct effects of radiation on DNA double-strand breaks dominate [164] [165]. Based on these studies, it is not anticipated that there will be any significant impact on the radiation risk portfolio due to the slight hypoxia that may be associated with the 8/32 environment proposed for exploration vehicles and, therefore, this would not be considered high priority at this time. In addition, no obvious factors that would alter the Space Radiation risk profile were identified in a review of relevant epidemiology data assessing the long-term impact of living at high altitude, which is the closest Earth-based analog for this type of environment.

The proposed 8/32 exploration environment is best approximated by high altitude environments on Earth with an equivalent air altitude in the range of 1,981 to 2,896 m (6,500 to 9,500 ft). A large amount of literature exists regarding the acute effects of high altitude on human physiology. Multiple epidemiology studies analyze the chronic health implications of living at high altitude, and many analyze effects on the cardiovascular system and cancer – risks of concern for space radiation [166] [167]. Because of multiple confounding factors, these studies are generally controversial and should be interpreted with caution. We reviewed several of these studies that showed a protective effect of living at high altitude on mortality from cardiovascular disease. The first study, from German Swiss citizens [168], shows a decreasing mortality due to stroke and coronary heart disease with increasing altitudes from 259 to 1,960 m (850 to 6,430 ft). A similar effect was seen in a second, recent study [169] where the relationship between altitude, life expectancy, and mortality for leading causes of death in the continental United States were analyzed. Here, altitude was inversely correlated with mortality from ischemic heart disease, but detrimental for chronic obstructive pulmonary disease, with no significant association with life expectancy, cancer, or stroke. The authors of the second study conclude that this protective effect is not related to changes in the classic risk factor for these diseases but may be attributable to an overall enhancement in cardiac efficiency and changes at the molecular level that may offer protective effects, such as the hypoxia-associated changes in hemoglobin and iron metabolism. Finally, we found one study conducted in the United States where the risk of cancer was inversely correlated with geographical elevation [167]. This study also found a significant decrease in mortality due to heart disease at higher elevations, although they did not control for known risk factors related to

diet and smoking. Of note is the fact that background levels of radiation are higher at increasing altitude due to diminishing shielding effects of the atmosphere; therefore, the interplay of complex factors must be considered in deciphering these results. Overall, we assume that changes in physiologic O_2 levels in the proposed exploration environment will be minimal and are not likely to significantly alter biological damage caused by low dose-rate space radiation and, therefore, are not likely to change the risk profile of the Space Radiation Program.

Exploration Medical Capability

HRP has assigned the Exploration Medical Capability (ExMC) Element the responsibility of addressing the overarching risk of unacceptable health and mission outcomes due to limitations of in-flight medical capabilities. A long-term change in atmosphere impacts ExMC's stance toward exploration risks and primarily affects Gaps 1.01: inadequate information on preflight medical screening capabilities for exploration class missions, 2.01: limited knowledge about incidence rates, probabilities, and consequences relative to loss of crew and/or loss of mission for the medical conditions on the Space Medicine Exploration Condition List (SMEMCL; JSC-65722), 4.04: lack of hardware for variable O_2 delivery that minimizes localized O_2 build-up.

The SMEMCL was created to define the set of medical conditions that are most likely to occur during any exploration DRM as the first step in addressing the aforementioned risk. The list was derived from the ISS Integrated Medical Group Medical Checklist (JSC-48522), the Flight Data File Medical Checklist (JSC-48031), in-flight medical incidence data in the Lifetime Surveillance of Astronaut Health (LSAH) repository, and NASA flight surgeon subject matter expertise. The list of conditions was prioritized for specific DRMs with the assistance of the ExMC Advisory Group, which is composed of flight surgeons and representatives from Space Medicine management, the astronaut office, the National Space Biomedical Research Institute (NSBRI), and inputted incidence data from the Integrated Medical Model (IMM) that is further described.

The purpose of the SMEMCL is to serve as an evidence-based foundation in determining which medical conditions could affect a crewmember during a given mission profile, which of those conditions would be of concern and require treatment, and for which conditions a gap in knowledge or technology development exists. This information will be used to focus research efforts and technology development. Atmospheric changes from sea level to 8 psi and 32% O_2 will change the incidence of diseases currently being researched such as AMS, add new diseases to consider such as chronic mountain sickness, and alter the diagnosis and treatment of diseases not directly induced by hypoxia such as a pneumothorax that needs increased O_2 for treatment. Gap 1.01 will be affected by the changing disease risk and requires a reevaluation of screening capabilities for AMS to ensure that crewmembers can tolerate long-duration missions.

The IMM addresses Gap 2.01 and is a stochastic model that uses Monte Carlo methodology to simulate medical events and estimate the impact of these medical events for a given DRM. Outcomes include Crew Health Index (CHI), probability of evacuation (EVAC), and probability of loss of crew life (LOCL). 20,000 trials are simulated for each DRM and probability distributions for CHI, EVAC, and LOCL are

determined. Thus, a change in cabin pressure will directly affect diseases such as AMS and DCS, but also affect the consequence of O_2-dependent diseases such as respiratory infection and anemia.

Treatment of these O_2 -dependent diseases requires directed delivery of concentrated O_2, which is being researched and developed by ExMC to close Gap 4.04. This capability may be impaired by a lower ambient cabin pressure and higher O_2 concentration, requiring a reevaluation of current efforts.

Though none of these concerns would preclude a change to an 8/32 environment, further research would help characterize the effect of this change on ExMC's Gaps and concerns. An experimental study, placing cohorts in an 8/32 environment, with sufficient power to be statistically significant, would provide valuable data about susceptibility to this environment, incidence of disease, and effectiveness of treatment modalities. Results from such a study would provide valuable input into IMM and allow for treatment testing and O_2 delivery.

Overall Synergistic Effects of 8/32 and Spaceflight Environment

The combination of hypoxia, hypobaria, and hypogravity can potentially worsen the physiologic changes due to these environments that have been described separately in the literature. To our knowledge, no data exist on the combination of all three environments, or hypobaria combined with hypogravity. Physiologic changes to HH and hypoxia combined simulated microgravity (head-down bed rest) described in the literature are summarized in Table 4.

Table 4. Physiologic Changes in Response to Hypoxia Combined With Hypobaria and Hypoxia Combined with Hypogravity

	Hypoxia + Hypobaria	Hypoxia + Hypogravity
CNS/Ocular	Acute mountain sickness (headache, nausea, weakness, fatigue, dizziness, difficulty sleeping) [192]	Acute mountain sickness symptoms when exposed to hypoxia and head-down bed rest [170] Minor reduction in cerebral blood flow and resistance with combination [194]
Cardiovascular	Systemic vasoconstriction [196] [193] Increased blood pressure [193] [195] Increased heart rate [193] [195] [197] Decreased stroke volume [193] Decreased cardiac output [193] Decreased maximal O_2 consumption (VO_2max) exercise performance [193]	Reduced VO_2max but may be due to inactivity of bed rest [170] Possible small improvement in orthostatic tolerance [170]
Respiratory	Pulmonary vasoconstriction [195] [197] Increased respiratory drive [193] Increased pulmonary blood pressure [193]	No significant change in pulmonary mechanics and gas exchange compared to hypoxia alone [170]
Hematological/Immunological	Reduced plasma volume [193] [197] Increased hematocrit [193] Increased erythropoiesis [193] [197] [190] Polycythemia [196] Increased blood viscosity [193] Increased thrombotic risk [190]	No significant change in hemoglobin, hematocrit, plasma fibrinogen, and plasma albumin compared to hypoxia alone [170]
Cognitive	Variable impairment on performance [193]	No significant difference in arithmetic, short-term memory, and maze tracing [170]
Nutritional	Reduced appetite, energy intake, and body mass irrespective of acute mountain sickness [191]	No articles found

Whereas some of these changes act in opposite ways, other changes may be synergistic. For example, Loeppky, et al. [170] found that subjects exposed to hypoxia (1,645 m [5,400 ft]) and -5° head-down bed rest had AMS symptoms, whereas subjects exposed to hypoxia only remained asymptomatic, suggesting an additive effect between hypoxia and reduced gravity. However, the same study found a small improvement in orthostatic tolerance attributed to increased plasma norepinephrine.

Clearly, much more research is needed. Without research and experience operating in a combined environment, predictions of physiologic changes from the combination of the 8/32 environment with the spaceflight environment will be very limited since no known data exist.

Furthermore, if exploration crews are to be exposed to similar CO_2 levels as the ISS, the effect of hypercapnia combined with HH in hypogravity will also need to be researched. CO_2 alone has widespread effects on human physiology, including:

- Altering O_2 binding: CO_2 causes a rightward shift of the oxyhemoglobin saturation curve, so that at a given ppO_2, less O_2 is bound to hemoglobin, resulting in worsened hypoxia especially during exercise or if a patient is in shock when O_2 demand is increased.

- Stimulating ventilatory response: CO_2 not only increases minute volume and respiratory rate in the short term, but it also appears to alter the pH and CO_2-dependent set point for respiratory drive after chronic exposure to CO_2 [14].

- Cerebral vasodilation: CO_2 is a potent cerebral vasodilator and is linked to elevated intracranial pressure. Silwka [171] measured cerebral blood flow (CBF) at the middle cerebral artery in healthy subjects exposed to 0.7% and 1.2% CO_2 environments for more than 23 days and found that CBF increased by as much as 35%; moreover, CBF did not return to baseline post-exposure. This persistence post-exposure is similar to the persistence of elevated intracranial pressure in some of the symptomatic astronauts who were subsequently diagnosed with VIIP, suggesting that CO_2 may play a contributory or exacerbating role in the VIIP syndrome in long-duration spaceflight.

- Altered bone homeostasis: CO_2 exposure results in a respiratory acidosis that appears to be compensated by the kidneys at higher levels (> 3% CO_2) and by the bone at lower levels (0.5 to 1.5% CO_2) [172]. The bone, which contains a large reserve of the body's bicarbonate and calcium carbonate, serves as a buffer for acidosis; chronic acidosis can result in the release of calcium carbonate and bone breakdown [14]. In addition, chronic acidosis is associated with cell-mediated bone resorption and increased urinary calcium excretion due to stimulated osteoclastic activity and suppressed osteoblastic activity [123] [173] [174]. Thus, there is concern about chronic hypercapnia exacerbating an astronaut's risk of developing kidney stones.

- Behavioral health and performance: Anecdotally, ISS crewmembers have been noted by ground controllers to be more irritable or lethargic when they are gathered in a small module for public affairs events, presumably due to local accumulation of CO_2. Terrestrially, mild visuomotor impairment has been observed in subjects exposed to 1.2% CO_2 [175]. Additionally, there

appears to be a dose-response relationship between CO_2 level and symptoms such as nausea, dizziness, derealization, fear of losing control, and paresthesia [176].

8/32 EVA Considerations

The purpose of the 8/32 environment is to facilitate a high efficiency EVA capability for NASA. Current EVA preparation protocols from the Earth normal ISS atmosphere take a minimum of 4.5 to 5 hours before a crewmember begins an EVA. This long preparation time leads to a limited number of longer EVAs. Short EVAs are impractical and single-person EVAs would be unsafe because there would be no rescue capability. Improved efficiencies with suit preparation and checkout may reduce this time, but not dramatically. The risk of injury and impaired performance during EVA is directly related to the time spent in the EVA suit, so any operational concept that maintains EVA efficiency and productivity while minimizing time spent in the suit would be the most effective solution for an Exploration Program with heavy EVA needs.

General Medical Concerns about Frequent EVAs

Given the main motivation behind a reduced environment such as 8/32 is to facilitate frequent EVAs, several general concerns about frequent EVAs are discussed here.

First, repeated cycling between suit pressure and habitable volume pressure could have detrimental effects on the crew. Intermittent hypoxia, defined as repeated episodes of hypoxia interspersed with episodes of normoxia, has been studied to enhance exercise performance in athletes, since the so-called "live high and train low" method can stimulate erythropoietin and red blood cell production and increase ventilation [177]. However, intermittent hypoxia is also associated with increased arterial blood pressure through activation of the renin-angiotensin system in healthy subjects [178] and enhanced sympathetic and blood pressure responses to acute hypoxia and hypercapnia [177]. Cumulative exposure to intermittent hypoxia may produce progressive brain injury and subsequent neurological impairment due to metabolic stresses and reactive free radicals during hypoxia [177]. Intermittent hypoxia appears to elicit the same ventilatory changes to hypoxia as chronic hypoxia [179]. Furthermore, patients with obstructive sleep apnea, who serve as a model for chronic intermittent hypoxia, have a high risk of cardiovascular disease, increased levels of inflammatory markers, oxidative stress, coagulation, and thrombosis [180] [181].

Second, EVAs by nature are strenuous activities, and musculoskeletal injuries are more likely as the number and frequency of EVAs increase. The current extravehicular mobility unit (EMU) has long been associated with shoulder injuries and fingernail delamination; the former is believed to be due to scapulothoracic restriction imposed by the planar hard upper torso (HUT) of the EMU. Astronauts have also been injured while donning or doffing the EMU due to the awkward arm and shoulder movements required to maneuver around the HUT and scye bearings [182]. Efforts to design new spacesuits for exploration are attempting to capture the lessons learned from the Shuttle-era EMU, with such innovations as a quick donning rear-entry suit. However, even the ideal spacesuit will likely require the astronauts to work against a pressure differential of 4.3 psi or greater, thus imposing a risk of musculoskeletal wear and tear over time. The more the astronauts work inside a pressurized suit, the

more likely they will sustain contusions, sprains, strains, and general musculoskeletal pain. The latter could mask or be mistaken for type I DCS, predisposing astronauts to more serious DCS or unnecessarily requiring hyperbaric treatment.

Third, ISS experience has shown that crew well-being and mental health are significantly influenced by the operational tempo and a balanced work-rest schedule. The longer exploration missions will require the same "marathon" mentality as the ISS compared to the Space Shuttle Program's "sprint" mentality. Activities such as EVA, science, spacecraft maintenance, and public outreach will compete for the crewmembers' time, while daily time for meals, exercise, hygiene, and relaxation must be preserved.

Behavioral Health Implications for an EVA-Intensive Mission

Anecdotal comments from Jack Stuster's review of astronaut journals highlight the heightened level of importance and increased stress felt regarding EVAs [183]:

- "I was pretty exhausted mentally after the EVA, but felt pretty good physically overall"
- "Today is EVA day. I'm starting to have that I-think-I-must-be-forgetting-something feeling."
- "It seems like the EVA stuff bonds folks. We feel each other's pain and understand the hardships associated with what we are doing."
- "After our EVAs were over, we had a day and a half off. It was one of the first times in which we had some time off 2 days in a row during the missions, so we planned dinner and a movie night."

Currently, EVAs are some of the most grueling and physically and mentally demanding activities required during a space mission. On EVA day, the schedule only accommodates the time for EVA, and the EVA astronaut is not required to exercise or complete other tasks.

Evidence indicates that sleep is significantly reduced during the time before an EVA [19]. Before an EVA, it is common for crewmembers to be too "wired" to sleep [17]. General practice has been not to schedule 2 consecutive days of EVA unless resources are limited. The proposed mission scenario with EVA every day or every other day can result in a heightened stress response, reduced sleep, and/or interrupted sleep in addition to the already reduced sleep in microgravity. This could have implications for task performance, memory, cognition etc.

During EVAs, the crew is especially vulnerable to the space environment. A dramatic shift in the perception of the mission will happen during an EVA-heavy mission, where astronauts will routinely expose themselves to an especially harsh and physically and mentally stressful environment. Increased training, mental preparation and safety vigilance will be necessary for this, and may have implications for selection as well.

Decreased Risk of Injury and Impaired Performance during EVA

Most of the mitigations that reduce DCS risk also apply to the reduction of injury and impaired performance during EVA. Moving traditional EVA work to the IVA role, short EVAs and single-person EVAs are all made possible by the 8/32 environment in conjunction with the MMSEV. Desert Research and Technology Studies (DRATS) in 2008 compared EVA performance for two-suited crewmembers in an

unpressurized rover (UPR) versus the same crew with a pressurized rover (MMSEV) using suitports and EVA suits as needed to complete mission objectives. Comparing a 1-day traverse in both conditions, the MMSEV condition showed a 31% increase in 1-day traverse distance, 57% increase in total productivity, 470% increase in productivity per EVA hour, 23% increase in boots-on-surface EVA time with a 61% decrease in total EVA time, decreased fatigue, and decreased discomfort [184].

The operational concepts enabled by the 8/32 environment allow significant EVA capability without unnecessary time spent in the suit. Less time in the suit also reduces the overall probability of injury. Strauss reported a likelihood of a crewmember reporting some medical symptom at 24.6% per Neutral Buoyancy Laboratory training session [185]. Scheuring, et al. reported a very similar likelihood of a minor injury at 0.24 per EVA [186]. Although these symptoms/injuries ranged from minor to significant, it is still a very high reporting rate and indicates that more effort needs to be focused on injury mitigation, human performance optimization, and increased EVA efficiency by moving some traditional EVA tasks into the IVA environment.

8/32 Pressure Mediated Considerations

Not all of the potential human issues from the 8/32 environment are related to the addition of mild hypoxia. Some of the hardware used by the astronauts is pressure sensitive. This section will discuss issues pertaining to operations at 8 psia irrespective of the F_IO_2.

Increased Insensible Water Loss

This is a well-known aspect of mountaineering due to several factors including humidity, temperature, and pressure differences at altitude, but there is evidence that a reduction in pressure alone will account for an increased insensible water loss that will need to be replaced with additional drinking water [187]. This increased water loss will also need to be considered by the ECLSS team.

Advanced Food Technology

The Advanced Food Technology (AFT) project team is investigating the possibility of a partially bioregenerative food system on the Martian surface or any other extended surface mission. Fresh fruits and vegetables and possibly other commodities can be grown hydroponically in environmentally controlled chambers. Other raw commodities can be launched from Earth in bulk and processed into edible ingredients. These processed ingredients along with the fresh fruits and vegetables and other packaged foods and ingredients can be used to prepare the meals in a galley. It is expected that due to “return on investment,” this concept of operations would not occur until a surface habitat is in continual operation for multiple years.

The 8/32 environment can affect operations during a surface mission where food processing (converting raw ingredients such as soybeans into tofu) or food preparation beyond simple heating and rehydration is conducted. At reduced pressure conditions, water boils at much lower temperatures, which slows the heat transfer into the food in the water. The combination of hypogravity and lower pressure may improve colloidal stability, but mixing, fluid transport, boiling, condensation, and natural convection are all processes likely to be affected negatively by the reduction in gravity. Thus, any equipment evaluation

must consider whether the equipment depends on physical phenomena that fail to exist in a hypogravity or hypobaric environment like Mars. At reduced pressure conditions, water boils at much lower temperatures, which slows the heat transfer into the food in the water. At that pressure, the boiling temperature for water is 84°C (183°F). To create safe and acceptable food, cooking and processing of food is dependent on time/temperature combinations. Also, certain resulting textures come from cooking. For example, if the starch in rice is not gelatinized at 83°C (181°F), then the rubbery texture is replaced by dry, granular textures. The AFT team has not conducted any tests at 8 psi, so there are no data on what would be required on the surface. A solution may be to use a pressure cooker, but that requires extra mass and volume and may not be the answer to all "cooking." Understanding the physical changes in the environment and the impact to food preparation and processing is critical to estimate the microbial load throughout the cook, quantify the risk of foodborne illness, and reduce the risk to acceptable levels.

A major research thrust for AFT is identifying a high O_2 barrier packaging material. Oxidation in food results in quality loss including nutrient breakdown and color and flavor changes. There is actually a potential advantage to the 8/32 environment because there would be less O_2 to deteriorate the food. A technology gap would be what degree does the 8/32 environment affect product quality and whether the packaging barrier requirements would be modified significantly.

Acoustics

The 8 psia environment might affect acoustics. There is an assumption that lower atmospheric pressure in a habitat will reduce the sound intensity of both noise and voice. For example, lower pressures are expected to necessitate higher air flow rate through the ECLSS, resulting in increased fan noise, which is countered by noise transmission in a thinner air. The balance between several factors related to acoustics is unknown since there can be off-setting effects. At a lower pressure, the acoustic radiation efficiency is reduced, so noise levels should be lower in general. However, it will be more difficult to project your voice. For voice communications, these are off-setting each other and the net effect is unknown. There may be an additional effect in hearing (there is with microphone response), which would likely require some further investigation, starting with a literature review and followed, if warranted, by some additional studies.

Crew Health Care Systems

An Exploration equivalent to the ISS Crew Health Care System (CHeCS) will consist of countermeasures, environmental health monitoring, and health maintenance. The impact of an 8/32 environment will have to be evaluated in terms of each of these elements.

The Countermeasures System (CMS) will provide aerobic and anaerobic exercise capabilities for crewmembers to minimize cardiovascular deconditioning, bone loss, and muscle atrophy due to disuse in microgravity. In general, the current CMS on the ISS are believed to be adequate in maintaining aerobic fitness and bone mineral density (although preservation of bone architecture is still being debated). However, CMS hardware may be reduced in exploration missions given a smaller habitable volume compared to the ISS. An 8/32 specific concern is that air pressure-dependent hardware such as

the ARED would work less effectively, requiring more mass and/or more frequent cylinder evacuations to maintain the same range of resistance.

Exercise protocols of lower intensity or shorter duration [15] have been proposed for an 8/32 environment, to preserve consumables and minimize hardware cycling, while reducing the risk of AMS, as exercise has been associated with more severe AMS symptoms at simulated altitude [52]. However, these potential benefits of reduced exercise protocols must be weighed against the risks of cardiovascular and musculoskeletal deconditioning in terms of ability to perform strenuous mission tasks (e.g., EVA) and long-term health consequences.

The Environmental Health System (EHS) will enable the monitoring of air and water quality, toxicology, radiation, and acoustics in the spacecraft. Generally speaking, all of the instruments used to perform EHS activities will need to be able to operate at lower ambient pressures corresponding to an 8/32 environment. In particular, the current compound-specific analyzers for combustion products (CSA-CP) and compound specific analyzers for oxygen (CSA-O_2) are currently rated to operate no lower than 13.9 psi and 9.5 psi, respectively [188]. These and other air sampling devices will especially need to be modified and/or tested to work in an 8/32 environment.

The Health Maintenance System (HMS) will enable nominal and contingency evaluation of crew health and provide treatment for a variety of illnesses and injuries. All medical hardware will also need to be certified to operate in an 8/32 environment. Additionally, air-dependent diagnostic hardware may have to be modified (e.g., blood pressure cuffs) or substituted with devices that are not air dependent (e.g., air-puff tonometer). In terms of therapeutics, medications may or may not be more stable in a reduced O_2 environment, given its combination with higher space radiation. Capability for supplemental O_2 and mechanical ventilation will be needed to treat a subset of conditions on the Exploration Medical Conditions List – both will have to be compatible with the spacecraft atmosphere. A defibrillator to treat sudden cardiac arrest or arrhythmia will also have to pose minimal fire risk.

Human Health and Performance Disposition of the 8/32 Environment

Based on the literature described in the paper, it is clear that the addition of HH to the spaceflight environment presents substantial concerns for human health and performance. A central theme from this review is our collective ignorance of the integrated physiologic response to living and working in a hypobaric, mildly hypoxic, hypogravity and possibly hypercapnic environment. The goal for any manned vehicle should be to operate under normoxic conditions, if possible. If mild HH is required to facilitate a rapid EVA capability, then the right balance needs to be achieved for when to utilize this environment and then for what duration.

With an upfront understanding of the need to maintain low $ppCO_2$ values, future spaceflight vehicles can be designed to operate the internal environment much lower than what is currently experienced on the ISS. Because elevated CO_2 is likely to exacerbate acclimatization to and the symptoms associated with hypoxia, we recommend that the CO_2 Spacecraft Maximum Allowable Concentration (SMAC) be updated to reflect the need for lower $ppCO_2$. Work to update the CO_2 SMAC is currently supported by

the Space Medicine and Toxicology groups and is expected to be included with the next open call for updates to the Human Integration Design Handbook.

Unlike $ppCO_2$, nothing can be done to alter the gravity environment of future exploration destinations. Gravity is the perfect antidote for many of the negative adaptations to the spaceflight environment. It is unclear to what degree lunar or Mars gravity may mitigate some of these negative changes. As we have stated previously, our concern is adding HH to the hypogravity (especially microgravity) and elevated $ppCO_2$ spaceflight environment. Of possible destinations, the moon and Mars both provide gravity and are the DRMs considering employment of the 8/32 environment for longer periods of time.

Although decreasing $ppCO_2$ and operating in a gravity field both provide positive benefits, only an increase in ppO_2 will truly reduce the hypoxic dose. Before any forward work evaluating the 8/32 environment, we recommend that the trade space should be reevaluated for any achievable increase in ppO_2. Any increase in ppO_2 would help alleviate the hypoxia mediated symptoms. Enrichment to 38% O_2 would meet the current NASA-STD-3001 requirements for a cabin ppO_2 > 155 mmHg, but enrichment to 40% O_2 at 8 psia would be considered truly normoxic based on P_IO_2.

Available ppO_2 Enrichment from 8/32 to 8.2/34

At nearly the same time that work on this report began, the NASA EAWG effort was revisited with a new working group title: Exploration Atmosphere Action Team. Within the context of recent Exploration Atmosphere Action Team meetings, the HRP 8/32 Tiger Team has been acting as the Human Health and Performance (HHP) subteam, which is one of five subteams including Flammability/Materials, ECLSS, Operations/EVA and Vehicle Design. The HHP subteam met separately with the other subteams to evaluate whether there was any available trade space to enrich the ppO_2.

The 8 psia cabin atmosphere was set by two primary factors: 1) DCS mitigation and 2) suitport operations. For DCS mitigation, any increase in cabin pressure would increase prebreathe time and therefore would not be acceptable unless the F_IO_2 could be enriched to maintain the ppN_2 at equivalent or lower levels than the 8/32 environment. For suitport operations, we learned that the suitport was not rigidly locked in to 8 psia, but rather was compatible up to 8.3 psia. Changing the environment from 8/32 to 8.3/32 does enrich the ppO_2 slightly, but the offsetting increase in prebreathe does not make this an acceptable choice alone.

The 32% O_2 limit was chosen for flammability concerns. Upon review of the EAWG final report, it was stated that a 36% O_2 cabin atmosphere would be possible with current materials [1]. Discussions with the ECLSS subteam did indicate a need for some control box limits, so we settled on 34% as a target with an acceptable upper limit of 36%. The final consensus of the HHP subteam was to increase the P_B to 8.2 psia and the O_2% to 34% and suggest a control box of 8.1 to 8.3 psia and 33.5% to 35% O_2. This improvement was deemed acceptable by the other subteams and has become a consensus recommendation for forward work and development from the Exploration Atmospheres Action Team.

Although the change from a target setpoint of 8/32 to 8.2/34 seems minor, it provides a substantial reduction in hypoxic dose without a change to ppN_2, which provides physiologic relief without negating

any of the operational benefits of suitport and reduced prebreathe. Table 5 provides the comparison of key physiologic parameters showing an overall increase of 11 mmHg to P_AO_2, a reduction of over 610 m (2,000 ft) of equivalent air altitude, and no change to ppN_2.

Table 5. Comparison 8/32 and 8.2/34 Environments with Reference to Earth Normal Atmosphere

P_B psia	O_2%	ppO_2 mmHg	P_AO_2 mmHg	EAA m (ft)	ppN_2 mmHg
14.7	21	160	109	0	600
Earth normal atmosphere given above for reference					
8.0	32	132	77	1880 (6170)	281
8.2	34	144	88	1213 (3980)	280
Difference		**+12**	**+11**	**-667 (-2190)**	**-1**

8.2/34 Comparison to 10.2/26.5

One serendipitous finding was that 8.2/34 is almost physiologically equivalent to the atmosphere of 10.2 psia and 26.5% O_2 used on the shuttle. A comparison of the two environments is shown in Table 6 demonstrating that the two environments are almost equivalent from a hypoxic dose, but that 8.2/34 presents a much lower tissue N_2 saturation level.

Table 6. Comparison of the 8.2/34 Environment to the Shuttle 10.2/26.5 Atmosphere

P_B psia	O_2%	ppO_2 mmHg	P_AO_2 mmHg	EAA m (ft)	ppN_2 (mmHg)
10.2	26.5	140	87	1265 (4150)	388
8.2	34	144	88	1213 (3980)	280
Difference		**+4**	**+1**	**-170**	**-108**

Any human health and performance data available from missions employing the 10.2/26.5 environment may be helpful toward understanding the implications of employing a mildly hypoxic environment during flight. Table 7 describes the number of days at 10.2/26.5 as well as the crew size and total man days. Days at 10.2/26.5 were calculated based on the assumption that cabin pressure was reduced on flight day 2 and held there until the completion of the last EVA.

The average duration at 10.2/26.5 was 6 days, with 22 of the 34 missions depressing to 10.2/26.5 for somewhere between 5 to 7 days. The longest mission using 10.2/26.5 was for 14 days, but that was only one mission and the next-longest missions were 9 days.

Table 7. Spaceflight Experience in at the 10.2 psia / 26.5% O_2 Environment

Flight	Launch	Landing	Crew Size	Last EVA	Days at 10.2/26.5	Man Days at 10.2/26.5
STS-41B	02/03/1984	02/11/1984	5	02/09/1984	6	30
STS-41C	04/06/1984	04/13/1984	5	04/11/1984	5	25
STS-41G	10/05/1984	10/13/1984	7	10/11/1984	6	42
STS-51A	11/08/1984	11/16/1984	5	11/14/1984	6	30
STS-51D	04/12/1985	04/19/1985	7	04/16/1985	4	28
STS-51I	08/27/1985	09/03/1985	5	09/01/1985	5	25
STS-61B	11/26/1985	12/03/1985	7	12/01/1985	5	35
STS-37	04/05/1991	04/11/1991	5	04/08/1991	3	15
STS-49	05/07/1991	05/16/1992	7	05/14/1992	7	49
STS-54	01/13/1993	01/19/1993	5	01/17/1993	4	20
STS-51	09/12/1993	09/22/1993	5	09/16/1993	4	20
STS-61	12/02/1993	12/13/1993	7	12/08/1993	6	42
STS-64	09/09/1994	09/20/1994	6	09/16/1994	7	42
STS-69	09/07/1995	09/18/1995	5	09/16/1995	9	45
STS-72	01/11/1996	01/20/1996	6	01/17/1996	6	36
STS-76	03/22/1996	03/31/1996	6	03/27/1996	5	30
STS-82	02/11/1997	02/21/1997	7	02/17/1997	6	42
STS-86	09/25/1997	10/06/1997	7	10/01/1997	6	42
STS-87	11/19/1997	12/05/1997	6	12/03/1997	14	84
STS-88	12/04/1998	12/15/1998	6	12/12/1998	8	48
STS-96	05/27/1999	06/06/1999	7	05/29/1999	2	14
STS-103	12/19/1999	12/27/1999	7	12/24/1999	5	35
STS-101	05/19/2000	05/29/2000	7	05/21/2000	2	14
STS-106	09/08/2000	09/20/2000	7	09/17/2000	9	63
STS-92	10/11/2000	10/24/2000	7	10/18/2000	7	49
STS-97	11/30/2000	12/11/2000	5	12/07/2000	7	35
STS-98	02/07/2001	02/20/2001	5	02/14/2001	7	35
STS-102	03/08/2001	03/21/2001	7	03/12/2001	4	28
STS-100	04/19/2001	05/01/2001	7	04/24/2001	5	35
STS-104	07/12/2001	07/24/2001	5	07/17/2001	5	25
STS-105	08/10/2001	08/22/2001	7	08/18/2001	8	56
STS-108	12/05/2001	12/17/2001	7	12/10/2001	5	35
STS-109	03/01/2002	03/12/2002	7	03/08/2002	7	49
STS-125	05/11/2009	05/24/2009	7	05/18/2009	7	49
Total					**202**	**1,252**

Human Health and Performance Risk Profile Changes from the 8/32 to 8.2/34 Environment

The analysis of potential human health and performance risks associated with the 8/32 environment indicated that many concerns warranted forward work, and that some concerns – such as an exacerbation of the VIIP syndrome – might preclude the use of the 8/32 environment. The change from 8/32 to 8.2/34 does not affect any of the EVA or pressure mediated concerns; however, for the hypoxia-related concerns, this change should provide significant improvement to the overall human health and performance risk profile. Although a quantified evidence-based likelihood and consequence analysis is not provided for each of the hypoxia mediated concerns, it is likely that a comparison of 8/32 to 8.2/34 would show a reduction in the likelihood and/or consequence for every hypoxia mediated symptom. This ppO_2 improvement may be enough to even eliminate some of the potential concerns.

One additional implication is that the independent pressure effect on hypoxic symptoms seems to be a function of hypoxic dose. The greater the hypoxic dose, the less an NH simulation is valid. The 8.2/34 environment with an EAA of approximately 1,219 m (4,000 ft) might be at a threshold for which simulating this environment could adequately be performed using a reduction in the F_IO_2 rather than having to use an O_2-enriched capable hypobaric chamber.

Based on the acceptance of 8.2/34 within the NASA engineering and materials community and the expected human health and performance risk reduction, it is recommended that forward work including human research should be performed at the revised 8.2/34 environment rather than 8/32.

Although the shift from 8/32 to 8.2/34 reduces the general concerns for impaired human health and performance, it does not eliminate all these concerns. Therefore, the overall amount of initial recommended forward work is likely to be the same in either environment. The difference is that there is a greater expectation that these studies may demonstrate the acceptability of the 8.2/34 environment and thus require less follow-up work and environmental countermeasure development.

Recommendations and Forward Work

This section will describe the suggested research needs and forward work to prepare for this environment. In some cases, this work is already being done and we have highlighted what specific HRP risks need to be better understood. The remaining recommendations will focus on suggested new areas of human research and will describe technical recommendations for implementing the 8.2/34 environment, including considerations for how to transition to this environment.

Additional Analyses Needed for 8.2/34 Environment

The primary purpose of this paper was to evaluate the human health and performance risks associated with the 8/32 environment. With a shift now to the 8.2/34 environment, we suggest two additional analyses as follow-on efforts to this paper.

1. Literature review of very mild altitudes up to 1,830 m (6,000 ft).

2. Mining of human health and performance data from the 10.2/26.5 shuttle exposures. This effort would provide a look into the short-term effects of mild hypoxia in the spaceflight environment.

Current Research Efforts in Need of Better Understanding

Certain risks are not currently well understood. In some cases, it was the uncertainty associated with these risks more than the addition of HH that was of concern. These current HRP risks include VIIP, immune dysfunction and OSaD, which are not well understood, and many of the challenges of the Exploration-class missions including longer durations and mild hypoxia and the cycling between the hypoxic IVA and slightly hyperoxic EVA environment. Continued research into the elevated $ppCO_2$ levels on the ISS and how this increased level affects human health and performance is needed. Additional research not directly associated with, but highly related to, the 8.2/34 environment would be the work needed to mitigate the risk of crewmember injury during EVA, work done to optimize performance in the EVA suit, and human factors engineering efforts to optimize vehicles for habitability.

Proposed New Research Needs

This section provides initial recommendations for research studies to aid our understanding of human adaptation to the 8.2/34 environment in conjunction with the spaceflight environment. These research needs are described at a very high level.

1. Validation of the 8.2/34 DCS mitigation strategy through hypobaric chamber studies – if DCS is not successfully mitigated with the 8.2/34 environment, then there is a need to reevaluate the atmosphere, operational concepts, prebreathe requirements, EVA frequency, and many other factors that are related to every other follow-on research study. Therefore, we recommend that the validation of the 8.2/34 environment for DCS mitigation is recommended to be the first major study associated with the 8/32 environment.
2. Short-term (7- to 14-day) exposures to the 8.2/34 environment using a hypobaric chamber that include a mission-like timeline, EVA simulations and the expected level of $ppCO_2$ also included. These 1- to 2-week exposures would allow several risks to be evaluated simultaneously, including VIIP, AMS, sensorimotor, sleep, OSaD, exercise, cardiovascular, immune, nutrition, bone, behavioral health, and possibly other concerns. Much of this work could be combined into work described in recommendation #1. Where possible, it would be beneficial to include an additional exposure using NH to evaluate the possibility of an independent pressure effect worsening the hypoxic dose at 8.2/34.
3. Longer-term exposures (>14 days) to the 8.2/34 environment. Results of recommendations #2 will help to determine what risks need further evaluation. Although hypobaric chamber usage is preferable, many of these evaluations could be performed with NH simulations.
4. Short- and long-term 8.2/34 exposures including bed rest. Although hypobaric chamber usage is preferable, these evaluations could possibly be performed with NH simulations.
5. Cell culture oxidative stress studies using bioreactor and the appropriate swings between the IVA and EVA environments.
6. Food preparation testing at 8.2 psia is needed to ensure palatability and ensure acceptable microbial loads are met.

7. Antarctica offers a mission-like analog to spaceflight that also includes a hypobaric environment (2,834 m [9,300 ft]) that may provide an opportunity to evaluate some concerns discussed in this paper.

Flight Demonstration of the 8.2/34 Environment

Upon completion of the validation of the DCS mitigation strategy and with an initial understanding of the short-term hypoxic symptoms, we recommend that the 8.2/34 environment and EVA operations be demonstrated in flight at a location with a margin of safety. This could include the ISS or a lunar waypoint habitat.

An alternative to using the 8.2/34 environment would be to employ the physiologically similar environment of 10.2/26.5 using the ISS airlock or some other modifiable habitable element. The 10.2/26.5 environment is already certified for use in the ISS airlock and would allow us to study the effects of an alternative atmosphere mixed with the spaceflight environment. If creating a habitable element on the ISS is not feasible, an NH simulation using a flight-compatible portable reduced O_2 breathing device could be considered. The crewmember would wear an oronasal facemask connected to the reduced O_2 source. This may preclude continuous and longer-duration exposures, but could provide valuable feedback on how short-duration exposure to hypoxia in the spaceflight environment affects cognitive performance and neurophysiology.

General Technology Recommendations

This section will recap some of the technical recommendations suggested to certify hardware and to mitigate some of the negative physiologic effects of the 8.2/34 and spaceflight environment.

- Improved CO_2 scrubbing will be needed for human habitation of a mildly hypoxic environment and is perceived to be quite possible by the NASA engineering community.
- Guidelines for the ECLSS control box for the 8.2/34 environment need to be further defined. The expectation is that the control box can operate in a tighter band around the setpoint than the ± 0.2 psi and ± 2% O_2 described in the EAWG report.
- Guidance on the rate of change from one atmospheric composition to another will need to be generated for the ECLSS controls.
- Existing CHeCS hardware, new medical hardware, exercise countermeasures, and human research equipment will need to be updated to ensure proper operation in the reduced pressure of the 8.2 psia environment.
- Finally, the IMM will need to updated to reflect changes in disease incidence and treatment based on the 8.2/34 environment.

Considerations for Transitioning Between Environments

This section will summarize some suggested mitigation strategies that will help alleviate symptoms or prepare the astronaut to occupy the 8.2/34 spaceflight environment. Gradual decompression from 14.7 psia to 8.2 psia will diminish many of the acute symptoms such as AMS and hypoxic-related sleep problems. Supplemental O_2 should be available during vehicle decompressions and throughout the

length of the mission should certain crewmembers not adapt as readily as others. This supplemental O_2 will also be used as DCS prevention during this depressurization.

An exact understanding of atmospheric and tissue inert gas exchange does not yet exist to precisely define when the inert gas tension in tissues comes into a new equilibrium after the breathing environment has changed. When a significant pressure reduction is used to reduce the tissue N_2 tension, then there is the additional complication of creating "silent bubbles" in the body that then hinder normal tissue N_2 exchange with the atmosphere. In the case of the 8.2/34 environment, the pressure reduction from 14.7 psia to 8.2 psia is done in concert with an increase in F_IO_2 from 21% to 34%. Both of these changes reduce ambient ppN_2 from 600 to 280 mmHg, but there is some uncertainty on when tissue N_2 tension comes into a new equilibrium. If we accept that a 360-minute theoretical half-time tissue compartment is key to our DCS applications, then the mathematics of simple exponential decay says that you need four half times (24 hr) to account for 94% of the difference between the initial and final tissue N_2 tension. Six half times (36 hr) brings the difference to 98% and by 8 half times (48 hr), the difference is negligible.

Based on research experience from the shuttle 10.2 psia staged denitrogenation protocol, it was clear that a direct depress to 10.2 psia created "silent bubbles" that manifested 12 to 16 hours later as early-onset venous gas emboli (VGE) and early onset Type II DCS symptoms while at the EVA pressure of 4.3 psia. A 60-minute prebreathe was instituted such that the first decompression to 10.2 psia would not theoretically supersaturate the 360-minute half-time compartment; the computed tissue ratio was 1.0. This removed the early-onset VGE and DCS in subsequent tests of the staged protocol [189]. In keeping with this same philosophy, preliminary analysis indicates the need to implement a 180-minute prebreathe before depressurization from 14.7 to 8.2 psia to keep the computed tissue ratio at 1.0. Since 100% O_2 is used for the 18-minute prebreathe, the tissue N_2 tension is lower than it would be if the astronaut was just exposed for 180 minutes to the 8.2/34 environment. So the computed time to achieve equilibrium to the 8.2/34 environment is reduced to 45 hours. If an EVA was to be performed before saturation at 8.2/34, then additional prebreathe beyond the expected 15 minutes would be needed, possibly as much as 30 minutes for the first EVA.

Crewmembers will need to be trained to understand the symptoms of hypoxia. When the application of the 8.2/34 environment is to be employed early in the mission phase, the crewmembers will have to adapt acutely to the spaceflight and hypoxic environment at the same time. Critical tasks should be avoided and workload stress should remain low during the atmospheric transition period.

Although hypoxic pre-conditiong is not a mitigation for DCS, it is a technique that uses bouts of hypoxic exposure before ischemic insults. This may not directly apply to the astronaut in the spaceflight environment, but the effect of pre-exposure to the hypoxic stimulus and how it prepares people to tolerate the hypoxic environment on subsequent trials has also been discussed. The degree of hypoxia, duration of exposure, and timing of the exposure would need further literature review before implementation in the crew training and mission preparation phases.

Conclusion

EVA is at the core of a manned space exploration program. With the 8/32 environment, NASA gains the capability for efficient EVA with low risk of DCS, but accrues the additional human health and performance risks associated with the addition of HH to spaceflight environment. This literature review of the human health and performance risks associated with the 8/32 cabin environment indicated many potential areas of concern including increased intracranial pressure, visual impairment, sensorimotor dysfunction, and oxidative damage. Forward work would also include validating the DCS mitigation strategy, identifying/treating AMS, developing new exercise protocols, effectively preparing food at 8 psia, ensuring quality sleep, and preventing suit-induced injuries.

The available engineering trade space provides the opportunity to move from 8/32 to 8.2/34, which increases the P_AO_2 by 11 mmHg and decreases the EAA by more than 610 m (2,000 ft). This significant improvement may reduce the likelihood and/or consequence of each discussed hypoxic symptom. Although the 8.2/34 environment is an improvement from the 8/32 environment, it does not eliminate all human health and performance concerns and needs to be evaluated through appropriately simulated research studies before flight implementation.

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Works Cited

[1] NASA Exploration Atmospheres Working Group, "Recommendations for exploration spacecraft internal atmospheres: The final report of the NASA exploration atmospheres working group. NASA Technical Publication NASA/TP-2010-216134," NASA Technical Publication , 2010.

[2] P. D. Campbell, "Recommendations for Exploration Spacecraft Internal Atmospheres: The Final Report of the NASA Exploration Atmospheres Working Group," Johnson Space Center, Houston TX, NASA Report JSC-63309, January 2006.

[3] W. H. Gerstenmaier, "Exploration Atmospheres," NASA Internal Memorandum, 2013.

[4] R. L. DeHart, *Fundamentals of Aerospace Medicine*, 2nd ed., R. L. DeHart, Ed. Baltimore, MD: Williams and Wilkins, 1996.

[5] H. Rahn and W. O. Fenn, *A graphical analysis of the respiratory gas exchange: the O2 - CO2 diagram.* Washington, DC: The American Physiological Society, 1956.

[6] J. Conkin and J. H. Wessel III, "Critique of the equivalent air altitude model," *Aviat Space Environ Med*, vol. 79, pp. 975-982, 2008.

[7] G. P. Millet and V. Pialoux, "Point:counterpoint: hypobaric hypoxia induces / does not induce different responses from normobaric hypoxia," *J. Appl. Physiol.*, vol. 112, pp. 1783-84, 2012.

[8] R. Mounier and J. V. Brugniaux, "Point:counterpoint: hypobaric hypoxia induces / does not induce different responses from normobaric hypoxia," *J Appl Physiol*, vol. 112, pp. 1784-86, 2012.

[9] O. Girard, et al., "Comments on point:counterpoint: hypobaric hypoxia induces / does not induce different responses from normobaric hypoxia.," *J Appl Physiol*, vol. 112, pp. 1788-95, 2012.

[10] J. Conkin and J. H. Wessel III, "A model to predict acute mountain sickness in future spacecraft," Johnson Space Center NASA Technical Publication NASA/TP-2009-214791, 2009.

[11] N. A. Richard and M. S. Koehle, "Differences in cardio-ventilatory responses to hypobaric and normobaric hypoxia: a review," *Aviation, Space and Environmental Medicine*, vol. 83, pp. 677-84, 2012.

[12] J. T. James, "The headache of carbon dioxide exposures," Society of Automotive Engineers Paper No. 07ICES-42, 2007.

[13] J. Law, S. Watkins, and D. Alexander, "In-flight carbon dioxide exposures and related symptoms:

association, susceptibility, and operational implications," NASA/TP-2010-216126, 2010.

[14] P. D. Cronyn, S. Watkins, and D. J. Alexander, "Chronic exposure to moderately elevated CO2 during long-duration space flight," Johnson Space Center, Houston, TX, NASA Technical Report NASA/TP-2012-217358, 2012.

[15] R. A. Scheuring, J. Conkin, J. A. Jones, and M. L. Gernhardt, "Risk assessment of physiological effects of atmospheric composition and pressure in Constellation vehicles," *Acta Astronautica*, pp. 727-739, 2008.

[16] M. R. Barratt and S. L. Pool, Eds., *Principles of Clinical Medicine for Space Flight*. New York, USA: Spring Science+Business Media LLC, 2008.

[17] A. Whitmire, et al., "Sleep Quality Questionnaire: Short duration missions," NASA Johnson Space Center NASA Technical Paper, Manuscript in preparation.

[18] H. W. Lane, S. M. Smith, B. L. Rice, and C. T. Bourland, "Nutrition in Space: Lessons from the past applied to the future," *Am. J. Clin. Nutr.*, pp. 801-805, 1994.

[19] L. K. Barger, J. P. Sullivan, S. W. Lockley, and C. A. Czeisler, "Development of an educational program for flight controllers working nightshifts (poster presentation)," in *NASA Human Research Program Investigators' Workshop*, Houston, Texas, 2012.

[20] T. H. Mader, et al., "Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight," *Ophthalmology*, vol. 118, no. 10, pp. 2058-69, Oct. 2011.

[21] "Clinical Practice Guideline for Spaceflight-Induced Intracranial Hypertension [internal document]," 2011.

[22] T. M. Gotoh, et al., "Acute hemodynamic responses in the head during microgravity induced by free drop in anesthetized rats," *Am J Physiol Regul Integr Comp Physiol*, vol. 286, no. 6, pp. R1063-8, Jun. 2004.

[23] E. Rostrup, et al., "The relationship between cerebral blood flow and volume in humans," *NeuroImage*, vol. 24, pp. 1-11, 2005.

[24] C. Imray, A. Wright, A. Subudhi, and R. Roach, "Acute mountain sickness: pathophysiology, prevention, and treatment," *Prog. Cardiovasc. Dis.*, vol. 52, no. 6, pp. 467-84, May 2010.

[25] M. H. Wilson, S. Newman, and C. H. Imray, "The cerebral effects of ascent to high altitudes," *Lancet Neurol.*, vol. 8, no. 2, pp. 175-91, Feb. 2009.

[26] I. Singh, et al., "Acute mountain sickness," *N. Engl. J. Med.*, vol. 280, pp. 175-184, 1969.

[27] G. Savourey, et al., "Evaluation of the Lake Louise acute mountain sickness scoring system in a hypobaric chamber," *Aviat. Space Environ. Med.*, vol. 66, no. 10, pp. 963-7, Oct. 1995.

[28] A. I. Sutherland, D. S. Morris, C. G. Owen, A. J. Bron, and R. C. Roach, "Optic nerve sheath diameter, intracranial pressure and mountain sickness on Mount Everest: A longitudinal cohort study.," *Br. J. Sports Med.*, vol. 42, pp. 183-88, 2008.

[29] Y. B. Yang, B. Sun, Z. Yang, J. Wang, and Y. Pong, "Effects of acute hypoxia on intracranial dynamics in unanesthetized goats," *J. Appl. Physiol.*, pp. 74:2067-71, 1993.

[30] M. M. Bosch, et al., "High incidence of optic disc swelling at very high altitudes," *Arch. Ophthalmol.*, vol. 126, no. 5, pp. 644-50, May 2008.

[31] P. H. Hackett, et al., "High-altitude cerebral edema evaluated with magnetic resonance imaging: clinical correlation and pathophysiology," *JAMA*, vol. 280, no. 22, pp. 1920-5, Dec. 1998.

[32] D. S. Morris, et al., "The eye at altitude," *Adv. Exp. Med. Biol.*, vol. 588, pp. 249-70, 2006.

[33] J. J. Bloomberg and A. P. Mulavara, "Changes in walking strategies after spaceflight," *IEEE Engineering in Medicine and Biology Magazine*, vol. 22, no. 2, pp. 58-62, 2003.

[34] G. Clement and M. F. Reschke, *Neuroscience in Space*. New York: Springer, 2008.

[35] W. H. Paloski, et al., "Risk of sensory-motor performance failures affecting vehicle control during space missions: A review of the evidence," *J. Grav. Physiol.*, vol. 15, no. 2, 2008.

[36] A. P. Mulavara, et al., "Locomotor function after long-duration space flight: Effects and motor learning during recovery," *Exp. Brain Res.*, vol. 202, no. 3, pp. 649-59, 2010.

[37] B. T. Peters, et al., "Dynamic visual acuity during walking after long-duration spaceflight," *Aviat. Space Environ. Med.*, vol. 82, no. 4, pp. 463-6, 2011.

[38] S. J. Wood, J. A. Loehr, and M. E. Guilliams, "Sensorimotor reconditioning during and after spaceflight," *NeuroRehabilitation*, vol. 29, pp. 185-195, 2011.

[39] F. Petrassi, S. Gaydos, J. Ramiccio, and P. Walters, "Hypoxic Hypoxia at Moderate Altitudes: State of the Science," U.S. Army Aeromedical Research Laboratory USAARL 2011-17, 2011.

[40] D. M. Connolly, "Oxygenation state and twilight vision at 2438 m," *Aviat. Space Environ. Med.*, vol. 82, pp. 2-8, 2011.

[41] W. D. Fraser, D. E. Eastman, M. A. Paul, and J. A. Porlier, "Decrement in postural control during mild hypobaric hypoxia," *Aviat. Space Environ. Med.*, vol. 58, pp. 768-772, 1987.

[42] S. H. G. Nordahl, O. J. O. Aasen T, and O. I. Molvaer, "Effects of hypobaric hypoxia on postural control," *Aviat. Space Environ. Med.*, vol. 69, pp. 590-5, 1998.

[43] S. H. G. Nordahl, T. Aasen, J. Risberg, J. O. Owe, and O. I. Molvaer, "Postural control and venous gas bubble formation during hypobaric exposure," *Aviat. Space Environ. Med.*, vol. 73, pp. 184-90, 2002.

[44] T. Nesthus, L. Rush, and S. Wreggit, "Effects of Mild Hypoxia on Pilot Performance at General Aviation Altitudes," FAA Civil Aeromedical Institute DOT/FAA/AM-97/9, 1997.

[45] A. Smith, "Hypoxia symptoms reported during helicopter operations below 10,000 ft: a retrospective survey," *Aviat. Space Environ. Med.*, vol. 76, pp. 794-798, 2005.

[46] M. S. Siniaia and A. D. Miller, "Vestibular effects on upper airway musculature," *Brain Res.*, vol. 736, no. 1-2, pp. 160-164, 1996.

[47] D. Singh, R. C. Kochhar, and S. K. Kacker, "Effects of high altitude on inner ear functions," *J. Laryngol. Otol.*, vol. 90, no. 12, p. 1113–1120, 1976.

[48] U. Dirnagl, K. Becker, and A. Meisel, "Preconditioning and tolerance against cerebral ischaemia: from experimental strategies to clinical use," *Lancet Neurol.*, vol. 8, pp. 398-412, 2009.

[49] K. B. Shpargel, et al., "Preconditioning paradigms and pathways in the brain," *Cleve. Clin. J. Med.*, vol. 75, no. Suppl 2, pp. S77-82, 2008.

[50] H. J. Steiger and D. Hanggi, "Ischaemic preconditioning of the brain, mechanisms and applications," *Acta Neurochir. (Wein)*, vol. 149, pp. 1-10, 2007.

[51] A. B. Montgomery, J. Mills, and J. M. Luce, "Incidence of acute mountain sickness at intermediate altitude," *J. Am. Med. Ass.*, pp. 732-734, 1989.

[52] R. C. Roach, et al., "Exercise exacerbates acute mountain sickness at simulated high altitude," *J. Appl. Physiol.*, vol. 88, no. 2, pp. 581-5, 2000.

[53] R. C. Roach, J. A. Loeppky, and M. V. Icenogle, "Acute mountain sickness: increased severity during simulated altitude compared with normobaric hypoxia," *J. Appl. Physiol.*, vol. 81, no. 5, pp. 1908-10, Nov. 1996.

[54] P. Anderson, W. D. Miller, K. A. O'Malley, and M. L. Ceridon, "Incidence and symptoms of high altitude illness in South Pole workers: Antarctic study of altitude physiology," *Clinical medicine*

Insights: Circulatory, Respiratory and Pulmonary Medicine, pp. 27-35, 2011.

[55] W. O. Fenn, H. Rahn, and A. B. Otis, "A theoretical study of the composition of the alveolar air at altitude," *Amer. J. Physiol.*, vol. 146, pp. 637-653, 1946.

[56] R. A. Seupaul, J. L. Welch, S. T. Malka, and T. W. Emmett, "Pharmacologic prophylaxis for acute mountain sickness: a systematic shortcut review," *Ann. Emerg. Med.*, vol. 59, no. 4, pp. 307-317e1, Apr. 2012.

[57] A. M. Luks, et al., "Wilderness Medical Society consensus guidelines for the prevention and treatment of acidic altitude illness," *Wildnerness Environ Med*, vol. 21, no. 2, pp. 146-55, 2010.

[58] G. S. Lipman, N. C. Kanaan, P. S. Holck, B. B. Constance, and J. H. Gertsch, "Ibuprofen prevents altitude illness: A randomized controlled trial for prevention of altitude illness with nonsteriodal anti-inflammatories," *Ann Emerg Med*, Mar. 2012.

[59] B. H. Subedi, et al., "Complications of steroid use on Mt. Everest," *Wilderness Environ Med*, vol. 21, no. 4, pp. 345-8, 2010.

[60] P. H. Hackett and R. C. Roach, "High-altitude Medicine," in *Wilderness Medicine*, P. S. Auerbach, Ed. St. Louis: Mosby, 2001.

[61] M. L. Gernhardt, "Development and evaluation of a decompression stress index based on tissue bubble dynamics," University of Pennsylvania Dissertation, 1991.

[62] A. F. J. Abercromby, M. L. Gernhardt, and J. Conkin, "Potential benefit of intermittant recompression in reducing decompression stress during lunar extravehicular activities," in *79th Annual Scientific Meeting of the Aerospace Medical Association*, vol. 79, Boston, Mar. 2008, p. AbstractNo425.

[63] J. Conkin, M. L. Gernhardt, A. F. J. Abercromby, and J. P. Dervay, "Delaying venous gas emboli formation with oxygen prebreathe and intermediate recompression," in *79th Annual Scientific Meeting of the Aerospace Medical Association*, Boston, Mar. 2008, p. AbstractNo52.

[64] M. L. Gernhardt and A. F. J. Abercromby, "Use of variable pressure suits, intermittant recompression and nitrox breathing mixtures during lunar extravehicular activities," *Undersea Hyperba. Med.*, vol. 36, no. 4, 2009.

[65] A. A. Pilmanis, J. T. Webb, N. Kannan, and U. Balldin, "The effect of repeated altitude exposures on the incidence of decompression sickness," *Aviat Space Environ Med*, vol. 73, pp. 525-531, 2002.

[66] A. Moellerken, et al., "Recompression during decompression and effects on bubble formation in hte pig," *Aviat Space Environ Med*, vol. 78, pp. 557-560, 2007.

[67] K. L. English, S. M. C. Lee, J. A. Loehr, R. J. Ploutz-Snyder, and L. L. Ploutz-Snyder, "Isokinetic strength changes following long-duration space flight on the International Space Station," *Aviat Space Environ Med*, submitted 2012.

[68] A. D. Moore Jr, P. A. Lynn, and A. H. Fieveson, "Aerobic exercise responses to long duration spaceflight - the first 10 ISS years," *Aviat Space Environ Med*, submitted 2012.

[69] T. Lang, et al., "Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight," *J Bone Miner Res*, vol. 19, no. 6, pp. 1006-1012, 2004.

[70] S. M. Smith, et al., "Benefits for bone from resistance exercise and nutrition in long-duration spaceflight: Evidence from biochemistry and densitometry," *J Bone Miner Res*, vol. 27, no. 9, pp. 1896-906, 2012.

[71] D. M. Bailey and B. Davies, "Physiological implications of altitude training for endurance performance at sea level: a review," *Br. J. Sports Med.*, vol. 31, no. 3, pp. 183-90, 1997.

[72] D. Boning, "Altitude and hypoxia training--a short review," *Br. J. Sports Med.*, vol. 31, no. 3, pp. 183-90, 1997.

[73] L. M. Edwards, et al., "The effect of high-altitude on human skeletal muscle energetic: P-MRS results from the Caudwell Xtreme Everest expedition," *PLoS One*, vol. 5, p. e10681, 2010.

[74] M. Faucher, et al., "Matched adaptations of electrophysiological, physiological, and histological properties of skeletal muscles in response to chronic hypoxia," *Pflugers Arch.*, vol. 450, pp. 45-52, 2005.

[75] H. Hoppeler, S. Klossner, and M. Vogt, "Training in hypoxia and its effects on skeletal muscle tissue," *Scand. J. Med. Sci. Sports*, vol. 18, no. Suppl 1, p. 38–49, 2008.

[76] M. Flueck, "Plasticity of the muscle proteome to exercise at altitude," *High Alt. Med. Biol.*, vol. 10, p. 183–193, 2009.

[77] J. P. Wehrlin and J. Hallen, "Linear decrease in V̇o2 max and performance with increasing altitude in endurance athletes," *Eur. J. Appl. Physiol.*, vol. 96, p. 404–412, 2006.

[78] M. Amann, et al., "Arterial oxygenation influences central motor output and exercise performance via effects on peripheral locomotor muscle fatigue in humans," *J. Physiol.*, vol. 575, p. 937–952, 2006.

[79] J. E. Peltonen, et al., "Effects of oxygen fraction in inspired air on force production and electromyogram activity during ergometer rowing," *Eur. J. Appl. Physiol. Occup. Physiol.*, pp. 76(6):495-503, 1997.

[80] C. J. Gore, et al., "Increased arterial desaturation in trained cyclists during maximal exercise at 580 m altitude," *J. Appl. Physiol.*, vol. 80, no. 6, pp. 2204-10, 1996.

[81] C. S. Fulco, et al., "Gender alters impact of hypobaric hypoxia on adductor pollicis muscle performance," *J. Appl. Physiol.*, vol. 91, no. 1, pp. 100-8, 2001.

[82] B. Braun, et al., "Women at altitude: carbohydrate utilization during exercise at 4,300 m," *J. Appl. Physiol.*, vol. 881, pp. 246-56, 2000.

[83] S. R. Muza, et al., "Women at altitude: ventilatory acclimatization at 4,300 m," *J. Appl. Physiol.*, vol. 91, no. 4, pp. 1791-9, 2001.

[84] C. J. Holloway, et al., "Cardiac response to hypobaric hypoxia: persistent changes in cardiac mass, function, and energy metabolism after a trek to Mt. Everest Base Camp," *FASEB J.*, vol. 25, no. 2, pp. 792-6, 2011.

[85] J. Kjaergaard, et al., "The effect of 18 h of simulated high altitude on left ventricular function," *Eur. J. Appl. Physiol.*, vol. 98, no. 4, pp. 411-8, 2006.

[86] N. Nishimura, K. Iwasaki, Y. Ogawa, and K. Aoki, "Decreased steady state cerebral blood flow velocity and altered dynamic cerebral autoregulation during 5-h sustained 15% O2 hypoxia," *J. Appl. Physiol.*, vol. 108, pp. 1154-1161, 2010.

[87] K. Iwasaki, Y. Ogawa, S. Shibata, and K. Aoki, "Acute exposure to normobaric mild hypoxia alters dynamic relationships between blood pressure and cerebral blood flow at very low frequency," *J. Cereb. Blood Flow & Metab.*, vol. 27, pp. 776-784, 2007.

[88] G. Czibik, "Complex role of the HIF system in cardiovascular biology," *J. Mol. Med.(Berl)*, vol. 88, no. 11, pp. 1101-11, Nov. 2010.

[89] S. Rey and G. L. Semenza, "Hypoxia-inducible factor-1-dependent mechanisms of vascularization and vascular remodelling," *Cardiovasc. Res.*, vol. 86, no. 2, pp. 236-42, May 2010.

[90] S. K. Mehta, R. P. Stowe, A. H. Feiveson, S. K. Tyring, and D. L. Pierson, "Reactivation and shedding of cytomegalovirus in astronauts during spaceflight," *J. Infect. Dis.*, vol. 182, no. 6, pp. 1761-4, 2000.

[91] B. E. Crucian, et al., "Immune System Dysregulation and Herpesvirus Reactivation Persist during Long-Duration Spaceflight.," in *18th IAA Humans in Space Symposium*, Houston, TX, April 11-15, 2011.

[92] B. E. Crucian and C. Sams, "Immune system dysregulation during spaceflight: clinical risk for exploration-class missions," *J. Leukoc. Biol.*, vol. 86, no. 5, pp. 1017-8, 2009.

[93] M. Klokker, A. Kharazmi, H. Galbo, I. Bygbjerg, and B. K. Pedersen, "Influence of in vivo hypobaric hypoxia on function of lymphocytes, neutrocytes, natural killer cells, and cytokines," *J. Appl. Physiol.*, vol. 74, no. 3, pp. 1100-6, 1993.

[94] R. T. Meehan, "Immune suppression at high altitude," *Ann. Emerg. Med.*, vol. 16, no. 9, pp. 974-9, 1987.

[95] A. Chouker, et al., "Strenuous physical exercise inhibits granulocyte activation induced by high altitude," *J. Appl. Physiol.*, vol. 98, no. 2, pp. 640-7, 2005.

[96] F. P. Bagai, et al., "Effects of spaceflight on innate immune function and antioxidant gene expression," *J Appl Physiol*, vol. 106, no. 6, pp. 1935-42, 2009.

[97] L. Buravkova and E. Mailyan, "Oxidative phosphorylation in rat skeletal muscles after space flight on board biosatellites," *J Gravit Physiol*, vol. 4, no. 2, pp. 127-8, 1997.

[98] C. De Luca, et al., "Monitoring antioxidant defenses and free radical production in space-flight, aviation and railway engine operators, for the prevention and treatment of oxidative stress, immunological impairment, and pre-mature cell aging," *Toxicol Ind Health*, vol. 25, pp. 259-67, 2009.

[99] A. R. Kennedy, J. Guan, and J. H. Ware, "Countermeasures against space radiation induces oxidative stress in mice," *Radiat Environ Biophys*, vol. 46, pp. 210-203, 2007.

[100] I. Kaufmann, et al., "Adenosine A2(A) receptor modulates the oxidative stress response of primed polymorphonuclear leukocytes after parabolic flight," *Hum Immunol*, vol. 72, no. 7, pp. 547-52, 2011.

[101] C. D. Steer, P. M. Emmett, S. J. Lewis, G. D. Smith, and J. H. Tobias, "Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism is associated with spinal BMD in 9-year-old children," *J Bone Miner Res*, vol. 24, no. 1, pp. 117-24, 2009.

[102] N. Tyagi, T. P. Vacek, J. T. Fleming, J. C. Vacek, and S. C. Tyagi, "Hyperhomocysteinemia decreases bone blood flow," *Vasc Health Risk Manag*, vol. 7, pp. 31-5, 2011.

[103] S. R. Zwart, et al., "Vision changes after spaceflight are related to alterations in folate- and vitamin B-12-dependent one-carbon metabolism," *J Nutr*, vol. 142, no. 3, pp. 427-31, 2012.

[104] Q. Liu, W. K. Ju, and e. al., "Oxidative stress is an early event in hydrostatic pressure induced retinal ganglion cell damage," *Invest. Ophthalmol. Vis. Sci.*, vol. 48, no. 10, pp. 4580-9, 2007.

[105] N. Ahmadi, et al., "Relation of oxidative biomarkers, vascular dysfunction, and progression of coronary artery calcium," *Am J Cardiol*, vol. 105, no. 4, pp. 459-66, 2010.

[106] K. Campbell, "Intensive oxygen therapy as a possible cause of retrolental fibroplasia; a clinical approach," *Med J Aust*, vol. 2, pp. 48-50, 1951.

[107] F. De Marco, et al., "Oxidative stress in HPV-driven viral carcinogenesis: redox proteomics analysis of HPV-16 dysplastic and neoplastic tissues," *PLoS One*, vol. 7, no. 3, p. e34366, 2012.

[108] M. Turanlahti, E. Pesonen, P. Lassus, and S. Andersson, "Nitric oxide and hyperoxia in oxidative lung injury," *Acta Paediatr*, vol. 89, no. 8, pp. 966-70, 2000.

[109] G. G. Eigenwillig, "Comment on "Mortality from cardiovascular diseases in the German uranium miners cohort study, 1946-1998" by Kreuzer M, Kreisheimer M, Kandel M, Schnelzer M, Tschense A, Grosche B (2006) Radiat Environ Biophys 45:159-166," *Radiat Environ Biophys*, vol. 46, no. 4, pp. 423-5;authorrely427, 2007.

[110] D. Nair and e. al., "Intermittent Hypoxia-induced Cognitive Deficits Are Mediated by NADPH Oxidase Activity in a Murine Model of Sleep Apnea," *PloS One*, vol. 6, no. 5, p. e19847, 2011.

[111] C. Xiao-Hong and e. al., "Chronic Intermittent Hypoxia Exposure Induces Memory Impairment in Growing Rats," *Acta Neurobiologiae Experimentals*, vol. 70, pp. 279-287, 2010.

[112] J. Guan, et al., "Effects of dietary supplements on space radiation-induced oxidative stress in Sprague-Dawley rats," *Radiat Res*, vol. 162, no. 5, pp. 572-9, 2004.

[113] J. A. Jones, P. K. Riggs, and e. al., "Ionizing radiation-induced bioeffects in space and strategies to reduce cellular injury and carcinogenesis," *Aviat. Space Environ. Med.*, vol. 78, no. 4 Suppl, pp. A67-78, 2007.

[114] S. M. Smith, S. R. Zwart, V. Kloeris, and M. Heer, *Nutritional biochemistry of space flight*. New York: Nova Science Publishers, 2009.

[115] M. Maggiorini, A. Muller, D. Hofstetter, P. Bartsch, and O. Oelz, "Assessment of acute mountain sickness by different score protocols in the Swiss Alps," *Aviat. Space Environ. Med.*, vol. 69, pp. 1186-92, 1998.

[116] N. Hamad and S. P. Travis, "Weight loss at high altitude: pathophysiology and practical implications," *Eur. J. Gastroenterol. Hepatol.*, vol. 18, pp. 5-10, 2006.

[117] S. Budweiser, F. Heinemann, K. Meyer, P. J. Wild, and M. Pfeifer, "Weight gain in cachectic COPD patients receiving noninvasive positive-pressure ventilation," *Respir. Care*, vol. 51, pp. 126-32, 2006.

[118] M. Lutter and E. J. Nestler, "Homeostatic and hedonic signals interact in the regulation of food intake," *J. Nutr.*, vol. 139, pp. 629-32, 2009.

[119] I. Aeberli, et al., "Disturbed eating at high altitude: influence of food preferences, acute mountain sickness and satiation hormones," *Eur. J. Nutr.*, vol. 52, no. 2, pp. 625-35, 2013.

[120] V. Shukla, et al., "Ghrelin and leptin levels of sojourners and acclimatized lowlanders at high altitude," *Nutr. Neurosci.*, vol. 8, pp. 161-5, 2005.

[121] M. Muzylak, J. S. Price, and M. A. Horton, "Hypoxia induces giant osteoclast formation and extensive bone resorption in the cat," *Calcif. Tissue Int.*, vol. 79, pp. 301-9, 2006.

[122] J. C. Utting, A. M. Flanagan, A. Brandao-Burch, I. R. Orriss, and T. R. Arnett, "Hypoxia stimulates osteoclast formation from human peripheral blood," *Cell Biochem. Funct.*, vol. 28, pp. 374-80, 2010.

[123] T. R. Amett, "Acidosis, hypoxia and bone," *Arch. Biochem. Biophys.*, vol. 503, no. 1, pp. 103-9, Nov. 2010.

[124] H. Tomiyama, R. Okazaki, D. Inoue, and e. al., "Link between obstructive sleep apnea and increased bone resorption in men," *Osteoporos. Int.*, vol. 19, pp. 1185-9, 2008.

[125] S. M. Smith, et al., "Tomiyama H, Okazaki R, Inoue D, et al. Link between obstructive sleep apnea and increased bone resorption in men. Osteoporos Int 2008;19:1185-92.," *J. Bone Miner. Res.*, 2012.

[126] Y. V. Bushov, A. V. Makhnaham, and K. T. Protasov, "Analysis of individual differences in human physiological reaction to combined hypoxic effect," *Human Physiol.*, pp. 302-306, 1994.

[127] J. Virues-Ortega, G. Buela-Casal, E. Garrido, and B. Alcazar, "Neuropsychological functioning associated with high-altitude exposure," *Neuropsych. Rev.*, pp. 197-224, 2004.

[128] D. S. Martin, D. Z. H. Levett, M. P. W. Grocott, and H. E. Montgomery, "Variation in human performance in the hypoxic mountain environment," *Exp. Physiol.*, pp. 463-470, 2009.

[129] M. Nicolas, et al., "A study of mood changes and personality during a 31-day period of chronic hypoxia in a hypobaric chamber," *Psychol. Rep.*, pp. 119-126, 2000.

[130] B. Bolmont, C. Bouquet, and F. Thullier, "Relationship of personality traits with performance in RT, psychomotor ability, and mental efficiency during a 31-day simulated climb of Mounte Everest in a hypobaric chamber," *Perceptual and Motor Skills*, pp. 1022-1030, 2001.

[131] B. Fowler, D. D. Elcombe, B. Kelso, and G. Porlier, "The human threshhold for hypoxia effects on perceptual-motor performance," *Human Factors*, pp. 61-66, 1987.

[132] J. L. Kramer, J. T. Coyne, and D. L. Strayer, "Cognitive function at high altitude," *Human Factors*, pp.

329-344, 1993.

[133] J. H. Mackintosh, D. J. Thomas, J. E. Olive, I. M. Chesner, and R. J. E. Knight, "The effect of altitude on tests of reaction time and alertness," *Aviat. Space Environ. Med.*, pp. 246-248, 1988.

[134] T. F. Hornbein, B. D. Townes, R. B. Shoene, J. R. Sutton, and C. S. Houston, "The cost to the central nervous system of climbing to extremely high altitude," *New Engl. J.Med.*, pp. 1714-1719, 1989.

[135] J. B. West, "Human physiology at extremely high altitudes on Mount Everest," *Science*, pp. 784-788, 1984.

[136] D. M. Denison, F. Ledwith, and E. C. Poulton, "Complex reaction times at simulated cabin altitudes of 5000 feet and 8000 feet.," *Aerospace Medicine*, pp. 1010-1013, 1966.

[137] J. H. Abraini, C. Bouquet, F. Joulia, M. Nicolas, and B. Kriem, "Cognitive performance during a simulated climb of Mount Everest: Implications of brain function and central adaptive processes under chronic hypoxia stress," *Euro. J. Appl. Physio.*, pp. 553-559, 1998.

[138] C. Bouquet, B. Gardette, C. Gortan, and J. H. Abraini, "Psychomotor skills learning under chronic hypoxia," *Neuroreport*, pp. 3093-3099, 1999.

[139] D. B. Watson, R. L. Martin, K. I. McAnally, S. E. Smith, and D. L. Emonson, "Effect of normobaric hypoxia on auditory sensitivity," *Aviat. Space Environ. Med.*, pp. 791-797, 2000.

[140] B. Fowler and A. Grant, "Hearing threshholds acute hypoxia and relationship to slowing in the auditory modality," *Aviat. Space Environ. Med.*, pp. 946-949, 2000.

[141] P. R. Burkett and W. F. Perrin, "Hypoxia and auditory threshholds," *Aviation, Space, and Environmental Medicine*, pp. 649-651, 1976.

[142] R. L. Cahoon, "Vigilance performance under hypoxia," *J. App. Psych.*, pp. 479-483, 1970.

[143] J. L. Kobrick, H. Zwick, C. E. Witt, and J. A. Devine, "Effects of extended hypoxia on night vision," *Aviat. Space Environ. Med*, pp. 191-195, 1984.

[144] G. Cavaletti, R. Moroni, P. Garavaglia, and G. Tredici, "Brain damage after high-altitude climbs without oxygen," *Lancet*, p. 101, 1987.

[145] R. S. Kennedy, W. P. Dunlap, L. E. Banderet, M. G. Smith, and C. S. Houston, "Cognitive Performance deficits in a simulated ascent climb of Mount Everest: Operation Everest II," *Aviat. Space Enviro. Med.*, pp. 99-104, 1989.

[146] O. Oelz, et al., "Physiological profiles of world-class high altitude climbers," *J. Appl. Physiol.*, pp.

1734-1742, 1986.

[147] G. R. Kelman, T. J. Crow, and A. E. Bursill, "Effect of mild hypoxia on mental performance assessed by a test of selective attention," *Aerospace Med.*, pp. 301-303, 1969.

[148] B. Shukitt-Hale, et al., "Hypobaric hypoxia impairs spatial memory in an elevation dependent fashion," *Behavioral and Neural Biology*, pp. 244-253, 1994.

[149] T. Crow and G. R. Kelman, "Psychological effects of mild acute hypoxia," vol. 43, 1973.

[150] W. Evans and N. F. Witt, "The interaction of high altitude and psychotropic drug action," vol. 10, no. 2, 1966.

[151] G. Schulze, H. Coper, and C. Faehndrich, "Adaptation capacity of biogenic amines turnover to hypoxia in different brain areas of old rats," *Neurochem. Internat.*, pp. 281-289, 1990.

[152] E. R. Kandel, S. H. James, and J. M. Thomas, *Principles of Neural Science*. New York: McGraw-Hill, 2000.

[153] D. Gozal, J. M. Daniel, and G. P. Dohanich, "Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in rats," *J. Neurosci*, pp. 2442-2450, 2001.

[154] D. J. Dijk, D. Neri, J. Wyatt, and J. Rhonda, "Sleep, performance, circadian rhythms, and light-dark cycles during two space shuttle flights," *Am. J. Physiol. - Regulatory, Integrative, and Comparative Physiology*, vol. 281, pp. R1647-R1664, 2001.

[155] A. Gundel, V. V. Polyakov, and J. Zulley, "The alteration of human sleep and circadian rhythms," *J. Sleep Res.*, vol. 6, pp. 1-8, 1997.

[156] M. M. Mallis and C. W. DeRoshia, "Circadian rhythms, sleep and performance in space," *Aviat. Space Environ. Med.*, vol. 76, no. 6, Suppl., pp. B94-107, 2005.

[157] T. Monk, D. Buysse, B. Billy, K. Kennedy, and L. Willrich, "Sleep and circadian rhythms in four orbiting Astronauts," *J. Biol. Rhythms*, vol. 13, pp. 188-201, 1998.

[158] J. V. Weil, "Sleep at high altitude," *High Alt. Med.Biol.*, pp. 180-189, 2004.

[159] J. M. Muhm, et al., "Sleep at simulated 2438m: Effects on oxygenation, sleep quality, and postsleep performance," *Aviat. Space Environ. Med.*, vol. 80, no. 8, pp. 691-697, 2009.

[160] R. J. Thomas, R. Tamisier, J. Boucher, Y. Kotlar, and K. Vigneault, "Nocturnal hypoxia exposure with simulated altitude for 14 days does not significantly alter working memory or vigilance in humans," *Sleep*, pp. 1195-1203, 2007.

[161] M. D. Weiss, et al., "A pilot study of sleep, cognition , and respiration under 4 weeks of intermittent nocturnal hypoia in adult humans," *Sleep Med.*, pp. 739-745, 2009.

[162] M. Durante and F. A. Cucinotta, "Heavy ion carcinogenesis and human space exploration," *Nat Rev Cancer*, vol. 8, no. 6, pp. 465-72, 2008.

[163] E. J. Hall and A. Giaccia, *Radiobiology for the Radiologist*, 7th ed. Lippincott Williams & Wilkins, 2011.

[164] R. D. Stewart, et al., "Effects of radiation quality and oxygen on clustered DNA lesions and cell death," *Radiat. Res.*, vol. 176, no. 5, pp. 587-602, Nov. 2011, Epub 2011 Aug 8.

[165] I. J. Spiro, C. C. Ling, R. Stickler, and J. Gaskill, "Oxygen radiosensitisation at low dose rate," *Br J Radiol*, vol. 58, no. 688, pp. 357-63, 1985.

[166] C. R. Weinberg, K. G. Brown, and D. G. Hoel, "Altitude, radiation, and mortality from cancer and heart disease," *Radiat Res*, vol. 112, no. 2, pp. 381-90, 1987.

[167] J. Hart, "Cancer mortality in six lowest versus six highest elevation jurisdictions in the U.S," *Dose Response*, vol. 9, no. 1, pp. 50-8, Apr. 2010.

[168] D. Faeh, F. Gutzwiller, M. Bopp, and S. N. C. S. Group, "Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland," *Circulation*, vol. 120, no. 6, pp. 495-501, Aug. 2009, Epub 2009 Jul 27.

[169] M. Ezzati, et al., "Altitude, life expectancy and mortality from ischaemic heart disease, stroke, COPD and cancers: national population-based analysis of US counties," *J. Epidemiol. Community Health*, Mar. 2011.

[170] J. A. Loeppky, et al., "Effects of prolonged head-down bed rest on physiological responses to moderate hypoxia," *Aviat. Space. Environ. Med.*, vol. 64, no. 4, pp. 275-86, Apr. 1993.

[171] U. Sliwka, J. A. Krasney, S. G. Simon, P. Schmidt, and J. Noth, "Effects of sustained low-level elevations of carbon dioxide on cerebral blood flow and autoregulation of the intracerebral arteries in humans," *Aviat. Space Environ. Med.*, vol. 69, no. 3, pp. 299-306, Mar. 1998.

[172] K. E. Schaefer, C. R. Carey, J. H. Dougherty Jr, C. Morgan, and A. A. Messier, "Effect of intermittent exposure to 3% CO2 on respiration, acid-base balance, and calcium-phosphorus metabolism," *Undersea Biomed Res*, vol. 6 Suppl, pp. S115-34, 1979.

[173] N. S. Krieger, K. K. Frick, and D. A. Bushinsky, "Mechanism of acid-induced bone resorption," *Curr. Opin. Nephrol. Hypertens.*, vol. 13, no. 4, pp. 423-36, Jul. 2004.

[174] D. A. Bushinsky, "Acid-base imbalance and the skeleton," *Eur. J. Nutr.*, vol. 40, no. 5, pp. 238-44, Oct. 2001.

[175] D. Manzey and B. Lorenz, "Joint NASA-ESA-DARA Study. Part three: effects of chronically elevated CO2 on mental performance during 26 days of confinement," *Aviat. Space Environ. Med.*, vol. 69, no. 5, pp. 506-14, May 1998.

[176] A. Colasanti, et al., "Carbon dioxide-induced emotion and respiratory symptoms in healthy volunteers," *Neuropsychopharmacology*, vol. 33, no. 13, pp. 3103-10, Dec. 2008.

[177] J. A. Neubauer, "Invited review: Physiological and pathophysiological responses to intermittent hypoxia," *J. Appl. Physiol.*, vol. 90, no. 4, pp. 1593-9, Apr. 2001.

[178] G. E. Foster, et al., "Intermittent hypoxia increases arterial blood pressure in humans through a Renin-Angiotensin system-dependent mechanism," *Hypertension*, vol. 56, no. 3, pp. 369-77, 2010.

[179] J. C. Kolb, *Physiological responses to intermittent hypoxia in humans*. Boca Raton, FL: Dissertation.com, 2004.

[180] C. Fava, M. Montagnana, E. J. Favaloro, G. C. Guidi, and G. Lippi, "Obstructive sleep apnea syndrome and cardiovascular diseases," *Semin. Thromb. Hemost.*, vol. 37, no. 3, pp. 280-97, Apr. 2011.

[181] A. Lurie, "Inflammation, oxidative stress, and procoagulant and thrombotic activity in adults with obstructive sleep apnea," *Adv. Cardiol.*, vol. 46, pp. 43-66, 2011.

[182] D. R. Williams and B. J. Johnson, "EMU Shoulder Injury Tiger Team Report.," Johnson Space Center, Houston, TX, NASA Technical Report NASA/TM-2003-212058, 2003.

[183] J. Stuster, "Behavioral Issues Associated with Long Duration Space Expeditions: Review and Analysis of Astronaut Journals," 2010.

[184] A. F. J. Abercromby, M. L. Gernhardt, and H. Litaker, "Desert Research and Technology Studies (DRATS) 2008: Evaluation of small pressurized rover and unpressurized rover prototype vehicles in a Lunar analog environment," NASA/TP-2010-216136, 2010.

[185] S. Strauss, "Extravehicular Mobility Unit Training Suit Symptom Study Report," NASA/TP-2004-212075, 2004.

[186] R. A. Scheuring, C. H. Mathers, J. A. Jones, and M. L. Wear, "Musculoskeletal injuries and minor trauma in space: Incidence and injury mechanisms in US Astronauts," *Aviat Space Environ Med*, vol. 80, pp. 117-24, 2009.

[187] H. Yamaguchi, M. Mohri, and K. Shiraki, " Evaluation of cutaneous insensible water loss during hyperbaric exposure in humans," *Aviat Space Environ Med*, vol. 70, pp. 990-5, 1999.

[188] "International Space Station CHeCS Medical Hardware Catalog [internal document]," 2011.

[189] J. Conkin, "Preventing decompression sickness over three decades of extravehicular activity," NASA Johnson Space Center NASA/TP-2011-216147, 2011.

[190] K. Wheatley, M. Creed, and A. Mellor, "Haematological changes at altitude," *J. R. Army Med. Corps.*, vol. 157, no. 1, pp. 38-42, Mar. 2011.

[191] M. S. Westerterp-Plantenga, "Effects of extreme environments on food intake in human subjects," *Proc. Nutr. Soc.*, vol. 58, no. 4, pp. 791-8, Nov. 1999.

[192] A. J. Pollard and D. R. Murdock, *The high altitude medicine handbook*. Oxon, UK: Radcliff Medical Press Ltd, 2003.

[193] D. S. Martin, D. Z. Levett, M. P. Grocott, and H. E. Montgomery, "Variation in human performance in the hypoxic mountain environment," *Exp. Physiol.*, vol. 95, no. 3, pp. 463-70, Mar. 2010.

[194] J. A. Loeppky, P. Scotto, T. W. Chick, and U. C. Luft, "Effects of acute hypoxia on cardiopulmonary responses to head-down tilt," *Aviat. Space Environ. Med.*, vol. 61, no. 9, pp. 785-94, Sep. 1990.

[195] R. Hainsworth, M. J. Drinkhill, and M. Rivera-Chira, "The autonomic nervous system at high altitude," *Clin. Auton. Res.*, vol. 17, no. 1, pp. 13-9, Feb. 2007.

[196] R. Hainsworth and M. J. Drinkhill, "Cardiovascular adjustments for life at high altitude," *Respir. Physiol. Neurobiol.*, vol. 158, no. 2-3, pp. 204-11, Sep. 2007.

[197] P. Angerer and D. Nowak, "Working in permanent hypoxia for fire protection-impact on health," *Int. Arch. Occup. Environ. Health*, vol. 72, no. 2, pp. 87-102, Mar. 2003.

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Extravehicular activity (EVA) is at the core of a manned space exploration program. Some elements of exploration may be safely and effectively performed by robots, but certain critical elements will require the trained, assertive, and reasoning mind of a human crewmember. To effectively use these skills, NASA needs a safe, effective, and efficient EVA component integrated into the human exploration program. The EVA preparation time should be minimized and the suit pressure should be low to accommodate EVA tasks without undue fatigue, physical discomfort, or suit-related trauma. Commissioned in 2005, the Exploration Atmospheres Working Group (EAWG) had the primary goal of recommending to NASA an internal environment that allowed efficient and repetitive EVAs for missions that were to be enabled by the former Constellation Program. At the conclusion of the EAWG meeting, the 8.0 psia and 32% oxygen (O2) environment were recommended for EVA-intensive phases of missions. This paper provides a literature review of the human health and performance risks associated with the 8 psia / 32% O2 environment.

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