Retrospective Evaluation of Clinical Symptoms Due to Mild Hypobaric Hypoxia Exposure in Microgravity

James H. Wessel III; Caroline M. Schaefer; Moriah S. Thompson; Jason R. Norcross; Omar S. Bekdash

INTRODUCTION: A habitat atmosphere of 34% oxygen (O_2) and 66% nitrogen (N_2) at 8.2 psia (56.5 kPa) is proposed to minimize the risk of decompression sickness during extravehicular activity. The resulting inspired O_2 partial pressure (P_IO_2) of 128 mmHg is similar to that experienced during portions of 41 Space Shuttle missions that used a "staged" denitrogenation (prebreathe) protocol with an atmosphere of 26.5% O_2 and 73.5% N_2 at 10.2 psia (70.3 kPa). We evaluated symptoms possibly linked to mild hypoxia in astronauts breathing a P_IO_2 of 127 mmHg.

METHODS: Environmental data were used to determine time in the shuttle at 10.2 psia and time at 14.7 psia (101.3 kPa). A total of 14 possible hypoxia symptoms were compared with symptoms collected during normoxic shuttle operations at 14.7 psia using logistic regression.

RESULTS: There were 134.1 d (788.8 person days) under the 10.2 psia staged condition with a mean of 3.17 $\pm$ 2.2 SD d/mission. There were 258.81 d at 14.7 psia (2192.95 person days). An average of 4.31 potentially hypoxia-related symptoms per mission day was documented under the staged condition compared with 4.08 per mission day during the normoxic condition. Logistic regression showed no symptoms were significantly associated with just the 10.2 psia condition.

DISCUSSION: Chronic exposure to a P_IO_2 of 127 mmHg is well-tolerated by healthy humans on Earth. A similar short-duration exposure on the shuttle resulted in no increased reporting of possible hypoxia-related symptoms. However, chronic mild hypoxia interactions with physiological changes due to microgravity adaptations remain unclear.

KEYWORDS: Space Shuttle, oxygen, carbon dioxide, extravehicular activity, astronauts, space adaptation, decompression sickness.

Wessel JH III, Schaefer CM, Thompson MS, Norcross JR, Bekdash OS. *Retrospective evaluation of clinical symptoms due to mild hypobaric hypoxia exposure in microgravity*. Aerosp Med Hum Perform. 2018; 89(9):792–797.

NASA's Exploration Atmospheres Working Group decided in 2005 that after balancing the primary concerns of materials flammability, mild hypoxia, and risk of decompression sickness (DCS), the exploration atmosphere (EA) would be 8.0 psia (55.2 kPa) and 32% oxygen (O_2) with a balance of nitrogen (N_2) to enable flexible and high efficiency extravehicular activity (EVA).[9,11] Re-examination in 2012 by the Exploration Atmosphere Working Team allowed for a small increase in pressure to 8.2 psia (56.5 kPa) and O_2 to 34%. This change lessened the hypoxic component since the inspired O_2 partial pressure (P_IO_2) increased from 117 to 128 mmHg, where $P_IO_2 = (P_B - 47) \times F_IO_2$. With the pressure unit as mmHg, P_B is ambient pressure, 47 is the vapor pressure of water at 37°C, and F_IO_2 is the dry-gas decimal fraction of O_2.

The EA reduces the mitigations needed to achieve acceptable risk of DCS by decreasing the partial pressure of N_2 (ppN_2), primarily through the reduction of the overall pressure of the spacecraft and secondarily through the enrichment of the atmosphere with O_2. The primary reason for O_2 enrichment is to reduce hypoxic stress, but this must be carefully balanced with flammability risk. For instance, the EA would be designated as an atmosphere of increased burning rate because 31.4% O_2 is the calculated upper limit that would not increase burning rate at 8.2 psia (56.5 kPa), yet another source indicated that burning rate for paper materials at the EA would be slightly reduced as compared to a normal sea level atmosphere.[10,16] Although NASA's material engineers deemed the EA acceptable for flammability concerns, they did so knowing that flammability and burning rate testing of expected materials to be

From NASA Johnson Space Center, Houston, TX.

This manuscript was received for review in April 2017. It was accepted for publication in June 2018.

Address correspondence to: Jason R. Norcross, KBRwyle, 2400 NASA Parkway, Houston, TX, 77058; jason.norcross-1@nasa.gov.

DOI: https://doi.org/10.3357/AMHP.4913.2018

used with the EA will be needed and some materials will be excluded for use with the EA.

Once the tissues of a crewmember are equilibrated at the EA with a ppN_2 of 5.4 psia (37.3 kPa), there is only a modest pressure difference between a spacesuit pressurized to 4.3 psia (29.6 kPa) and the tissues that can be reduced by a short period of in-suit O_2 prebreathe (i.e., denitrogenation). Additional DCS risk reduction enabled through use of the EA includes intermittent recompressions between the EVA and vehicle pressures and shorter EVA lengths.[2,3,6] The benefits of the EA are further enhanced when combined with suitports rather than airlocks for EVA egress and ingress. The EA combined with suitports enables faster suited vehicle egress and ingress, may allow for single person EVA, ensures a short delay to EVA, and provides the option of multiple short EVAs per day on the lunar or Martian surface. Suitports also serve to keep dust outside the vehicle and, importantly, features a vestibule with an extremely small volume of consumable (internal atmospheric) gases that is lost per EVA during detachment from the suitport.[1,2,4]

NASA's Human Health and Performance Directorate personnel evaluated the possible impacts of mild hypobaric hypoxia during spaceflight on astronaut crew health given the proposed EA. Two reports generated by Norcross et al. document those findings.[11,12] One recommendation was that archived data from past shuttle missions that used the 10.2 psia and 26.5% O_2 atmosphere with a P_IO_2 of 127 mmHg be analyzed for possible effects of hypobaric hypoxia on shuttle crews. The purpose for the atmospheric change in the shuttle cabin was to facilitate effective, efficient, and safe prebreathe protocols for missions designed around one or more EVAs. The reason for the staged protocol was to partially denitrogenate tissues before a 40- to 70-min in-suit prebreathe period in the suit with 100% O_2 to further reduce the risk of DCS before EVA at 4.3 psia. The P_IO_2 on those select missions matched the proposed P_IO_2 for the EA.

Although the International Space Station (ISS) campout prebreathe protocol employs the same 10.2-psia and 26.5% O_2 environment immediately before EVA, the duration of these exposures are less than 12 h each. Therefore, the longer 10.2 psia shuttle missions represent the primary dataset to examine for hypoxia-related issues during NASA's spaceflight experience to compare with shuttle spaceflight experience under normoxic (air) conditions with a P_IO_2 of 149 mmHg.

METHODS

Environmental Data Collection

The shuttle telemetry was recorded on a millisecond basis beginning directly before launch and ending shortly after landing. The raw environmental data (O_2, CO_2, cabin pressures) was accessible through the Archive Data Retrieval Interface Tool (ADRIFT), a subprogram within NASA's proprietary Java Mission Evaluation Workstation System software that is designed to retrieve, display, and analyze both real-time and recorded telemetry data from NASA manned missions. The desired subset of shuttle flight information was then converted into a format usable by Microsoft Excel 2013. These data files were edited for errors due to signal loss and data corruption due to, for example, cosmic ray interference. After editing, the Excel files were annotated for the following times: launch, pressurization to 14.7 psia, 14.7 psia reached, depressurization to 10.2 psia,

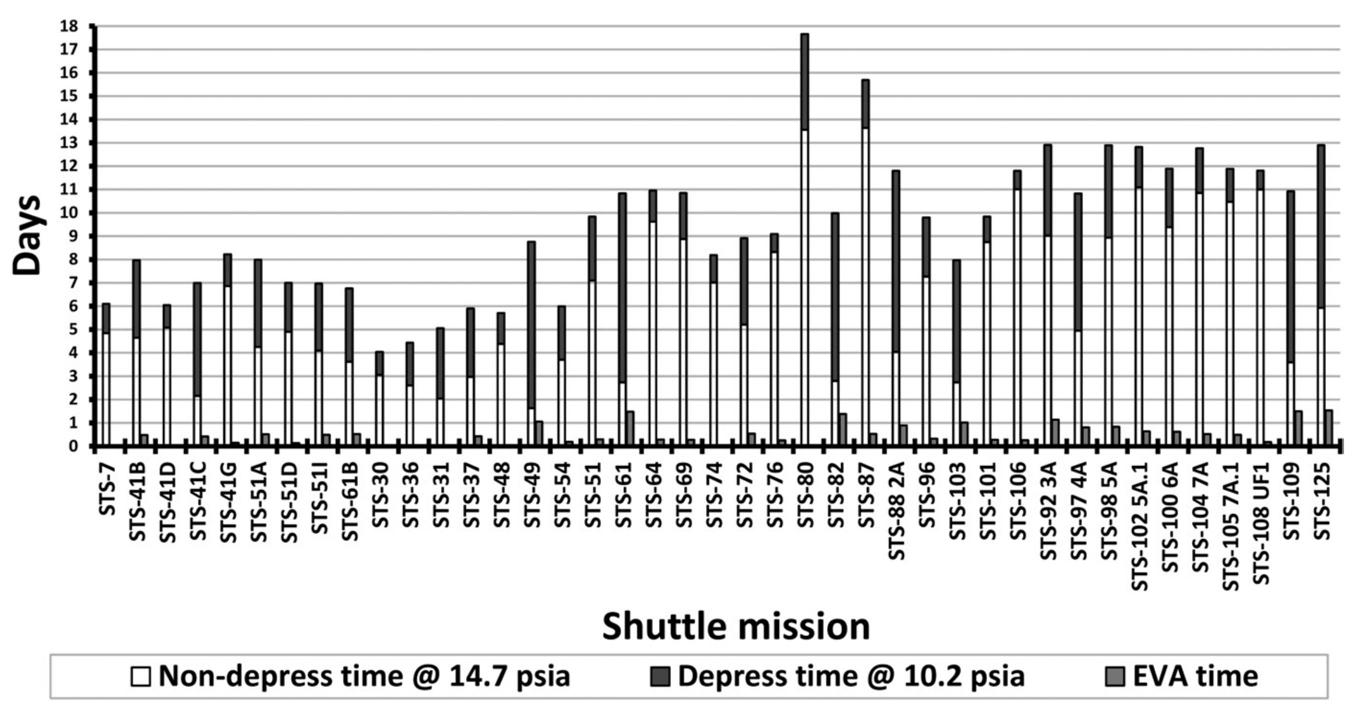

Fig. 1. Length of time as days at the conditions of 14.7 psia, 10.2 psia, and EVA for 41 shuttle missions partially conducted at 10.2 psia.

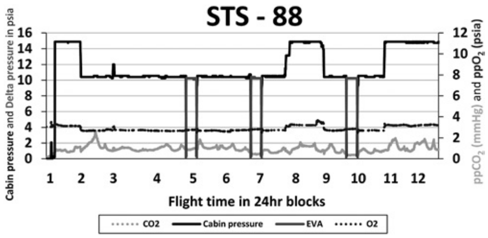

Fig. 2. Example of a shuttle mission's timeline depicting cabin pressure (solid black line), three EVA times (solid dark gray lines), ppO_2 (dotted black line), and $ppCO_2$ (dotted light gray line). This figure shows an interrupted 10.2-psia depressurization after about 8 d.

10.2 psia reached, depressurization to vacuum (e.g., start of EVA), vacuum reached, repressurization to 10.2 psia (e.g., end of EVA), 10.2 psia reached, repressurization to 14.7 psia, and landing. The unique times associated with all those events were compiled for calculations of exact times at 14.7 psia, 10.2 psia, and EVA duration for each mission. The 10.2 missions were also processed to determine minimum, maximum, and average values for ppO_2 and $ppCO_2$.

Analysis of Shuttle Crewmember Medical Records

A medical debrief between the Flight Surgeon and each individual crewmember was conducted at the conclusion of a mission 1 to 3 d after landing, during which the health of the crewmember over the mission was discussed. The Shuttle Postflight Medical Debrief documents contain a space adaptation symptoms (SAS) table that details the presence and severity of various signs and symptoms by flight day for each crewmember, including nausea, vomiting, loss of appetite, stomach awareness, headache, impaired concentration, disorientation, irritability, drowsiness, malaise/sluggishness, loss of initiative or motivation, sweating, flushed feeling, and "others." Symptom severity was documented as none, mild, moderate, or severe. The data from the Shuttle Postflight Medical Debrief documents as well as supplementary information from in-flight private medical conferences was queried from the Lifetime Surveillance of Astronaut Health (LSAH) database to determine whether there was evidence of an association between symptom frequency or severity and exposure to the 10.2-psia condition. Fortuitously, many of the symptoms of SAS overlap with symptoms of exposure to hypobaric hypoxia. We identify this exposure as the number of days spent at 10.2 psia, which equals 'depress time' in our equation to follow. Crewmember demographic information (age at launch, sex, EVA participation) and additional mission information (shuttle docking to ISS or Mir) were also queried from the LSAH database.

Data Limitations

Time reporting used by the ADRIFT results were not equivalent with the Shuttle Postflight Medical Debrief documents, which reported SAS by flight day. By convention, the launch day is considered to be flight day 1 and flight day 2 starts after the first on-orbit sleep. However, flight-day reporting varied between documents and could not be reliably correlated with Greenwich Mean Time. Thus, time reporting discrepancies did not allow for accurate flight-day correlation between environmental exposure conditions and the reported symptoms. Instead, total number of days of exposure to the 10.2-psia staged condition and symptom presence were used for analysis.

Analysis

Logistic regression was used to determine the relationship between reported SAS and the amount of time spent exposed to the 10.2-psia and 14.7-psia conditions. This method was chosen due to an inability to attribute SAS to specific flight days and correlate the reports to times of exposure within the symptom dataset. Severity of symptoms were infrequently reported and therefore not used in our analyses. Using a logistic regression allows the total number of flight days to be viewed as "trials" and number of flight days with a given symptom as "events." From this, the odds of reporting a symptom for a specific person mission can be calculated as:

$$\frac{P\,(reporting\ a\ symptom)}{1-P\,(reporting\ a\ symptom)}$$

For example, if a crewmember reported a headache in 4 of 14 flight days, the odds of reporting a headache would be:

$$\frac{4/14}{10/14}=0.4$$

This is used in the regression equation to calculate coefficients for our variables of interest. A separate regression was performed for each of the 14 symptoms listed in the SAS table. Since reports of SAS were collected as individual symptoms and, as previously mentioned, could not be positively correlated to specific flight days, a multivariate approach analyzing the overall presence of any symptom was not conducted. Symptoms could have all occurred on the same day or on all different days. This could lead to overestimating or underestimating the true presence of symptoms over the course of a mission. Covariates included in the regression equations were sex (male or female), age at launch (continuous years),[14,15] crewmember EVA participation (yes or no), and mission docking (none, ISS, or Mir). EVA participation and docking to another vehicle were included due to their possible effects on crewmembers' hypoxic exposure. The environment a crewmember experienced while performing an EVA was mildly hyperoxic at a P_IO_2 of 175 mmHg and the additional volume added by vehicle docking could have affected the overall atmosphere

Table I. Environmental Data from 41Missions Using the 10.2-psia Staged Condition.

GAS	ENTIRE MISSION $\mu \pm \sigma$	10.2 psia $\mu \pm \sigma$	10.2 psia $\mu \pm \sigma$ MINIMUM	14.7 psia $\mu \pm \sigma$	14.7 psia $\mu \pm \sigma$ MINIMUM
ppO_2 (psia)	3.02 ± 0.1	2.75 ± 0.1	2.71 ± 0.1	3.17 ± 0.1	3.07 ± 0.2
$ppCO_2$ (mmHg)	2.04 ± 0.6	1.95 ± 0.6	not available	2.14 ± 0.7	not available

composition. Sex was included because several studies have shown the differences in space adaptation among relevant body systems between men and women.[7,8,13] We excluded $ppCO_2$ from the analysis as a covariate, as a particular $ppCO_2$ exposure could not be directly tied to a particular SAS and the average $ppCO_2$ level of the mission did not provide the level of detail needed because $ppCO_2$ varied more than ppO_2 levels throughout the flight day. Outcome variables for the regression equations used days reported of the specific symptom as the number of events that occurred and total flight days as the number of trials. Analyses adjusted for repeated measures of crewmembers who flew multiple shuttle missions by using generalized estimating equations in the regression procedure. Below is a representation of the regression equation.

$$\ln\left(\textit{Odds of reporting symptom}\right) = \beta_0 + \beta_1\left(\textit{depress time}\right) + \beta_2\left(\textit{sex}\right) + \beta_3\left(\textit{age}\right) + \beta_4\left(\textit{EVA}\right) + \beta_5\left(\textit{docking}\right)$$

RESULTS

Of the 135 shuttle missions, 126 were included in the primary analysis; 9 missions were excluded due to a lack of postflight medical debriefs ($N = 8$) or the use of a different staged EVA depressurization protocol ($N = 1$); 41 shuttle missions used the 10.2-psia staged protocol; and 86 remained at 14.7 psia throughout the mission. Data included 250 distinct crewmembers, resulting in 521 person-missions. Crewmembers experienced 134.1 d (788.8 person-days) under the 10.2-psia staged condition, averaging 3.2 ± 2.2 d/mission, with one mission reaching a maximum of 8.1 d. The percentage of EVA time vs. time at 10.2 psia ranged from 0 to 32.8% by mission. The primary reason for lowering the shuttle cabin's atmospheric pressure was to reduce DCS risk during EVAs, yet there were eight missions that featured a 10.2-psia depressurization without resultant EVAs, for various operational reasons. For the remaining 33 missions with EVAs, there was a direct correlation between the duration of time at 10.2 psia and the amount of EVA time ($R^2 = 0.78$). Mission duration at 14.7 psia, 10.2 psia, and EVA time are described in **Fig. 1**.

Of the 10.2 missions, 7 had an interrupted 10.2-psia depressurization, one of which is illustrated in **Fig. 2**. For this analysis, these interrupted depressurizations were summed into a single depressurization. Similar figures were generated for all 10.2-psia missions to create visual representations for evaluation of the breathing gas constituency over time.

Shuttle environmental data are summarized in **Table I**. Minimum ppO_2 values reported from the 10.2-psia missions are consistent with Space Shuttle Flight Rule A13-53, which required minimum ppO_2 values of 2.43 psia (125.6 mmHg) at 10.2 psia, and 2.37 psia (122.5 mmHg) at 14.7 psia. The $ppCO_2$ values were also consistent with Space Shuttle Flight Rule A13-52, with maximum do-not-exceed values of 7.5 mmHg for both

Table II. Mission and Crew Information for 10.2-psia Staged and 14.7-psia Nonstaged Missions.

	10.2-psia STAGED MISSIONS ($N = 41$)	14.7-psia MISSIONS ($N = 86$)
Mission elapsed time in days, μ (σ)	9.58 (3.04)	10.09 (3.88)
Depressurization exposure time in days, μ (σ)	3.21 (2.18)	NA
Docking, *N* (%)		
None	27 (67.5%)	60 (69.77%)
ISS	11 (27.5%)	20 (23.26%)
Mir	2 (5.0%)	6 (6.98%)
Crew size, median [range]	5 [4,7]	5 [2,8]
	10.2-psia STAGED PERSON MISSIONS ($N = 175$)	**14.7-psia PERSON MISSIONS ($N = 346$)**
Age at launch in years, μ (σ)	42.41 (4.87)	42.79 (5.21)
Men, *N* (%)	149 (85.14%)	292 (84.39%)
EVA participants, *N* (%)	66 (37.71%)	34 (9.83%)

pressures. Of the 41 10.2-psia missions, 37 had $ppCO_2$ levels above 3 mmHg and 10 of these missions had $ppCO_2$ at or above 7.6 mmHg for short periods of time. Across all 10.2-psia staged missions, 63.4% (247.6 person days) of all $ppCO_2$ values were above 3 mmHg and 0.08% (0.3 person day) of $ppCO_2$ values were above 7.6 mmHg.

As shown in **Table II**, 10.2-psia missions had similar mission elapsed time and vehicle docking rates to 14.7-psia missions. The crew on those two mission types were also similar in age and gender composition. A higher percentage of crewmembers participated in EVAs for staged protocol missions than crewmembers of nonstaged protocol missions, which was an expected result because the 10.2-psia staged protocol was specifically used in missions that had a high frequency of EVAs with shorter rest intervals in between.

Of the 14 SAS in the data, only 10 regression equations could be produced due to a low reporting rate of 4 symptoms: drowsiness, irritability, loss of initiative or motivation, and 'other.' As shown in **Table III**, none of the coefficients for depress time showed any significance ($\alpha = 0.05$). False

Table III. Coefficients and *P*-Values of Time Exposed to the 10.2-Staged Condition.

EQUATION OUTCOME SYMPTOM	DEPRESS TIME β_1 COEFFICIENT	*P*-VALUE
Stomach Awareness	0.0515	0.0624
Loss of Appetite	0.0249	0.8636
Nausea	−0.0031	0.9366
Vomiting	0.0200	0.5302
Flushed Feeling	−0.0001	0.9992
Sweating	−0.0037	0.9773
Headache	−0.0068	0.8435
Malaise/Sluggishness	−0.0803	0.1119
Loss of Initiative or Motivation	*	*
Impaired Concentration	−0.0456	0.6000
Irritability	*	*
Drowsiness	*	*
Disorientation	−0.0107	0.9194
Other	*	*

* Regression equation could not compile.

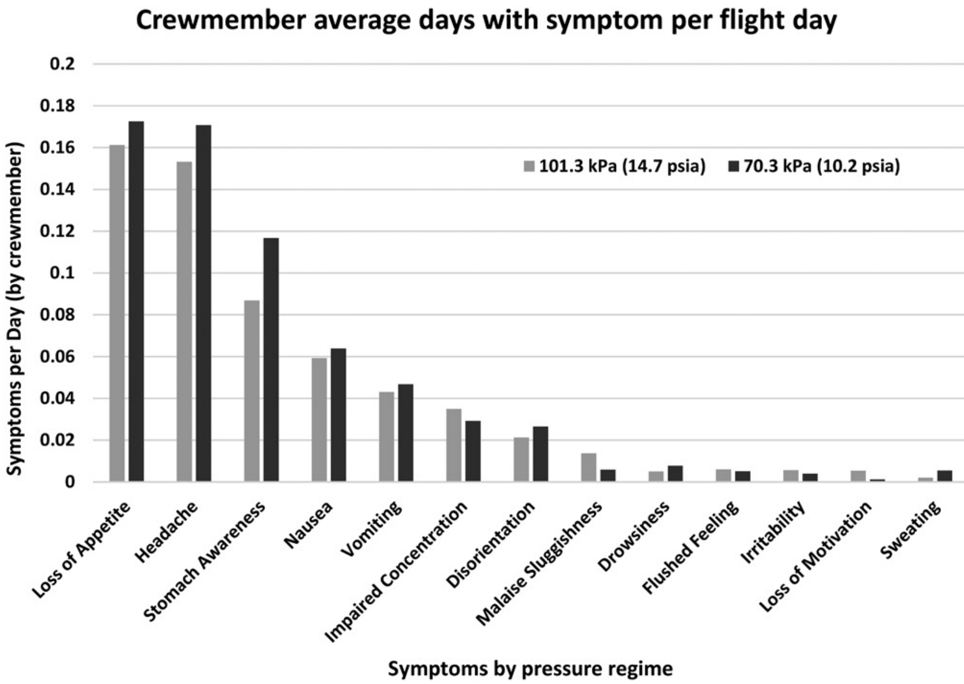

Fig. 3. Space adaptation symptoms for both pressure regimes as average number of symptoms per flight day per crewmember. Logistic regression found no significant difference in the prevalence of any symptom and the time spent at 10.2 psia or 14.7 psia.

discovery rate adjusted *P*-values using the method described by Benjamini and Hochberg were produced to reduce Type I error.[5] This method of adjustment for multiple comparisons is less conservative than other methods (i.e., family-wise error rate) and provides more power. Therefore, none of the regression equations show a statistically significant effect of time spent at the 10.2-psia depressurized condition on reported SAS. **Fig. 3** shows the average number of symptoms per flight day per crewmember for both 14.7-psia and 10.2-psia mission types.

DISCUSSION

Terrestrial experience indicates that chronic exposure to a comparable P_IO_2 of 127 mmHg [4000 ft (1219 m) altitude] is well-tolerated by healthy humans. Similar levels of hypoxia experienced by crewmembers during shuttle missions at a pressure of 10.2 psia for up to 8.1 d resulted in no increased reporting of possible hypoxia-related symptoms. While no direct link between in-flight symptoms and a 10.2-psia shuttle atmosphere was found, this does not ensure that a mildly hypoxic atmosphere with a P_IO_2 of 127 mmHg will not have a detrimental effect on astronaut health over longer duration missions, particularly if the effects of chronic microgravity, coupled with hypoxia, on human physiology are synergistic in nature. The combination of stressors that will be present during missions beyond low-Earth orbit, such as microgravity, headward fluid shift, increased hematocrit, vision impairment intracranial pressure syndrome, fatigue, sleep loss, stress, increased $ppCO_2$ levels, and increased radiation dose, may cause crewmembers to become more sensitive to hypoxic conditions.[11] Further study is warranted to determine if the EA will directly result in increased hypoxia symptomology, particularly when combined with in-flight microgravity exposures or during short- and long-term lunar and Martian exploration missions under hypogravity conditions. Unfortunately, current constraints on the ISS preclude the use of the exact pressure and F_IO_2 of the EA, and the Quest airlock can only provide very short-term (<1 d) exposure to the 10.2-psia condition. Ultimately, concerns associated with the mildly hypoxic EA during spaceflight may only be resolved for longer duration by surveillance of crewmembers who experience the EA for increasing durations of time during future spaceflight missions.

ACKNOWLEDGMENTS

The study team is indebted to Jackie Reeves and Dr. Andrew Abercromby for their editorial review of this manuscript. We are grateful for technical assistance rendered by Drs. Johnny Conkin and Millennia Young. This work was made possible through the Human Health and Performance Contract (NNJ15HK11B) between the National Aeronautics and Space Administration and KBRwyle. Funding for this research was provided by the NASA Human Research Program. Conclusions are those of the authors and are not necessarily endorsed by the National Aeronautics and Space Administration.

Authors and affiliations: James H. Wessel III, M.S., Jason R. Norcross, M.S., and Omar S. Bekdash, M. Eng., KBRwyle, Houston, TX; Caroline M. Schaefer, M.P.H., MEI Technologies, Inc., Houston, TX; and Moriah S. Thompson, M.D., Mayo Clinic, Rochester, MN.

REFERENCES

1. Abercromby AF, Chappell SP, Gernhardt ML. Desert RATS 2011: Human and robotic exploration of near-Earth asteroids. Acta Astronaut. 2013; 91:34–48.
2. Abercromby AF, Conkin J, Gernhardt ML. Modeling a 15-min extravehicular activity prebreathe protocol using NASA' s exploration atmosphere (56.5 kPa/34% O2). Acta Astronaut. 2015; 109:76–87.
3. Abercromby AF, Gernhardt ML, Conkin J. Potential benefit of intermittent recompression in reducing decompression stress during lunar extravehicular activities. [Abstract]. Aviat Space Environ Med. 2008; 79(3):425.
4. Abercromby AF, Gernhardt ML, Jadwick J. Evaluation of dual multi-mission space exploration vehicle operations during simulated planetary surface exploration. Acta Astronaut. 2013; 90(2):203–214.

5. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society Series B. 1995; 57(1):289–300.
6. Gernhardt ML, Abercromby AF, Conkin J. Potential fifty percent reduction in saturation diving decompression time using a combination of intermittent recompression and exercise. Proceedings of the 2007 Undersea and Hyperabaric Medical Society meeting. Dunkirk, MD. Kensington (MD): Undersea and Hyperbaric Medical Society; 2007.
7. Goel N, Bale TL, Epperson CN, Kornstein SG, Leon GR, et al. Effects of sex and gender on adaptation to space: behavioral health. J Womens Health (Larchmt). 2014; 23(11):975–986.
8. Kennedy AR, Crucian B, Huff JL, Klein SL, Morens D, et al. Effects of sex and gender on adaptation to space: immune system. J Womens Health (Larchmt). 2014; 23(11):956–958.
9. NASA Exploration Atmospheres Working Group. Recommendations for exploration spacecraft internal atmospheres: the final report of the NASA exploration atmospheres working group. NASA/TP-2010-216134. Houston (TX): National Aeronautics and Space Administration Johnson Space Center; 2010.
10. NFPA. 99B Standard for Hypobaric Facilities. Quincy (MA): National Fire Protection Association; 2018.
11. Norcross JR, Conkin J, Wessel JH III, Norsk P, Law J, et al. Evidence report: risk of hypobaric hypoxia from the exploration atmosphere. Houston (TX): NASA Johnson Space Center, NASA Human Research Program; 2015.
12. Norcross JR, Norsk P, Law J, Arias D, Conkin J, et al. Effects of the 8 psia/32% O_2 atmosphere on the human in the spaceflight environment. NASA/TM-2013-217377. Hanover (MD): National Aeronautics and Space Administration; 2013.
13. Reschke MF, Cohen HS, Cerisano JM, Clayton JA, Cromwell R, et al. Effects of sex and gender on adaptation to space: neurosensory systems. J Womens Health (Larchmt). 2014; 23(11):959–962.
14. Sulaiman ZM, Pilmanis AA, O'Connor RB, Baumgardner F. Relationship between age and susceptibility to decompression sickness. A review. DTIC Document Report No. AL/CF-TR-1994-0095. Brooks Air Force Base: United States Air Force; 1995.
15. Webb JT, Pilmanis AA, Balldin UI, Fischer JR. Altitude decompression sickness susceptibility: influence of anthropometric and physiologic variables. Aviat Space Environ Med. 2005; 76(6):547–551.
16. West JB. Fire hazard in oxygen-enriched atmospheres at low barometric pressures. Aviat Space Environ Med. 1997; 68(2):159–162.