NOVEMBER 2025 • VOLUME 96 • NUMBER 11

# Aerospace Medicine and Human Performance

THE OFFICIAL JOURNAL OF THE AEROSPACE MEDICAL ASSOCIATION

# Aerospace Medicine and Human Performance

NOVEMBER 2025 VOLUME 96 NUMBER 11 [ISSN 2375-6314 (print); ISSN 2375-6322 (online)]

**This journal, representing the members of the Aerospace Medical Association, is published for those interested in aerospace medicine and human performance. It is devoted to serving and supporting all who explore, travel, work, or live in hazardous environments ranging from beneath the sea to the outermost reaches of space.**



**AEROSPACE MEDICAL ASSOCIATION** is an organization devoted to charitable, educational, and scientific purposes. The Association was founded when the rapid expansion of aviation made evident the need for physicians with specialized knowledge of the flight environment. Since then, physicians have been joined in this Association by professionals from many fields and from many countries, all linked by a common interest in the health and safety of those who venture into challenging environments.

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*Aerospace Medicine and Human Performance* [ISSN 2375-6314 (print); ISSN 2375-6322 (online)], is published monthly by the Aerospace Medical Association, 631 US Highway 1, Suite 307, North Palm Beach, FL 33408. Periodicals postage paid at Alexandria, VA, and at additional mailing offices. POSTMASTER: Send address changes to *Aerospace Medicine and Human Performance,* 631 US Highway 1, Suite 307, North Palm Beach, FL 33408.. Phone (703) 739-2240. Printed in U.S.A. CPC Int'l Pub Mail #0551775.

# Aerospace Medicine and Human Performance

NOVEMBER 2025 VOLUME 96 NUMBER 11

# 2026 AsMA & UHMS Annual Scientific Meeting "Boundless Frontiers—Relentless Progress"

## Sheraton Denver Downtown Hotel
## Denver, CO, United States; May 17–21, 2026

# Call for Abstracts Deadline: Jan. 4, 2026; *NO Exceptions!*

The 2026 AsMA-UHMS Annual Scientific Meeting will be held in Denver, CO, United States. The theme for the 2026 Annual Scientific Meeting is **"Boundless Frontiers—Relentless Progress."** As many of you are aware, the Aerospace Medical Association (AsMA) will be meeting in conjunction with the Undersea and Hyperbaric Medicine Society (UHMS) for the next 5 years and, hopefully, into the distant future. John Peters, the Executive Director of UHMS, is now also AsMA's Executive Director, alongside Gisselle Vargas, the AsMA Deputy Executive Director. There is much happening in the aviation, space, and sea communities. For example, the air traffic system is getting a much-needed overhaul, though the FAA has reached its quota for ATC hires this year. Unmanned aerial systems continue to make headlines, with reports of drones spotted over New Jersey's night skies and the use of drones to deliver weaponry. New pilots are also being hired. NASA is constantly being invigorated by the development of commercial space rockets, discussions about placing nuclear reactors on the Moon to produce power, the upcoming voyage to the Moon, and the ongoing plans to send explorers to Mars. With these facts, AsMA is counting on all members to continue presenting new research and passing on knowledge to our two memberships, which will provide us with more information to take into the next year and start the process all over again—we are looking forward to an extraordinary meeting in Denver!

The Annual Scientific Meeting is the premier international forum to learn and discuss evolving trends and multidisciplinary best practices in research, clinical applications, human performance, and flight safety. The 2026 AsMA-UHMS Annual Scientific Meeting welcomes abstracts in the many areas related to Aerospace Medicine. For a complete list, see the box on p. 2 of this form.

**AsMA ABSTRACT SUBMISSION PROCESS**

**LIMIT: 350 words/2500 characters including spaces; NO Tables or Figures or References should be included in the abstract.** All abstracts must be submitted via the electronic submission system link on the meeting website: https://asma-uhms-asm.org/abstracts/asma-call-for-abstracts.html.

**Those applying should not wait for their funding to be approved before submitting, but should submit as soon as possible.**

**ATTENTION:** You MUST use personal email addresses when entering your abstracts and those of your co-authors.

**ABSTRACT PRESENTATION TYPES**

*The Annual Scientific Meeting features four types of presentation formats.*

**1. Interactive Presentations (Posters):** Individual interactive (poster) presentations are integrated into a session, grouped by topic. The presentation must be submitted as a PowerPoint with up to a maximum of 10 slides. Video and audio clips cannot be embedded but can be uploaded during presentation submission. Presentations are on display for 4 full days, each in an assigned space. Authors will be asked to present their poster for a single designated 45-min period on one of those days.

**2. Slide:** Standalone 15-minute slide presentation with questions/discussion that will be integrated into an oral slide session, grouped by topic. PowerPoint presentations will be organized by topic area and presented during 90-minute blocks of time, 6 periods of 15 minutes each. Individual PowerPoint Oral presentations are limited to 15 minutes, including 3–5 minutes for questions and discussion.

**3. Panel:** Invited Presentation that will link to support a Panel Overview containing five (non-case study) or six (case study) abstracts presented as a cohesive whole. Panels also have 90 minutes, ideally 5 presentations of 15 minutes each followed by a 15-minute discussion period.

**4. Workshop:** Invited Presentation that will link to and support a Workshop Overview. Overview abstracts should reflect the material to be presented in this long format for up to 8 hours of CME credit.

**PRESENTATION CATEGORIES**

*There are two presentation categories based on the topic. (Templates and examples are provided for each type and will be available on the abstract submission website). Authors will be required to enter abstract text under the headings as described below.*

**1. Original Research:** Material that is original in nature and has not been previously presented. Original analysis of a hypothesis involving data collection and analysis. Headings include Introduction, Methods, Results, and Discussion.

**2. Education:** Typically, a discussion of information that is already available.

***a. Program/Process Review:*** Description of a program or process that is used to solve a problem or accomplish a task. Headings include Background, Description, and Discussion.

***b. Tutorial/Review:*** An educational session intended as a review of established material. Headings include Introduction, Topic, and Application.

***c. Case Study:*** A single clinical or human performance event. Headings include Introduction, Case Description, and Discussion.

**PANEL GUIDANCE**

**Panels** must be composed of a coordinated sequence of 5 abstracts that flow logically from one to another supporting the central theme. Panels must contain abstracts that allow 15 minutes of structured discussion at the end of the session.

**Case Study Panels:** Case Study Panels can have 6 abstracts and are intended to highlight a particular institution, community, or aeromedical issue, usually presented from the same institution or aeromedical community.

***It is the responsibility of the Panel Chairperson to enter all supporting abstracts and to ensure that all supporting abstracts clearly describe how each supports the Panel theme.*** If the Panel theme is not clearly identified and/or the abstracts do not support a central theme, the Scientific Program Committee may decline the proposed Panel in total. Unrelated abstracts from a laboratory or organization do not constitute a Panel (unless they are Case Studies).

Panel Chairs are also responsible for preparing questions and discussion points to facilitate a moderated discussion with the audience during the sixth period. Each Panel speaker should cite or link directly to the Panel theme, and at the end of their talk should provide a logical segue to the next abstract.

**WORKSHOP GUIDANCE**

Rules for workshops and the review process are similar to those for Panels (above). Individual abstracts must be entered for each invited presenter and all necessary information must be entered in the same manner as all other abstracts, including financial disclosure statements. Course materials should be made available for registrants.

A separate registration fee is charged for Workshops registration. For additional information contact Gisselle Vargas, Deputy Executive Director, at gvargas@asma.org.

**AsMA ABSTRACT SUBMISSION PROCESS**

All abstracts must be submitted via the electronic submission system linked to on the association's website: *https://asma-uhms-asm.org/abstracts/asma-call-for-abstracts.html*. Click on the link to the abstract submission site--available on the AsMA home page and Meetings page on or about September 1, 2025. Authors with questions regarding the abstract submission process should contact AsMA directly at (703) 739-2240, x101 (Mrs. Rachel Trigg), email rtrigg@asma.org or x102 (Mrs. Stella Sanchez), email ssanchez@asma.org.

The following information is required during the submission process: Abstract title, presenting author information (including complete mailing and email addresses and telephone numbers), topic area (from list provided on back of form), contributing authors names, emails and institutions, abstract content **(LIMIT: 350 words/2500 characters including spaces), at least 2 Learning Objectives** (the Accreditation Council for Continuing Medical Education requires this for all presentations). In addition, three (3) multiple choice or True/False questions and answers are required for each Interactive Presentation, Slide, and Panel presentation for enduring materials for CME credit. Read instructions online for additional details. ***Interactive presentations must be uploaded as a PowerPoint in advance of the meeting no later than February 23, 2026, 11:59 PM ET.***

**PLEASE NOTE:** All Presenters (including panelists) are required to register for the meeting. *There is a discounted fee for non-member presenters. Registration limited to the day of presentation will be available on site.*

**Financial Disclosure/Conflict of Interest/Ethics**

Abstracts will not be accepted without a financial disclosure form. The form is included as part of the website abstract submission process. The presenting author must agree to comply. Scientific presentations at AsMA-sponsored events will adhere to the highest standards of scientific ethics, including appropriate acknowledgment or reference to scientific and/or financial sources. Presenters must avoid the endorsement of commercial products in their abstracts and during their presentations. There must be no advertisements on Posters, slides, or handout materials.

**Presentation Retention Policy**

AsMA will use live capture technology to record all oral presentations during the meeting. Recorded presentations will be made available to registrants after the meeting. Authors are required to provide permission for live capture and a nonexclusive license to repurpose the content. PDF copies of Poster presentations must be uploaded to the designated submission site.

**Permissions and Clearances**

It is the author's responsibility to obtain all necessary permissions and clearances prior to submission of the abstract. AsMA assumes no liability or responsibility for the publication of any submitted material.

**Acceptance Process**

Abstracts will be reviewed by a minimum of three members of the AsMA Scientific Program Committee. Acceptance will be based on the abstract's originality, relevance, scientific quality, and adherence to the guidelines provided. Criteria for non-acceptance include, but are not limited to: insufficient, inconsistent, or ambiguous data; commercialism; or reviews of previously published literature. Abstracts must be 100% complete upon submission, including all final data and results. How well authors abide by submission and format guidelines will also be one of the criteria used to determine acceptance of abstracts.

***Presenters are limited to one Slide OR Interactive Presentation AND one Panel presentation unless given specific prior permission by the Scientific Program Committee Chair, Amanda Lippert, at sciprog@asma.org.*** Following review by the Scientific Program Committee in January, all contributors will receive a notification of acceptance or non-acceptance by email. Accepted abstracts will be published in *Aerospace Medicine and Human Performance*.

While the Scientific Program Committee strives to honor the presenter's desired presentation format, for reasons such as space limitations or dissimilar content, an abstract may be changed to an alternative presentation format. Assignment of an abstract to either a poster or a slide presentation will be recommended by the Scientific Program Committee, but the final decision will be made by the Program Committee Chair.

**Abstract Withdrawal**

Withdrawing abstracts is strongly discouraged. However, if necessary, a request to withdraw an abstract should be sent to Amanda Lippert, the Scientific Program Chair, at sciprog@asma.org and Rachel Trigg at rtrigg@asma.org. The request for withdrawal must include the abstract title, authors, ID number, and reason for withdrawal. Abstract withdrawal decisions must be sent to the Scientific Program Chair as soon as possible.

**Mentorship**

**Optional review / feedback for all presenters at AsMA 2026**

AsMA is continuing its mentorship initiative for all authors for the 2026 Scientific Meeting. You have the option to submit a draft of your abstract to a group of senior AsMA members for review and feedback. If you have questions about this opportunity, please e-mail sciprog@asma.org. E-mail your abstract to sciprog@asma.org no later than December 15, 2025. The Program Mentor Group will review provide feedback via e-mail by December 22, 2025. The abstract will still need to be finalized in the submission system.

**TOPIC AREAS:** (These will be listed on a drop-down menu on the submission site. They are used to organize the abstracts into sessions.)

**1: Human Performance**
- 1.1 Personnel Selection
- 1.2 Training
- 1.3 Hypobaric & Hyperbaric Physiology
- 1.4 Thermal Physiology
- 1.5 Acceleration / Vibration/ Impact
- 1.6 Fatigue
- 1.7 Neurophysiology & Sensory (inc. Vision, Auditory, Vestibular, Spatial Disorientation)
- 1.8 Aerospace Human Factors & Psychology
- 1.9 Aerospace Human Systems Integration

**2: Clinical Medicine**
- 2.1 Aviation Medicine
- 2.2 Health Promotion and Wellness Programs
- 2.3 Medical Standards / Aircrew Health
- 2.4 Occupational / Environmental Medicine
- 2.5 Operational Medicine
- 2.6 Hyperbaric Medicine

**3: Travel and Transport Medicine**
- 3.1 Travel Medicine
- 3.2 Aeromedical Transport / Air Evacuation
- 3.3 Air Transport Medicine
- 3.4 Commercial
- 3.5 Pandemic Preparedness

**4: Space Medicine**
- 4.1 Space Medicine
- 4.2 Space Operations

**5: Safety and Survivability**
- 5.1 Escape / Survival
- 5.2 Flight Safety / Accident Investigation

6: Other
- 6.1 History of Aerospace Medicine
- 6.2 Ethics

Follow the link on our website: *https://asma-uhms-asm.org/abstracts/asma-call-for-abstracts.html*
- **Submission hard deadline: Sunday, January 4, 2026, 11:59 PM ET (there will be no extensions)**
- Notice of acceptance by Saturday, January 31, 5 pm ET.
- **No updates to abstracts will be accepted after Saturday, February 28, 2026, 11:59 PM ET**
- **Interactive presentations (posters): PDF/PPT must be submitted to the UHMS by Monday, February 23, 11:59 PM ET - NO updates will be accepted after this date, not even on site.**

# Aerospace Medical Association

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**Please Send CV or Bio to the Journal Department:** rtrigg@asma.org

You will automatically receive access to the online journal with your membership.

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| ☐ Student[2] | $50 |
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| ☐ Allied Membership[4] | $50 |
| ☐ Technician | $130 |
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[1]**Must be 65 yrs old + 25 yrs of AsMA membership**
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**(see list online:** https://www.asma.org/membership/individual**)**

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☐ Bank Transfer

***NOTE:*** all Bank Transfers must include a $35.00 US processing fee.

*Please contact AsMA Membership Department at skildall@asma.org for bank details.*

**For United States Federal Income Tax purposes**, you can deduct as a charitable contribution the price of the membership renewal less the estimated cost of your ***Aerospace Medicine and Human Performance*** journal subscription. We estimate the cost to produce the journal to be $100 per year. Any membership contribution in excess of $100 per year is tax deductible.

**For Non-U.S. members**, the entire membership fee is related to the activities of the Aerospace Medical Association to improve the professional knowledge and practice of its members. This includes subscription to the Association's professional journal, itself part of the education effort of the Association.

**Specialties: Please select from the following list of specialties all that apply to you.**

- ☐ Administrative Medicine – physicians
- ☐ Aerospace and Aviation Medicine
- ☐ Aerospace Flight Nursing
- ☐ Aerospace Human Factors & Human Engineering
- ☐ Aerospace Physiology
- ☐ Airline Medical Director
- ☐ Allergy
- ☐ Anesthesiology
- ☐ Aviation Medical Examiner
- ☐ Biochemistry
- ☐ Bioengineering
- ☐ Biomedical Engineering
- ☐ Biophysics
- ☐ Cardiology or cardiovascular disease
- ☐ Certified in Aerospace Physiology
- ☐ Dermatology
- ☐ Development & Manufacturing Industry
- ☐ Diplomate, ABPM, Cert in Aero Med
- ☐ Emergency Medicine
- ☐ ENT
- ☐ Environmental Sciences
- ☐ Epidemiology
- ☐ Family Practice
- ☐ Forensic Medicine
- ☐ Gastroenterology
- ☐ General Practice
- ☐ General Surgery
- ☐ Geriatrics
- ☐ Hand Surgery
- ☐ Human Performance
- ☐ Human Systems Integration
- ☐ Hyperbaric Medicine
- ☐ Industrial or Occupational Medicine
- ☐ Industrial or Traumatic Surgery
- ☐ Internal Medicine
- ☐ Legal Medicine
- ☐ Life Insurance Medicine
- ☐ Life Science
- ☐ Maxillofacial Surgery
- ☐ Medical Anthropology
- ☐ Military Command
- ☐ Neurological Surgery
- ☐ Neurology
- ☐ Nuclear Medicine
- ☐ Nursing/Patient Transport
- ☐ Obstetrics and Gynecology
- ☐ Occupational Diseases
- ☐ Ophthalmology
- ☐ Optometry
- ☐ Orthopedic Surgery
- ☐ Otolaryngology and Otology
- ☐ Pathology
- ☐ Pediatrics
- ☐ Pharmacology
- ☐ Physical Medicine & Rehabilitation
- ☐ Physiology
- ☐ Plastic Surgery
- ☐ Preventive Medicine – General
- ☐ Proctology
- ☐ Psychiatry
- ☐ Psychology
- ☐ Public Health
- ☐ Pulmonary Disease
- ☐ Radiology & Roentgenology
- ☐ Research and Research Scientist
- ☐ Rheumatology
- ☐ Space Medicine
- ☐ Sports Medicine
- ☐ Surgery
- ☐ Thoracic Surgery
- ☐ Toxicology
- ☐ Tropical Medicine
- ☐ Urology

**Please consider joining one or more of the following Constituent Organizations:**

- Aerospace Human Factors Association
- Aerospace Medicine Student and Resident Organization
- Aerospace Nursing and Allied Health Professionals Society
- Aerospace Physiology Society
- American Society of Aerospace Medicine Specialists
- International Airline Medical Association
- International Association of Military Flight Surgeon Pilots
- Life Sciences & Biomedical Engineering Branch
- Society of NASA Flight Surgeons
- Society of U.S. Air Force Flight Surgeons
- Society of U.S. Army Flight Surgeons
- Society of U.S. Naval Flight Surgeons
- Space Medicine Association
- Space Surgery Association

# Fellows of the Aerospace Medical Association

Warren Silberman, D.O.

Any AsMA member actively working in aviation or space medicine should consider striving to become a Fellow of the Aerospace Medical Association (AsMA). Fellowship represents the highest level of organizational membership, an honor that reflects not only activity but also fidelity to and alignment with the principles and mission of AsMA. Fellows are ambassadors of everything our Association stands for.

### Fellowship Mission Statement

"AsMA fellowship denotes recognition as the highest level of organizational membership. It is not simply a matter of checking boxes but is based on a foundation of activity, strengthened by intangibles that demonstrate dedication to AsMA's principles."

The selection process is therefore designed to align directly with AsMA's mission and values.

Out of a total membership of approximately 2000, there are 438 Fellows. The voting process for the fellowship was modified in 2007. Under the guidance of the then-Chair of the Fellows Group, GEN George Anderson, a committee was formed that recommended the items that the committee felt were important in becoming a Fellow. The conclusion came down to five categories: AsMA Activity with subcategories: Meeting Attendance, AsMA Committee Work, AsMA Leadership, National & International Leadership, ASMA Awards, and Journal Service; Communication, which included: Presentations, Teaching, Education & Experience in Aerospace Medicine, Education, Additional Degrees, Internship, Residency & Fellowship, Coursework, and Board Certification; and the last general category: Extreme Environments and Related Activities, which included the subcategories: Scuba Diving, Cold Environments, and Aviation with its subcategories: Certification as a pilot, Maintenance Work, Parachuting, and Additional Aviation Activity.

The final decisions as to who becomes a fellow ultimately fall to the Chair of the Fellows Group, and they have two committees that make the recommendations. They are the Fellows Evaluation Committee (FEC) and the Fellows Nominating Committee (FNC). The FEC reviews each candidate's application to make sure that they placed the appropriate responses in each item and, at the same time, are not taking credit for items that are not. Each candidate is now expected to provide a copy of their current curriculum vitae. The FNC performs one final check, ensuring that none of its committee members are aware of any adverse information. They have the option to move any candidates with a close score into the approved column. Currently, the minimum score to make a fellow is 130.

The call for nominations generally occurs after the AsMA Council meeting in November of each year. The Chair of the FEC will ensure that each nominee has several committee members review their application. The current Open Water system that AsMA uses for the application scores the candidate as they complete their applications. The FEC chair averages the scores of each nominee and then emails their results to the FNC chair. Each nominee is given 30 days to complete their application, but this is generally extended. Once the FNC has reviewed each nominee, the final list is emailed to the Chair of the Fellows, who then forwards it to all current Fellows. It is at this point that the actual AsMA Fellows can speak with the Chair should they have any objections to a candidate. The FNC generally completes its task by March or April. This process reduces the likelihood of objections to the final slate at the Monday evening Fellows Meeting.

To ensure transparency, the points chart and the entire process are located in the Fellows section of the Members website: https://www.asma.org/members-only/member-services/fellows/.

The Associate Fellows group sends the Fellows Chair a list of their membership who they feel have enough points and are ready to be considered. Each Fellow can nominate up to two individuals each year. These individuals do not have to be from the Associate Fellows group.

The Fellows have firmly fixed several items in the scoring process. Each nominee must have at least 7 years of continuous membership in AsMA, and a minimum of 5 points total from AsMA meeting attendance and committee participation.

Here are some pitfalls and recommendations for completing the application. First, a nominator should ensure that their nominee has a minimum of 7 years of AsMA membership and that their membership is up to date at the time of recommendation. Any AsMA member who contemplates becoming a Fellow must maintain accurate personal records of their committee membership, all aerospace organizations they belong to, the aerospace medicine presentations they give, the teaching they conduct, the dates, and the aerospace coursework they complete, along with the dates and details of each. Regarding the articles that an individual writes, they must be related to aerospace medicine, as an article that a FEC committee member feels is not relevant will be rejected.

At the end of the online application, there is a place to write an 800-word statement. I advise people to ensure they list items that are not accounted for in the application itself. Some examples include serving as commander of one of the aeromedical laboratories or being the flight surgeon in charge during deployment.


DOI: https://doi.org/10.3357/AMHP.9611PP.2025

CONTACT DETAILS:
**Email:** President@asma.org • **Website:** www.asma.org • **Facebook:** Aerospace Medical Association • **X:** @Aero_Med • **YouTube:** @Aero_Med

# Acute Mountain Sickness Symptoms After Rapid Ascent to 4900 m

Joshua T. Murphey; Hayden W. Hess; Jacqueline Schwob; Brian A. Monaco; Brian M. Clemency; David Hostler



**INTRODUCTION:** Acute mountain sickness (AMS) is a common condition in individuals ascending rapidly to high altitudes and often presents with headaches, fatigue, and gastrointestinal symptoms. AMS is prevalent above 13,000 ft (4000 m), but some individuals experience it at lower elevations. This pilot study assessed the prevalence and timing of AMS symptoms in unacclimatized individuals exposed to 16,000 ft (4900 m) in a controlled hypobaric environment.

**METHODS:** A total of 10 healthy, unacclimatized men and women were exposed to an altitude of 16,000 ft (4900 m) for 5 h. Physiological parameters, including heart rate (HR), oxygen saturation ($S_pO_2$), and respiratory rate (RR), were recorded alongside AMS symptom severity using the 2018 Lake Louise Questionnaire (LLQ) and divided into low, moderate, and high responders based on severity.

**RESULTS:** All subjects experienced some degree of AMS symptoms, with LLQ scores increasing over time. Two subjects could not complete the full exposure due to moderate and severe symptoms. HR increased ($\Delta = 7.0 \pm 0.6$), while $S_pO_2$ remained stable but lower than baseline ($\Delta = 9 \pm 4.2$). LLQ score increases were strongly correlated with HR, $S_pO_2$, and RR. RR remained stable across subjects but varied between AMS severity groups.

**DISCUSSION:** This pilot study demonstrated that unacclimatized individuals rapidly exposed to 13,000 ft (4900 m) develop AMS symptoms in a controlled environment. The correlation between LLQ scores and physiological changes offers insight into AMS pathophysiology, supporting the need for further research into AMS susceptibility and genetic factors.

**KEYWORDS:** acute mountain sickness, hypoxia, altitude sickness, hypobaric chamber, symptoms.

**Murphey JT, Hess HW, Schwob J, Monaco BA, Clemency BM, Hostler D.** ***Acute mountain sickness symptoms after rapid ascent to 4900 m*****. Aerosp Med Hum Perform. 2025; 96(11):958–963.**

Acute mountain sickness (AMS) is a prevalent and potentially debilitating medical condition that develops following rapid ascent to high altitude. Characterized by fatigue, loss of appetite, headache, sleep disturbances, and diminished affect,[1] AMS typically emerges within 6–12 h of exposure to altitudes exceeding 11,500–13,000 ft (3500–4000 m). However, various reports indicate that some individuals experience AMS at altitudes as low as 8000 ft (2500 m).[1–3] The Lake Louise Questionnaire (LLQ),[4] most recently revised in 2018, remains the principal tool for symptom-based assessment and classification of AMS severity.[5] While the LLQ has demonstrated utility in the field, its performance in controlled laboratory environments and its relationship to objective physiological metrics remain incompletely characterized.

Despite the long-standing history of high-altitude research,[6] important gaps persist in the understanding of AMS pathophysiology.[1] Proposed mechanisms include a marked increase in extracellular cerebral edema, vasogenic intercellular edema, an acute increase in plasma volume from carbonic anhydrase in the renal system, and an increase in oxidative stress coupled with neuronal damage from increased intracranial pressure.[5–7] However, the symptom complex associated with AMS is nonspecific and overlaps with other altitude-related and infectious diseases, complicating early identification and intervention. For example, initial AMS symptoms are often attributed to other

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This manuscript was received for review in February 2025. It was accepted for publication in July 2025.

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DOI: https://doi.org/10.3357/AMHP.6661.2025

benign conditions (e.g., common cold or flu) when outside a controlled setting. Since not easily differentiated from other conditions, treatment may be delayed, leading to the development of more severe conditions—high-altitude cerebral edema (HACE) or high-altitude pulmonary edema (HAPE).[7–9] Previously, it was thought that untreated AMS directly caused HACE and, to some degree, HAPE. However, studies have shown that the pathophysiology differs, and the exact mechanisms behind HACE and HAPE are still being investigated.[5,6,10] It is important to note that the onset of AMS symptoms varies from person to person. It is generally accepted, however, that mild symptoms will occur within 1–2 h of ascent to high altitude.[1,7,10]

Field studies of AMS are expensive, time-consuming, and can be complicated by adverse environmental conditions such as wind, cold, and precipitation. Furthermore, subjects in field studies are often trained climbers with previous experience acclimatizing or are in the process of acclimation. This makes generalizability difficult, as AMS is not limited to mountaineers, climbers, or alpinists. The expansion of expedition tourism and the mobile nature of military operations open high-altitude destinations to nearly everyone. Studying unacclimatized individuals without previous hypobaric exposure in a controlled hypobaric environment allows generalization to a much broader population. Controlled hypobaric hypoxia exposure in a hypobaric chamber provides a platform for testing interventions that unacclimated individuals may use.

This pilot study was conducted to evaluate the onset and severity of AMS symptoms in healthy, unacclimated individuals during acute exposure to 16,000 ft (4900 m) in a hypobaric setting. A secondary objective was to assess the feasibility of stratifying AMS severity using the LLQ and to explore its potential utility as a correlative measure in future studies examining physiological and cognitive predictors of AMS. The findings from this study are intended to inform the development of larger-scale studies and support the validation of self-report tools in controlled, yet operationally relevant, environments.

## METHODS

### Subjects

A total of 10 healthy ($N = 10$, 8 men) unacclimated individuals without previous high-altitude exposure were recruited from the community. The study protocol was approved in advance by the University at Buffalo Institutional Review Board (IRB# FWA00008824). Each subject provided written informed consent before participating. After written consent was obtained from each subject, familiarization with the 2018 LLQ was provided before the protocol visit. To ensure the safety and reliability of our results, each subject underwent a physical examination with a study physician, which included musculoskeletal, neurological, cardiovascular, and pulmonary assessments. Subjects with any history of neurological, metabolic, pulmonary, or cardiovascular disease or illness, those who had traveled to moderate or high altitude within 1 wk of testing, and those who self-reported as claustrophobic were excluded. In addition, subjects who reported being smokers or currently taking any medications that are known to affect pulmonary, cardiovascular, or neurological function were excluded. Subjects abstained from taking antioxidant supplements for 24 h, alcohol, caffeine, nicotine, and exercise for 12 h, and food for 2 h before the testing.

### Procedure

Subjects reported to the Center for Research and Education in Special Environments laboratory. The laboratory is located 600 ft (183 m) above sea level. They voided their bladder and were weighed in clothing before entering the hypobaric chamber. Euhydration was confirmed by urine-specific gravity ≤1.020 (Master-Sur/Nα; Atago USA Inc., Bellevue, WA, United States). The hypobaric chamber was decompressed to 16,000 ft (4900 m) at a rate of ~1000 ft (325 m)/min and remained at that pressure for a maximum of 5 h. Up to three subjects underwent altitude exposure simultaneously. Heart rate (HR) and arterial oxygen saturation ($S_pO_2$) were recorded every 5 min (Masimo SET Rainbow, Irvine, CA, United States), blood pressure (BP) and respiratory rate (RR) were measured manually every 15 min, and AMS severity was assessed every 30 min via the LLQ. Mean arterial blood pressure (MAP) was calculated by:

$$MAP = DBP + \frac{1}{3}\,(\text{SBP-DBP}).$$

Hypobaric hypoxia exposure was terminated if subjects were unable to equalize inner ear pressure during ascent, their $S_pO_2$ dropped below 70% and could not be stabilized through pressure breathing,[11] they exhibited an LLQ score greater than 7, experienced severe nausea or headache, showed signs or symptoms of HACE or HAPE, or upon their request. When a termination criterion was met, the subject was provided 100% supplemental oxygen for the remainder of the experimental session while data collection continued for other subjects. Subjects were then returned to sea level and monitored until their vital signs returned to baseline.

### Statistical Analysis

Mean and standard deviations were calculated for anthropometric characteristics. $S_pO_2$, HR, RR, LLQ, and MAP changes across altitude exposure were compared for statistical significance (GraphPad Prism, Boston, MA), and a robust nonlinear regression was used to identify any outliers. Analysis of variance was used to examine differences within and between subjects; a Tukey post hoc analysis was used to determine where the analysis of variance differences were. Pearson's correlation coefficients were used to compare physiological measurements to AMS symptom scores. Preliminary analysis revealed subjects fell into one of three groups: no clinical AMS (None, LLQ = 1), mild AMS (Mild, LLQ = 4), and moderate AMS (Mod, LLQ = 6+). A one-way analysis of variance was used to reveal differences between groups. Data are presented as means ± SD with an alpha level ≤0.05.

**Table I.** Subject Anthropomorphic Information.

| CHARACTERISTIC | MEAN ± SD | RANGE |
|---|---|---|
| Age (yr) | 28 ± 8 | 19–44 |
| Mass (kg) | 83.1 ± 12.2 | 71.6–108.4 |
| Height (cm) | 177 ± 10 | 160–193 |
| BMI ($kg \cdot m^{-2}$) | 26.55 ± 3.2 | 21.5–30.9 |
| Resting HR (bpm) | 62 ± 6 | 52–82 |

## RESULTS

Anthropometric data are presented in **Table I**. All subjects were well-hydrated before experimental testing (urine specific gravity = 1.009 ± 0.001). HR and $S_pO_2$ differed from baseline ($\Delta$ = 27 ± 3.8, $P < 0.001$; $\Delta$ = 9 ± 4.2, $P < 0.0001$, respectively). HR increased over time ($\Delta$ = 7.0 ± 0.6, $P$ = 0.04), while $S_pO_2$ remained stable throughout the 5-h exposure (**Fig. 1A and B**). MAP ($\Delta$ = 3.1 ± 13.7, $P$ = 0.57) and RR (0.3 ± 0.5, $P$ = 0.25) did not change over time or from baseline but were different between subjects who experienced only a high-altitude headache and those who had Mild and Mod AMS ($\Delta$ = 1.3 ± 0.15, $P$ = 0.006; $\Delta$ = 3.16 ± 0.33, $P < 0.001$, respectively) and between Mild and Mod AMS ($\Delta$ = 1.91 ± 0.17, $P < 0.05$) (**Fig. 2A and B**).

Of the 10 subjects, 2 could not complete the 5-h experimental exposure. One subject lasted 1 h and 30 min, while the other lasted 1 h and 5 min before being placed on supplemental oxygen. Both reported an LLQ score of 6 just before the administration of oxygen. One subject experienced severe gastrointestinal symptoms and headache, while the other experienced severe lightheadedness respective to the total exposure times previously stated.

Lake Louise Scores increased over time (3.0 ± 1.0, $P < 0.001$, **Fig. 3A**). Subjects were grouped into NONE (0–2), MILD (3–5), or MOD (6–9) based on their peak LLQ score (**Fig. 3B**). Regardless of LLQ score, however, all subjects experienced a high-altitude headache. Additionally, two subjects reported gastrointestinal symptoms, one mild and one moderate. Fatigue and lightheadedness were reported by six subjects exhibiting mild to moderate AMS symptoms. The average onset time for subjects who experienced MOD AMS was 2:25 (hh:mm). The average onset time for MILD AMS was 1:03 (hh:mm). The LLQ demonstrated a strong positive correlation with HR [r(8) = 0.78, $P < 0.05$]. Conversely, LLQ exhibited a strong negative correlation with $S_pO_2$ [r(8) = −0.9, $P < 0.05$] and RR [r(8) = −0.7, $P < 0.05$]. No significant correlation was found between LLQ and MAP (**Fig. 4**).

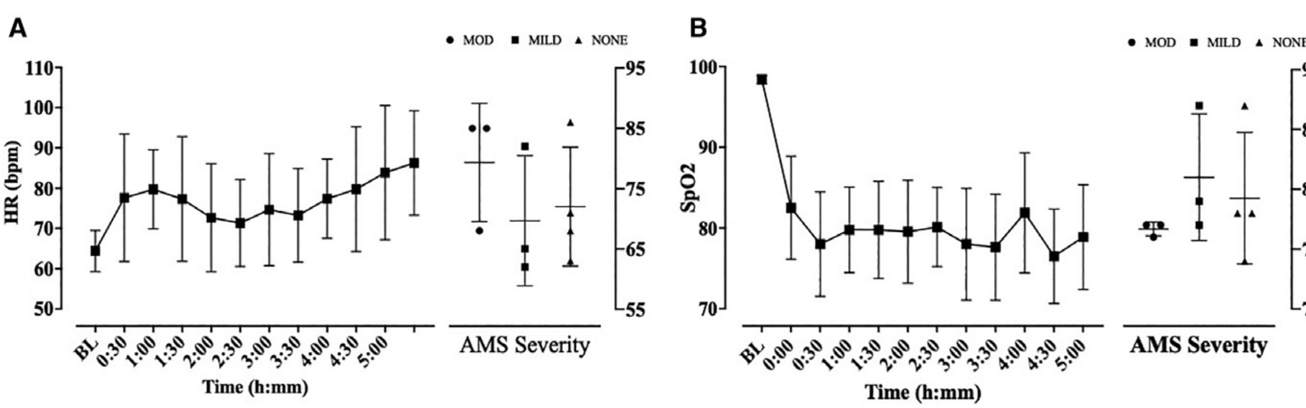


**Fig. 1.** A) Heart rate (HR) and B) blood oxygen saturation ($S_pO_2$) over time ($P < 0.001$) from baseline (BL) and HR time effect ($P = 0.04$). Individual data points by group (AMS Severity) are for moderate AMS (Mod), mild AMS (Mild), and no AMS (None). All data are shown as mean ± SD.

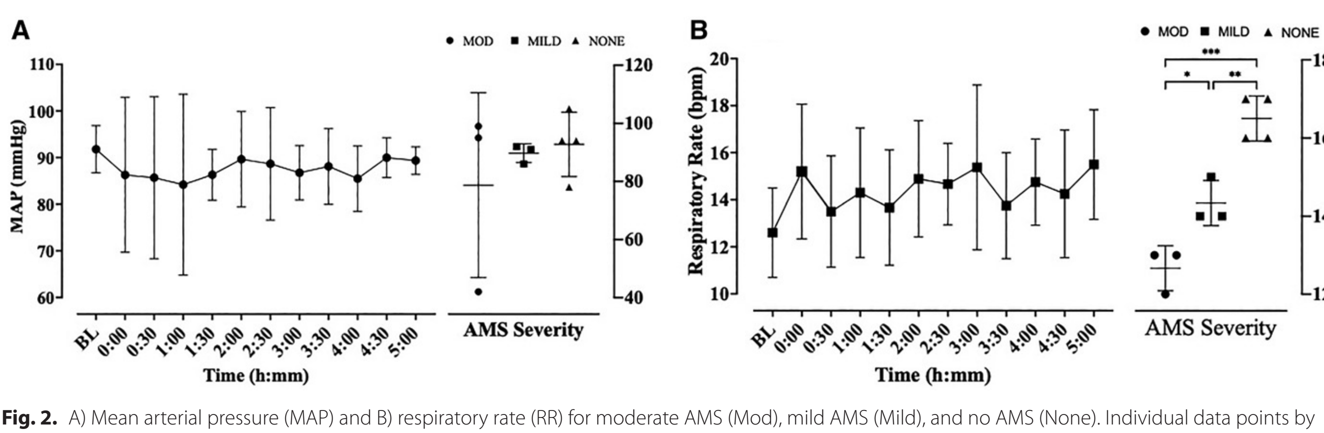


**Fig. 2.** A) Mean arterial pressure (MAP) and B) respiratory rate (RR) for moderate AMS (Mod), mild AMS (Mild), and no AMS (None). Individual data points by group (AMS Severity) show None differed from Mod and Mild (***$P < 0.001$, **$P = 0.006$, respectively) and between Mild and Mod (*$P < 0.05$). All data are shown as mean ± SD.

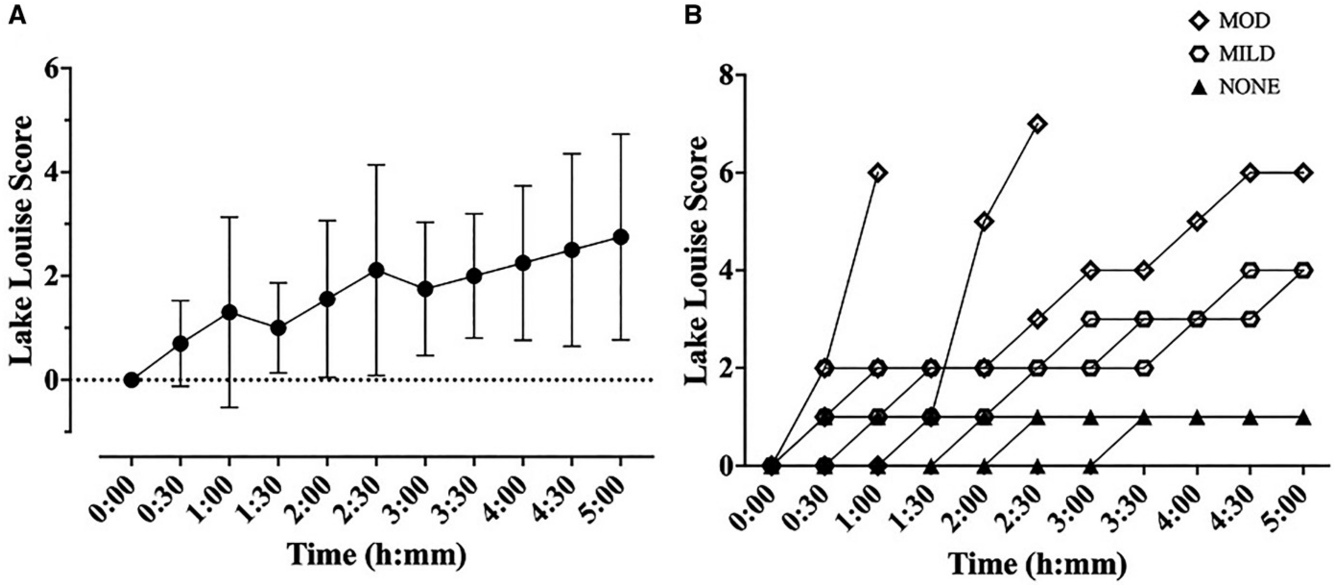


**Fig. 3.** A) Group Lake Louise Questionnaire (LLQ) scores and time effect ($P < 0.001$). B) Individual LLQ scores ($P < 0.01$) and time effect ($P < 0.001$). All data are shown as mean ± SD.

## DISCUSSION

This study established an experimental protocol for inducing AMS symptoms in a controlled hypobaric environment. The results provide insight into the physiological and symptomatic responses to hypoxia. Subjects showed increased HR and LLQ scores over time, indicating physiological stress and symptom development during exposure. In contrast, MAP and RR remained stable over the 5-h exposure across all subjects, suggesting these parameters did not significantly change once subjects reached 16,000 ft (4900 m). However, those who experienced no clinical AMS had higher RR when compared to those who experienced Mild and Mod AMS symptoms (Fig. 2B). $S_pO_2$ also remained stable during hypobaric exposure but was reduced from baseline ($\Delta = 19 \pm 4.2$, $P < 0.001$).

Correlative analyses revealed that higher LLQ scores, indicative of more severe AMS symptoms, were associated with increased HR and lower $S_pO_2$ and RR, reflecting the body's attempt to maintain adequate oxygen levels and sufficient ventilation under hypoxic stress. No relationship was found between LLQ and MAP, indicating that subjective AMS symptoms were not directly related to changes in arterial pressure. Further analysis showed that increased RR was associated with higher MAP, while a complex association was observed between RR, HR, and $S_pO_2$, emphasizing the connection between respiratory and cardiovascular reactions. These findings are consistent with known physiological responses to acute hypobaric hypoxia, such as resting minute ventilation and $SpO_2$, which have been independently shown as AMS predictors.[12] There was a positive ($r = 0.75$) relationship between MAP and RR and a modest inverse relationship between MAP and LLQ, $S_pO_2$, and HR ($r = -0.14$, $-0.26$, and $-0.7$, respectively).

The findings align with existing literature on AMS, which identifies hypoxia as a primary trigger for AMS symptoms such as headache, nausea, and fatigue.[13–15] Hypoxemia is a critical factor in AMS development, leading to increased cerebral blood flow, potentially contributing to cerebral edema and intracranial pressure.[16,17] The increased RR shown between subjects who experienced Mild and Mod AMS symptoms compared to those in the None group sheds light on why some subjects were more susceptible to a low-pressure hypoxic environment than others. Given the differences in RR between groups was not a result of exposure time, it is likely RR is not directly related to AMS severity; rather, RR is driven by $O_2$ and $CO_2$ sensing drive RR. This further supports the notion that individual susceptibility and the body's response to

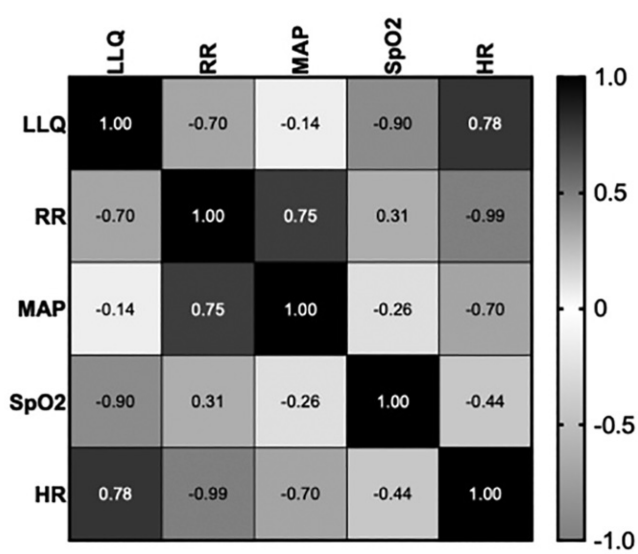


**Fig. 4.** Pearson's correlation heat map for all research variables. LLQ: Lake Louise Questionnaire score; RR: respiratory rate; MAP: mean arterial pressure; $S_pO_2$: arterial oxygen saturation; and HR: heart rate.

hypoxia play crucial roles in AMS development.[9,17] Recent research highlights the importance of understanding the molecular and cellular mechanisms underlying AMS.[18–20] For instance, hypoxia-inducible (HIF-1) and vascular endothelial growth factors are implicated in the body's response to hypoxia, influencing vascular permeability and cerebral edema.[21,22] The interplay between these factors and physiological responses, such as increased HR and altered RR, provide a deeper understanding of AMS pathophysiology.[1] Based on the literature, it is likely that the subjects who experienced worse AMS have an increased HIF-1 response, a blunted hypoxic ventilatory response (HVR), are more sensitive to changes in $CO_2$ and $O_2$, or possibly a combination. As HIF-1, HVR, and $O_2/CO_2$ sensitivity are linked to genetics, future studies should include observations of both to elucidate how much influence genetics has on AMS in unacclimatized individuals. Individual variability in $O_2/CO_2$ chemosensitivity is multifactorial, extending beyond genetic determinants, HVR, and HIF-1 signaling. Notably, heightened sympathetic activation—linked to increased peripheral chemoreceptor activity—has been implicated in a myriad of diseases, including hypertension, depression, Type II diabetes, ulcerative colitis, and chronic inflammatory diseases.[23] Although the present cohort was screened to exclude cardiovascular, pulmonary, renal, and metabolic conditions, they were not screened for generalized anxiety, depression, or chronic stress. These factors have been associated with elevated sympathetic tone and diminished parasympathetic modulation, potentially contributing to augmented $O_2/CO_2$ sensitivity. This, in turn, may underlie the elevated RR, more rapid onset, and increased severity of AMS symptomology that was observed during the study.[24,25]

In this model of rapid exposure to hypobaric hypoxia, subjects experienced a range of AMS symptoms, including headaches, gastrointestinal issues, fatigue, and lightheadedness. Approximately a third of the subjects experienced severe symptoms, one-third had moderate, and the remaining had minor symptoms and did not reach the clinical threshold for mild AMS. Peak symptom severity was associated with the time of symptom onset. Subjects who experienced the most severe symptoms reported the earliest onset of mild symptoms, highlighting the importance of not dismissing any mild symptoms that occur early during altitude exposure to avoid unnecessary AMS progression. This observation could potentially serve as a valuable diagnostic aid for self-monitoring during rapid ascent.

The onset of AMS was consistent with known patterns of AMS development.[26] These symptoms reflect the body's acute response to hypoxia and the challenges of maintaining homeostasis at high altitudes, and the reported LLQ scores indicate a significant variation in high altitude affinity between individuals. Though all subjects experienced the minimum criteria for AMS diagnosis—a high-altitude headache—AMS severity over the 5-h exposure time varied considerably, with some subjects meeting termination criteria and needing supplemental oxygen well before the end of exposure to others only experiencing a mild headache. Since all subjects were free from other illnesses and had not traveled to high altitudes in the past, none of the symptoms of AMS could be associated with a diagnosed illness or chronic disease. These findings further support a possible genetic correlation to how individuals respond to acute exposure to high altitude outside of people with known evolutionary genetic mutations for survival at high altitude, as is seen in Andean and Tibetan populations.[22,27]

The study had several limitations that must be considered when interpreting the results. The small sample size limits the generalizability of the findings. However, since this was a pilot study, the distribution of symptom severity allows us to power a future trial to examine the genetic influences on AMS severity, as genome-wide association studies such as Maclinnis et al., Ronen et al., and Yu et al. need larger cohorts to elucidate differences.[28–30] Additionally, the biological sex imbalance may have influenced the results, as gender differences in AMS susceptibility have been reported.[31–33] The stringent exclusion criteria, while necessary for safety, may result in a sample that is not representative of the general population who access high altitudes, particularly those at higher risk of AMS due to underlying health conditions or smoking. However, two-thirds of this healthy cohort experienced moderate to severe AMS symptoms in a relatively short exposure. Although a hypobaric chamber provides a controlled setting, it cannot perfectly replicate all aspects of true high-altitude exposure, such as cold temperatures and physical exertion associated with climbing, but it allows the isolation of the effects of hypobaria from these potentially confounding co-conditions found in nature.[17] The maximum exposure duration of 5 h may not be sufficient to observe the full spectrum of AMS symptoms, which can develop over a longer period at high altitudes.[9,27,34]

This study successfully validated the experimental protocol for inducing AMS symptoms in a controlled hypobaric environment. The protocol safely elicited mild symptoms of AMS in all subjects and moderate symptoms in 30% of subjects. The strong correlations between LLQ scores, HR, $S_pO_2$, and RR provide valuable insights into the physiological and symptomatic responses to hypoxia. These findings align with recent research on AMS and highlight the complex interactions between cardiovascular and respiratory systems in response to acute hypobaric stress. Future research should focus on further exploring these relationships and investigating potential interventions to mitigate the adverse effects of AMS, with an emphasis on understanding the underlying molecular and cellular mechanisms.[8,19]

## ACKNOWLEDGMENTS

*Financial Disclosure Statement:* The authors have no competing interests to declare.

*Authors and Affiliations:* Joshua T. Murphey, M.S., Hayden W. Hess, Ph.D., and Jacqueline Schwob, B.S., Exercise and Nutrition Sciences, and Brian A. Monaco, M.D., Brian M. Clemancy, D.O., M.B.A., and David Hostler, Ph.D., Exercise and Nutrition Sciences and the Department of Emergency Medicine, University at Buffalo, Buffalo, NY, United States.

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# Using Echocardiography to Study the Effects of Hypoxia and Altitude on Heart Function

María Carolina Cabrera Schulmeyer; Daniel Patiño-García; Manuel Alvear; Danilo Aravena; Claudio Montiglio

**INTRODUCTION:** Physiological assessment of military pilots and aircrew is performed annually. This includes a simulation of a flight at maximum altitude (25,000 ft/7620 m) with acute hypoxia, where they can recognize their symptoms. By detecting the symptoms of hypoxia, they will take corrective actions to avoid hypoxia-induced impairment. However, there is little evidence of what happens in the heart under these conditions. Cardiac function can be evaluated noninvasively with transthoracic echocardiography. The objective was to evaluate the effect of hypoxia and altitude during this simulation on systolic and diastolic cardiac function, pulmonary artery systolic pressure, and cardiac output with transthoracic echocardiography.

**METHODS:** A total of 72 volunteers (33.90 ± 8.49 yr, 73.6% male) were studied. A baseline transthoracic echocardiography assessment was performed, and systolic and diastolic function were assessed in both left and right ventricles. Cardiac output and pulmonary artery systolic pressure were estimated. Measurements were repeated at 25,000 ft, with and without oxygen, when saturation was below 80%.

**RESULTS:** A significant decrease was observed under hypoxic conditions when evaluating both right ventricular (RV) systole (RV 12.25 ± 3.1 to 8.9 ± 2.3 $cm \cdot s^{-1}$) and diastole (RV 6.8 ± 3.5 to 4.8 ± 2.8 $cm \cdot s^{-1}$ and RV 8.5 ± 5.2 to 5.71 ± 4.1 $cm \cdot s^{-1}$). However, cardiac output remained stable (7.87 ± 0.58 to 7.68 ± 0.49 $L \cdot m^{-2}$).

**DISCUSSION:** Echocardiography is a useful tool for evaluating left and right cardiac ventricular function. The right ventricle, both in its systolic and diastolic function, was the most affected during a simulated hypobaric and hypoxic flight.

**KEYWORDS:** hypoxia, hypobaric, echocardiography, systolic, diastolic, tissue Doppler, cardiac output, pulmonary artery pressure.

**Cabrera Schulmeyer MC, Patiño-García D, Alvear M, Aravena D, Montiglio C. *Using echocardiography to study the effects of hypoxia and altitude on heart function*. Aerosp Med Hum Perform. 2025; 96(11):964–968.**

The understanding of cardiac physiology in the military population is always of great interest, both in normal conditions and when the myocardium is subjected to extreme conditions such as high altitude and hypoxia. Hypoxia as encountered at high altitude has long been recognized as a cardiac stress due to the inverse relationship between altitude and barometric pressure. Individuals engaged in flight activities always have a latent risk of exposure to low oxygen concentrations in the event of an accident or system malfunction, which could lead to hypoxia and the risk of sudden in-flight incapacitation.

Transthoracic echocardiography is a noninvasive imaging test that provides high quality data. It gives information on the morphological and functional characteristics of the heart and an assessment of left and right ventricular systolic and diastolic function. This information allows accurate diagnoses and patient management decisions to be made. It is important to consider that the use of echocardiography also allows the evaluation of cardiac physiology both in normal and abnormal conditions.[1]

At the aerospace medicine center in the Clinical Hospital of the Chilean Air Force, medical assessment of all pilots and crews is performed. One of the tests is simulation of flight at maximum altitude (25,000 ft/7620 m) and during acute hypoxia

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This manuscript was received for review in December 2024. It was accepted for publication in July 2025.

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DOI: https://doi.org/10.3357/AMHP.6627.2025

so that the subjects can recognize the symptoms of hypoxia. Thus, training is required in the face of abnormal situations and to avoid flight emergencies or accidents due to low oxygen pressure in real life.

Hypobaric chambers are used to expose aircrews to a high-altitude environment in a controlled manner to allow them to become familiar with the signs and symptoms of hypoxia in a safe environment.[2–4]

The working hypothesis in this study was that cardiac function would be decreased during acute hypoxia in air crews at 25,000 ft. The objective of this study was to determine the extent of any hypoxia-induced changes in the systolic and diastolic function of both ventricles, cardiac output, and pulmonary artery systolic pressure.

## METHODS

This study was a one-group pre-test/post-test design. After ethical approval by the Scientific Ethics Committee of the Clinical Hospital of the Chilean Air Force (Approval No. HF 72,307), each volunteer signed an informed consent after being provided with detailed explanation of the study procedures. The study was performed to the standards set by the Declaration of Helsinki.

### Subjects

The inclusion criteria were healthy men and women between 18–60 yr of age who voluntarily signed an informed consent form. Exclusion criteria were as follows: subjects with hypertension, any type of arrhythmia, and poor echocardiographic windows. Subjects with evidence of barotitis were excluded. Subjects with abnormalities on their baseline echocardiogram, such as valvular heart disease or cardiomyopathy, were also excluded. Specifically, pulmonary systolic arterial pressure (PsAP) was measured and, if it was abnormal, the volunteer was excluded.

### Equipment

The Physiological Training Program is a process of instruction and simulation in conditions as close to real life as possible that mimic the complex conditions of flight. Physiological variables like heart rate and blood oxygen saturation ($S_pO_2$) were measured constantly.

To know what changes occur in the myocardium both at high altitude and in the face of acute hypoxia, its systolic-diastolic function, cardiac output, and pulmonary artery systolic pressure were evaluated using transthoracic echocardiography as a noninvasive monitoring system during training (Ultrasound SonoScape X5 Exp/X5/X5 Pro, Medical Corp., China 20,054,866). The echocardiography operator was highly qualified with postgraduate level specialist training. The operator also underwent aeromedical training at the Clinical Hospital of the Chilean Air Force in its aerospace medicine center (CEMAE) by attending theoretical courses and participating in the activities at altitude and during hypoxia as a student. The echocardiographer learned how to diagnose her own hypoxia symptoms and passed this training prior to starting the study. A volunteer, part of the research group, was evaluated with the same echocardiography equipment at the same altitude and conditions to which the volunteers were to be subjected to demonstrate that the images and the Doppler worked with the same quality and that the equipment would not suffer alterations or damage due to changes in altitude.

### Procedure

It seemed interesting to explore the systolic and diastolic function of both ventricles, as well as cardiac output and systolic pulmonary artery pressure. Tissue Doppler imaging is an accurate Doppler technique that is largely independent of the operator and preload. It is also quick to measure. Therefore, it was chosen and used for this purpose, positioning the transducer at the free edge of the mitral (left function) and tricuspid (right function) annulus where e prima (e′) and a prima (a′) waves were measured for evaluating diastolic function and s prima (s′) for systolic function. Measurement techniques do not correspond to the standards currently used in the assessment of left ventricular (LV) systolic function. Measuring LV ejection fraction using the Simpson Biplane method would have been too time consuming. The same criteria for the right ventricle (RV) were applied. RV ejection fraction has been demonstrated not to be a good parameter for assessing RV function. Tricuspid annular plane systolic excursion requires changing the system to M mode, which is again time consuming.

Diastolic function was measured using tissue Doppler assessing a′ and e′. The advantages are they are load independent and easy to capture for a video loop. The e′ and a′ waves reflect the pressure gradient at different times during diastole. The ratio between them was not calculated as we assumed that they would follow a trend during normoxia and hypoxia.

Finally, cardiac output was estimated by measuring the area of the outflow tract, the LV velocity integral, and multiplying it by the heart rate. Measurements were taken at three points in time, one at baseline, at 25,000 ft (7620 m) with oxygen, and finally at 25,000 ft without oxygen. For each measurement an echocardiography loop was recorded to do a revision and measurements after finishing the simulation and reinterpreting the data at a later stage. During the Hypoxic period, the time for doing echocardiography was extremely short, so we needed to do a proper selection of each variable. Tissue Doppler was selected because of its accuracy and low time consumption for obtaining the echocardiographic loop.

### Statistical Analysis

For the statistical analysis, jamovi (version 2.3)[5] was used to analyze the data. The assumption of normality was checked using the Kolmogorov-Smirnov test. The assumption of homogeneity was met given that there were no factors specified between subjects. A descriptive analysis was carried out where the categorical variables are presented as frequency tables, while summary measures were calculated [mean ± SD or median (interquartile range)] for quantitative variables.

**Table I.** Demographic and Clinical Characteristics of 72 Volunteers.

| VARIABLE | MEN ($N$ = 53, 73.6%) MEAN ± SD OR MEDIAN (IQR) | WOMEN ($N$ = 19, 26.4%) MEAN ± SD OR MEDIAN (IQR) | CALCULATED STATISTICS ($t$-TEST) | df | $P$-VALUE |
|---|---|---|---|---|---|
| Age | 34.3 ± 9.2 | 32.7 ± 6.0 | 0.67 | 70.0 | 0.505 |
| Weight | 79.6 ± 10.7 | 62.0 ± 5.7 | 0.83 | 70.0 | <0.001 |
| Height | 1.75 ± 0.1 | 1.63 ± 0.00 | 7.03 | 70.0 | <0.001 |
| BMI | 26.0 ± 2.9 | 23.2 ± 1.9 | 3.85 | 70.0 | <0.001 |
| HR (60–80 bpm)* | 78.0 (15.0) | 98.0 (19.0) | −4.93 | 70.0 | <0.001 |
| CO (4.0–6.5 $L \cdot min^{-1} \cdot m^{-2}$)* | 8.1 (0.9) | 7.5 (0.4) | 1.23 | 70.0 | 0.223 |
| PsAP (<30.0 mmHg)* | 3.0 (6.1) | 2.1 (2.6) | 1.02 | 70.0 | 0.312 |
| s′LV | 16.1 ± 3.5 | 16.5 ± 3.0 | −0.50 | 70.0 | 0.616 |
| e′LV (>10 $cm \cdot s^{-1}$)* | 11.9 ± 4.0 | 13.2 ± 3.8 | −1.21 | 70.0 | 0.231 |
| a′LV (1.9–8.8 $cm \cdot s^{-1}$)* | 10.0 (6.0) | 10.0 (5.0) | −1.29 | 70.0 | 0.201 |
| s′RV (>9.5 $cm \cdot s^{-1}$)* | 12.0 ± 3.3 | 12.2 ± 3.0 | −0.14 | 70.0 | 0.887 |
| a′RV (>10 $cm \cdot s^{-1}$)* | 6.0 (4.0) | 8.0 (3.0) | 0.07 | 70.0 | 0.945 |
| e′RV (1.9–5.5 $cm \cdot s^{-1}$)* | 8.0 (5.0) | 9.0 (6.0) | −1.59 | 70.0 | 0.116 |

Data are presented as the mean ± SD or median (IQR). IQR: interquartile range; HR: heart rate; CO: cardiac output; PsAP: pulmonary artery systolic pressure; s′LV: systole (s wave) of the left ventricle; e′LV: diastole (e wave) of the left ventricle; a′LV: diastole (a wave) of the left ventricle; s′RV: systole (s wave) of the right ventricle; e′RV: diastole (e wave) of the right ventricle; a′RV: diastole (a wave) of the right ventricle; df: degree of freedom.
*Reference values for cardiac function in a healthy general population.

The difference between the observed pre-test and post-test values were analyzed using the paired $t$-test for parametric variables or the paired Wilcoxon rank test for nonparametric variables. $P < 0.05$ was considered statistically significant.

## RESULTS

The characteristics of the subjects studied are shown in **Table I**. A tendency to have higher BMIs was observed in men.

The pre/post results of the echocardiographic variables studied in both the pre-test and the post-test in the aircrew members are shown in **Fig. 1**. The baseline echocardiogram of all volunteers was normal. The basal heart rate of female volunteers was significantly higher than that of males.

A significant increase in heart rate, as well as pulmonary artery systolic pressure, was evident ($P < 0.0001$) (**Fig. 2A, C**) without modifying cardiac output ($P = 0.9427$) (**Fig. 2B**). No significant changes were found in LV systole ($P = 0.5919$) (**Fig. 2D**). However, a decrease in LV diastole was observed when evaluating a′ LV ($P = 0.0006$) without modifying e′ LV ($P = 0.1419$) (**Fig. 2E, F**). Furthermore, a significant decrease was observed when evaluating both right ventricular systole (s′ RV) ($P < 0.0001$) and diastole (e′ RV and a′ RV) ($P < 0.0001$ and $P = 0.0006$, respectively) in response to acute hypobaric hypoxia at 25,000 ft (7620 m) (**Fig. 2G–I**).

## DISCUSSION

An impairment of systolic and diastolic function of the RV was detected in this study; however, cardiac output remained stable. When cardiac function was assessed, both heart rate and pulmonary artery systolic pressure increased in response to acute hypoxia, but no changes were observed in LV systolic function or cardiac output, which remained normal during all three echocardiographic assessment times. Acute hypoxia

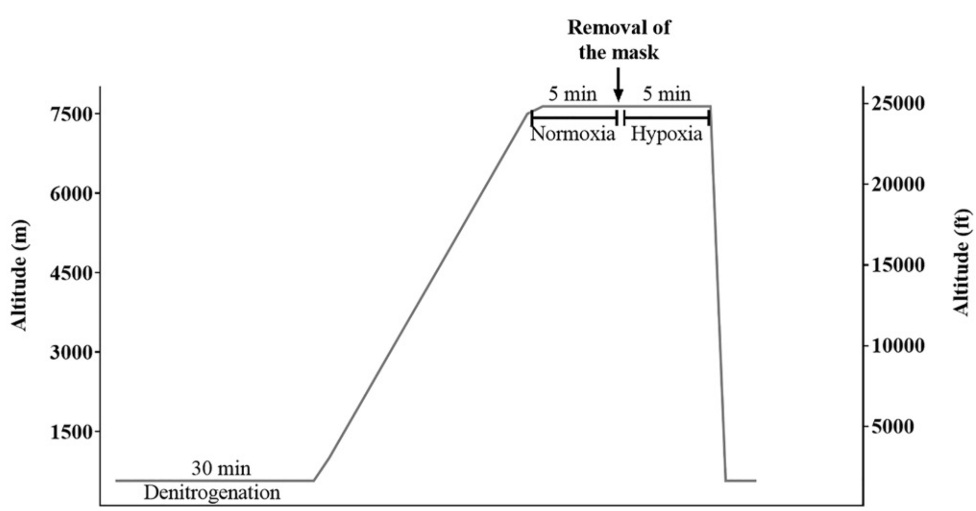


**Fig. 1.** Study protocol.

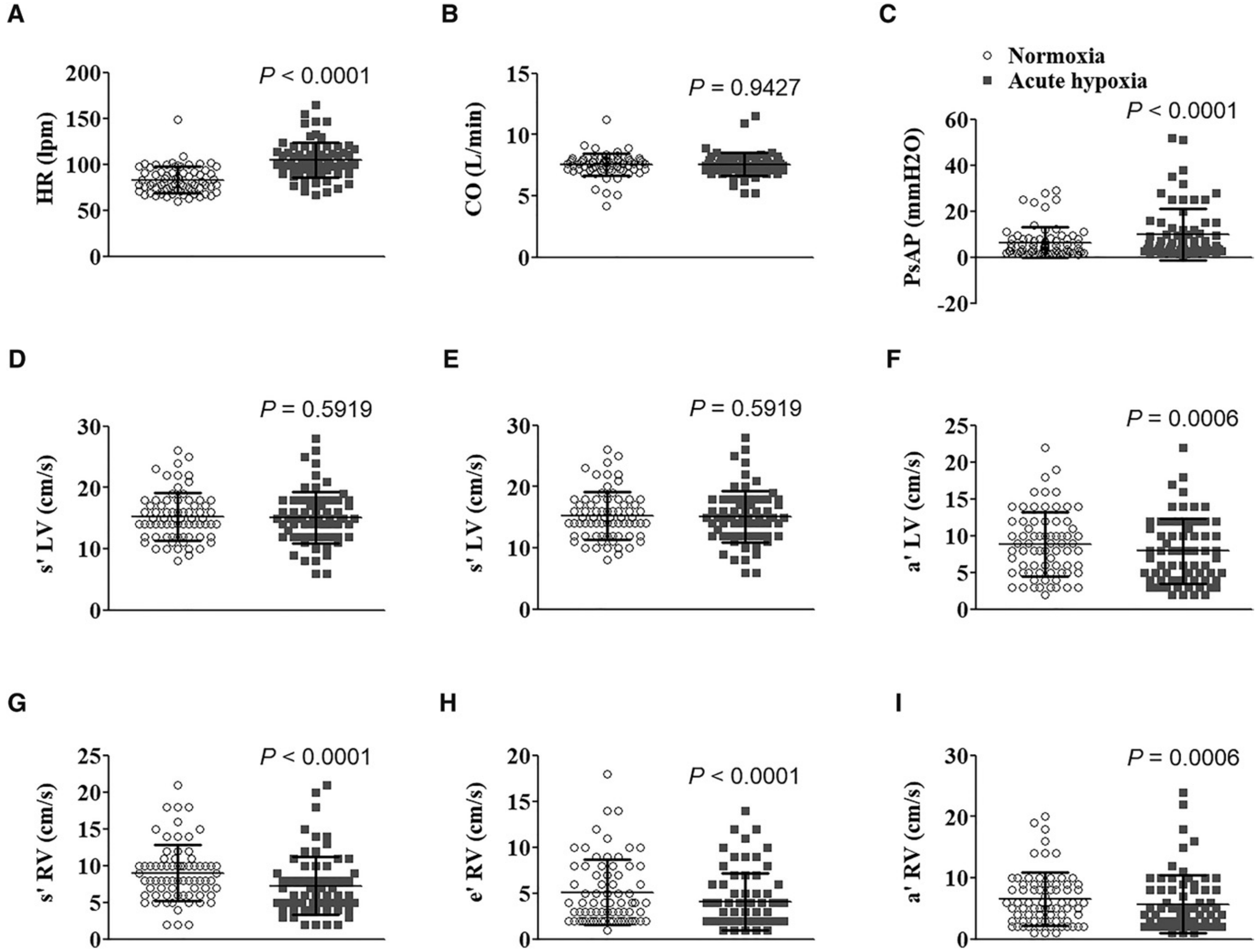


**Fig. 2.** Study results. HR: heart rate; CO: cardiac output; PsAP: pulmonary systolic artery pressure; s′ LV: s prima left ventricle; a′ LV: a prima left ventricle; s′ RV: s prima right ventricle; e′ RV: e prima right ventricle; a′ RV: a prima right ventricle.

statistically significantly decreased right ventricular function, with a decrease in s′, e′, and a′ values.

As the RV probably does not achieve good relaxation in acute hypoxia, this prevents the right atrium from generating a good filling of the RV, and thus it is not able to overcome the resistance of the pulmonary artery. This would generate retrograde volume accumulation and dilatation of both right chambers. Because of low pulmonary artery pressure, a secondary effect would be vasoconstriction of the pulmonary artery and not a primary phenomenon as has been proposed in the case of chronic hypoxia.

The basal heart rate was elevated in volunteers, which may have been due to anxiety about the simulated flight. In general, altitude studies only go up to 20,000 ft (6096 m) in the case of aviation and this study reached 25,000 ft (7620 m). Although previous studies have evaluated alterations in cardiac function in response to chronic hypoxia at altitude (more than 10 d of exposure), the present study investigated the effects of acute high altitude on biventricular function.

The physiological response of pulmonary circulation during chronic hypoxia is to increase pulmonary arteriolar resistance, resulting in elevated PsAP. In this study only a mild and nonsignificant elevation of PsAP was seen. Maufrais et al.[6] analyzed the left and right ventricles in 24 trekking volunteers, and they found higher volumes in the RV but in chronic hypoxia.

The case of mountaineers where myocardial function has been studied with echocardiography is different because they experience an acclimation process and preconditioning for hypoxia, and subjects have been trained and were not acutely subjected to hypoxia, but rather gradually and sequentially to what became a chronic hypoxia model and not the acute model that is being proposed here.[7–9] However, it is important to differentiate acute hypoxia from chronic hypoxia, since during the latter there are adaptive changes in pulmonary and cardiac physiology, as in the case of inhabitants of places located above 13,120 ft (4000 m) or in the case of trained mountaineers.[10,11]

Acute hypoxia at altitude results in impaired right ventricular diastolic function in aircrews. However, RV diastolic function is rarely quantified in experimental studies, generating a gap in knowledge that needs to be addressed to understand the physiological response of RV systolic and diastolic function in response to different stimuli and/or pathophysiological conditions such as hypoxia, so it was thought that there could be an acute deterioration of RV diastolic function and that this alteration could eventually be the cause of the deterioration in tissue oxygenation.[12,13]

It is proposed that echocardiography can play an important role during flight simulation, since it would allow the diagnosis and evaluation of some changes in the cardiac cavities and great vessels in their function in the face of acute hypoxia at high altitude.[14]

The decision about which parameters to study with transthoracic echocardiography was based on the existing literature, the data that would be of interest to evaluate, and the set time for doing the echocardiographic assessment. It will be interesting in the future to explore other variables of myocardial function such as strain (myocyte acceleration and deceleration), strain rate, and speckle tracking. For this purpose, an ultrasound machine with higher technology software is required.[15]

In the future, we plan to compare the men's group with the women's group separately. We believe that there are differences in women due to a greater tachycardia and greater impairment of RV function due to altitude and hypoxia. We are also already working on a protocol where the groups will be separated by sex to look for physiological end echocardiographic differences that probably exist. We will try to integrate more variables to measure such as the ejection fraction with the Simpson technique and E and A waves from transmitral inflow.

We must acknowledge several study limitations. All the subjects were studied in a sitting position, which is not the best position for doing an echo. The time for doing a focused echocardiography was extremely short according to the air force protocols for crews at 25,000 ft (7620 m). The study was carried out on volunteers who knew they would be subjected to special conditions, which probably caused them some anxiety and fear of failure, and that they would be observed and monitored during the entire simulation.

There are few studies that measure the values studied in this sample of aircrews. Thus, it is difficult to determine a precise baseline value for each parameter studied. The use of tissue Doppler can also be controversial and under-explored in the literature given its relative novelty, but obtaining the data is very fast, which was an attractive argument when planning the study. It was chosen due to its greater accuracy and greater operator independence, knowing that there is practically no literature to compare.

In conclusion, this study, carried out in 72 healthy volunteers at 25,000 ft (7620 m) and in hypoxia, shows that the most affected chamber is the RV and that there is a clear tendency to maintain cardiac output. The data suggest that acute hypoxia decreases right ventricular function in the subject studied, with impaired systolic and diastolic RV function as assessed by tissue Doppler. However, the overall trend was toward preservation of LV function.

## ACKNOWLEDGMENTS

*Financial Disclosure Statement:* The authors have no competing interests to declare.

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# Targeting Serotonin Pathways for Astronaut Safety and Performance

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**INTRODUCTION:** Exposure to microgravity has physiological consequences that can impair astronaut safety and performance. Many can be directly linked to fluctuations in plasma serotonin levels on Earth, like bone loss, nausea, and fatigue. Yet the metabolic activity of serotonin in space is not well known. This study measured plasma serotonin levels and bone density in the mouse hindlimb unloading (HU) model, an established Earth analog of microgravity-induced bone loss.

**METHODS:** The HU model has been used for decades to simulate axial unloading and fluidic shifts experienced in microgravity. Over a 30-d period, mice were suspended by their tails, with blood plasma collected at days 1, 15, and 30. Plasma was assessed for the presence of serotonin protein using an enzyme-linked immunosorbent assay and quantified. At day 30, microcomputed tomography of femur structural changes in HU mice was correlated with plasma serotonin increases.

**RESULTS:** Serotonin in plasma from HU mice showed increases in plasma serotonin at every timepoint compared to normally loaded mice. Between days 15–30, there was a 1.87-fold increase in serotonin levels found for normal mice while a significantly larger increase of 2.5-fold was found in the HU mice.

**DISCUSSION:** The HU mouse model showed plasma serotonin is elevated in HU mice, which corresponds to cortical and trabecular bone loss. These data suggest that elevated plasma serotonin may have a role in microgravity-induced bone loss. Specific serotonin receptor antagonists may be a safer countermeasure than currently used bisphosphonates to protect against astronaut bone loss.

**KEYWORDS:** microgravity, bone loss, serotonin, hind limb uploading.

**Casey TJ, Kubik AJ, Allen NG, Zilberman AH, Whitman BM, Hunt JC, Juran CM, French J, Blaber EA. *Targeting serotonin pathways for astronaut safety and performance*. Aerosp Med Hum Perform. 2025; 96(11):969–975.**

Spaceflight has heralded a new frontier for human exploration and scientific discovery, but has revealed significant challenges and inadequacies in the human capacity for life beyond Earth. For decades, clinical researchers and astronauts have documented the deleterious effects of long-term exposure to microgravity on various aspects of human physiology, notably the neurological and musculoskeletal systems. Many of these pathophysiological challenges are known to involve the neurohormone serotonin on Earth.[1,2] Surprisingly, little is known about the metabolic activity of serotonin in microgravity.

The amount of bone loss experienced by astronauts is about 1% of total bone mass per month,[3] which is roughly 10 times the level observed in postmenopausal women from decreased estrogen levels.[4] Historically, NASA has used various methods to combat bone loss, including intense, frequent exercise while in space, which has been inadequate for mitigation of bone loss.[5] Mineral/hormonal supplementation with vitamin D and estrogen, respectively, have also been tried, as have bisphosphonates, but these have had limited success.[6] Exogenous estrogen has been shown to promote a state of hypercoagulability that can lead to deep venous thromboses.[7] This is particularly problematic in space, where it has been found that microgravity

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This manuscript was received for review in April 2025. It was accepted for publication in July 2025.

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DOI: https://doi.org/10.3357/AMHP.6712.2025

independently leads to a state of hypercoagulability.[8] It is thought to be due to cephalad fluid shifts, causing altered blood flow dynamics and promoting stasis.[9] Additionally, bisphosphonates can cause nausea/vomiting, hypocalcemia, and mandibular osteonecrosis.[10]

The mechanism by which osteoporosis occurs on Earth is thought to be due in large part to the elevated plasma levels of serotonin or 5-hydroxytryptamine (5-HT). Specifically, gut-derived serotonin, as compared to brain-derived, is linked to bone metabolic imbalances. Primarily produced in the enterochromaffin cells of the intestines, 5-HT aids in digestion and bone regulation.[11,12] Gut derived 5-HT is then released into the plasma by food moving in the lumen of the gut during peristalsis, likely by the mechanosensitive Piezo 2 receptors, where it is reabsorbed by platelets in the intestinal veins.[13] Platelets then move 5-HT into bone, where it activates the 5-HT1b receptors on progenitor osteoblasts to inhibit osteoblast formation,[14] thereby serving as an important means to regulate bone formation. Osteoblasts serve to build bone from calcium ions in the blood, while osteoclasts break bone down and release calcium back into the bloodstream, which can induce hypercalcemia, kidney stones, and nausea.[15] Given that bone demineralization is a potential issue for astronaut safety and performance, particularly on long duration missions, the lack of information about 5-HT in microgravity is a critical knowledge gap that needs to be addressed.

Because hypercalcemia and inefficient calcium levels may lead to severe health concerns, the level of calcium in the blood is tightly regulated by several hormones. Parathyroid hormone is produced by the parathyroid glands in the neck and serves to raise calcium levels. Conversely, the hormone calcitonin, made by parafollicular C cells, depresses calcium levels. Physiologically, calcium plays a vital role in musculoskeletal function by controlling the regulatory proteins actin and myosin in sarcomeres. At the presynaptic junction in nerves, calcium ions permit neurotransmitter release, allowing the action potential to fire. High levels of extracellular calcium decrease neuromuscular membrane excitability and can lead to cardiac arrhythmias and nephrolithiasis.[16] Hypercalcemia may also contribute to the downregulation of somatosensory function following initial and prolonged exposure to microgravity. Clinically, hypercalcemia presents as nausea, emesis, lethargy, fatigue, neuromuscular incoordination, nephrolithiasis, abdominal pain, and psychiatric symptoms.[17] Many of these symptoms have been experienced by astronauts during or immediately upon return from spaceflight.[18]

Researchers have used the hindlimb unloading (HU) model in rodents to simulate microgravity on Earth. Originally developed in the 1980s, HU involves suspending the hind limbs in the air, mirroring the axial unloading and cephalad fluid shifts astronauts experience in space.[19] We were unable to find any prior literature directly studying the effects of 5-HT on microgravity-induced challenges such as bone loss, nor could we find any information on 5-HT levels in the HU model. In this paper, we focused on evaluating the possibility that simulated microgravity exposure could be linked to an elevation in plasma 5-HT concomitant with an increase in bone demineralization.

## METHODS

### Animals

All animal experiments were conducted with prior approval from the Rensselaer Polytechnic University Institutional Animal Care and Use Committee (IACUC # BLA-001-22). Using a custom HU cage modified for social housing, 16-wk-old B6/129SF2/J female mice ($N$ = 10 per condition) underwent HU and were maintained that way for 30 d. Corresponding normally loaded (NL) control mice were maintained in identical housing conditions to the HU mice, except for the tail suspension apparatus and associated hardware. All animals were acclimated to the test cages for 3 d prior to the attachment of orthopedic traction tape. Animals were fed standard chow (Prolab® IsoPro® RMH 3000, LabDiet, St. Louis, MO, United States) and continuously provided water with twice daily health checks to ensure consumption and drinking. If an animal was deemed unfit to continue the study, it was removed. A 12-h light/dark cycle and temperature between 23–25°C were maintained throughout the experiment. After 30 d, the animals were euthanized by carbon dioxide inhalation and secondary cervical dislocation. Immediately following euthanasia, blood and other tissues were collected and stabilized accordingly.

### Procedure

Peripheral blood was collected in EDTA coated tubes. The tubes were centrifuged at 2000 × g for 10 min. Plasma samples were collected and assessed for serotonin concentration using three biological replicates and three technical replicates at a 1:4 dilution by the Novus Serotonin colorimetric ELISA accompanied by concentration standard curve.

Microcomputed tomography (μCT) was used to image and analyze cortical bone morphometric parameters of the femoral shaft and trabecular parameters of the femoral head and distal femur. The right hindlimbs were dissected at the femoral head and fixed in 4% paraformaldehyde for 48 h. Following fixation, hindlimbs were washed twice with 1X phosphate buffered saline without calcium and magnesium additives (PBS-/-) and stored in a final volume of PBS with calcium and magnesium additives (PBS+/+) at 4°C until scanning.

Fully intact hindlimbs were wrapped in PBS-soaked gauze to prevent drying and mounted horizontally inside 0.6 mL microcentrifuge tubes for high resolution μCT scanning (Bruker SkyScan 1276, Kontich, Belgium) at the University of Massachusetts Amherst Animal Imaging core facility. The μCT was set to operate at a source voltage of 65 kV and a tube current of 166 μA using a 0.25 mm aluminum filter. All bones were scanned at a pixel resolution of 4.05 μm using an exposure time of 710 ms/frame with three averaging frames. Images were captured using a rotation step of 0.5° through a rotational angle of 180°.

Raw cross-sectional images were processed through the NRecon reconstruction software (SkyScan, version 1.7.4.2;

Bruker, Kontich, Belgium) to generate a stack of 2D cross-sectional slices using a modified Feldkamp algorithm with geometrical correction. Reconstruction was carried out with the following parameters: automatic misalignment compensation, a Gaussian smoothing kernel of 2, a beam hardening correction of 36%, a ring artifact correction of 6, and a dynamic contrast range of 0–0.10. The reconstructed images were visualized in 3D using the volume rendering software CTVox (Bruker, version 3.3.1) and each specimen was manually rotated in DataViewer (Bruker, version 1.5.6.2) to align the bone along the appropriate analysis axis. The CTAnalyser software, CTAn (Bruker, version 1.20.3.0), was then used to define the appropriate volume of interest (VOI). For analysis of the cortical femur, VOIs were defined as a 140-slice region (1 mm) around the midpoint of the femur. Distal femur VOIs were defined as a 140-slice trabecular region (1 mm) at the distal metaphysis, beginning 5 slices above the distal epiphyseal growth plate (distal physis) and extending proximally. Lastly, femoral head VOIs were defined as a 25-slice cancellous region (0.1 mm) around the midpoint between the start of the femoral head and the proximal epiphyseal growth plate. Standardized task lists were performed using BatchMan and cortical and trabecular parameters were computed. Cortical parameters measured were total cross-sectional area (T.Ar), cortical bone area (Ct.Ar), bone area fraction (B.Ar/T.Ar), cortical thickness (Ct.Th), endosteal perimeter (Es.Pm), and periosteal perimeter (P.Pm). Cancellous parameters reported include bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N), trabecular separation (Tb.Sp), structure model index (SMI), connectivity density (Conn.Dn), and trabecular pattern factor (Tb.Pf).

#### Statistical Analysis

All statistical analyses were performed using GraphPad Prism (version 9.5, GraphPad Software, Boston, MA). Two types of data were analyzed: serotonin concentration and microCT-derived bone metrics. For microCT-derived bone metrics, measurements were obtained from nine biological replicates per group, and for serotonin concentration, measurements for eight biological replicates were assessed. Data were assessed for normality and analyzed using unpaired, two-tailed *t*-tests to compare normally loaded (control) and hindlimb unloaded (experimental) groups. Results are reported as mean ± SD, and significance was defined as $P < 0.05$.

## RESULTS

Serotonin in plasma from NL and HU mice showed increases at every time point as shown in **Fig. 1**. Increased concentration in the NL mice is likely associated with changes in muscle activity due to the altered cage environment. Vivarium comparisons to controls from several previous studies have concluded the HU cage can induce biologically significant changes in the cardiac and musculoskeletal systems without suspension. Fig. 1 shows that on day 1 of HU, serotonin levels were already 14.2% higher in plasma concentration than NL controls and elevated at both day 14 and 30 (36.4% and 47.6%, respectively). Comparative

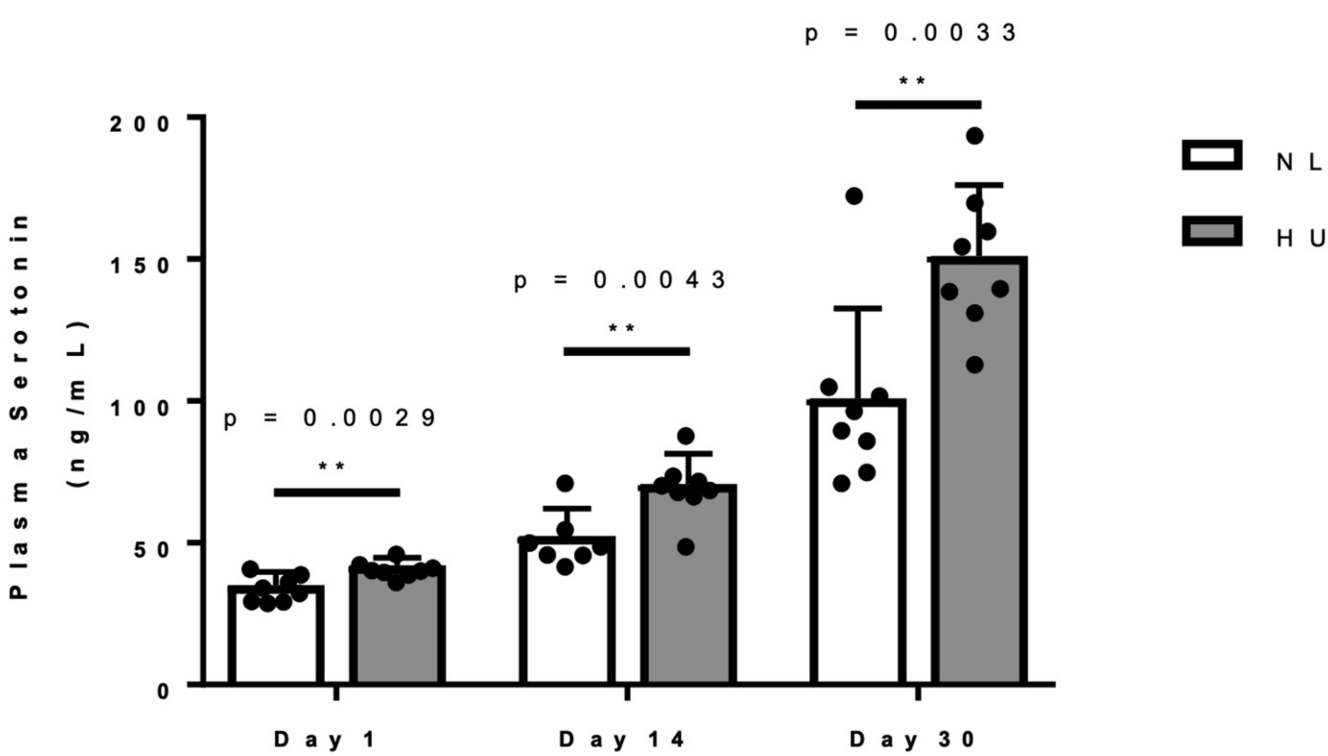


**Fig. 1.** Serotonin in plasma from normally loaded (NL) and hindlimb unloaded (HU) mice are shown. Bars plot the mean concentration in $ng \cdot ml^{-1}$ and SD error bars. Individual data points are coplotted to demonstrate data spread. Unpaired Student *t*-tests with significance of $P < 0.05$ were used.

analysis of serotonin between days 1 and 14 illustrates that serotonin concentration in HU mice increases at a faster rate (1.66×) than the NL animals (1.25×).

Between day 15 and 30 the NL animals continue to increase plasma serotonin concentration by 1.87× while the HU increased 2.5×. The average serotonin plasma concentration quadratic trajectory expression change, fit from day 1–30, show the HU mice have a trend toward continued increase while the NL trend shows a lesser growth curve and earlier plateau (**Fig. 2**).

Trabecular and cortical bone architectures were evaluated by μCT to investigate the potential correlation between elevated 5-HT levels and bone loss during unloading. In the trabecular bone of the distal femur, bone volume fraction (BV/TV%), trabecular number, and trabecular thickness all demonstrated a significant decrease in the HU animals [$t(48) = 2.3$, $P = 0.026$]. As shown in **Fig. 3**, BV/TV% was reduced to 1.119 ± 0.3398 [$t(18) = 3.292$, $P = 0.004$] and the trabecular number dropped to 0.3912 ± 0.129 [$t(18) = 3.235$, $P = 0.0046$]. Trabecular thickness decreased to 0.001538 ± 0.0006612 mm [$t(18) = 2.326$, $P = 0.0319$]. Interestingly, results also demonstrate an HU-associated decrease in Conn.Dn of 166 ± 68.35 [$t(18) = 2.428$, $P = 0.0259$], while Tb.Pf and SMI showed no significant changes between either experimental group. These data demonstrate that cancellous bone is the principally load-sensitive architecture of the femur and may be the structure most affected by plasma serotonin due to dysregulation of osteogenic metabolism. Within the cortical shaft of the femur, no significant sources of variation were detected within B.Ar/T.Ar, P.Pm, or Es.Pm between HU and NL animals. Ct.Th of the femur shaft showed a trend toward cortical thinning, although this did not reach statistical significance (**Fig. 4**).

## DISCUSSION

There is compelling data that gut serotonin has a powerful effect on bone metabolism. The source of serotonin to the bone is also known to be a regulatory factor, with brain-derived serotonin promoting osteoblast function and increased bone deposition,[20] while gut-derived serotonin reduces pre-osteoblast proliferation and encourages osteoclast specialization. Pre-osteoblast proliferation involves gut-derived serotonin receptors, including Hrt1b (5-hydroxytryptamine receptor in mice and humans), which can inhibit proliferation when bound. Elevated gut-derived serotonin has also been shown to prevent association of Forkhead box protein O1 with cAMP response element binding protein, resulting in suppressed osteoblast proliferation. Serotonin can additionally increase osteoclast differentiation by mechanisms which include amplifying receptor activator of nuclear factor kappa B ligand via activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) activation of NF-kB pathways.

Serotonin regulated bone metabolism would, therefore, favor osteoblast inhibition and encourage osteoclast resorption of bone matrix, resulting in the release of calcium into the blood stream. In fact, this process of calcium allocation is part of fetal development. For example, during pregnancy maternal bone calcium is known to spike to support fetal bone growth, and maternal recovery occurs after breast feeding is concluded.

Surprisingly, little is known about plasma serotonin activity in microgravity. Using an analog of microgravity-induced bone loss, the mouse HU model, we were able to show that increases in plasma serotonin correlates to femur architecture changes. These architectural changes demonstrate a weakening trabecular morphology in HU, but not NL mice despite rising

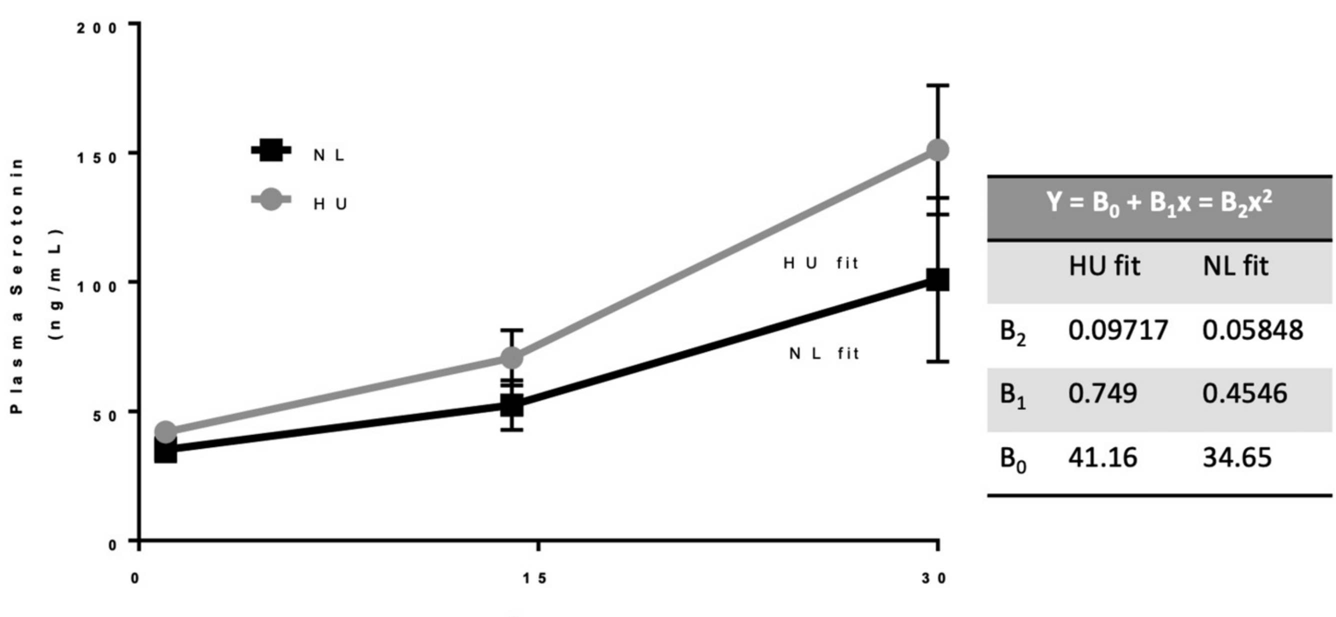


**Fig. 2.** Serotonin levels plotted as a trend showing serotonin levels in the NL animals. Parabolic growth cure metrics are reported in the insert table ($R^2 = 0.9077$ and 0.7052, respectively).

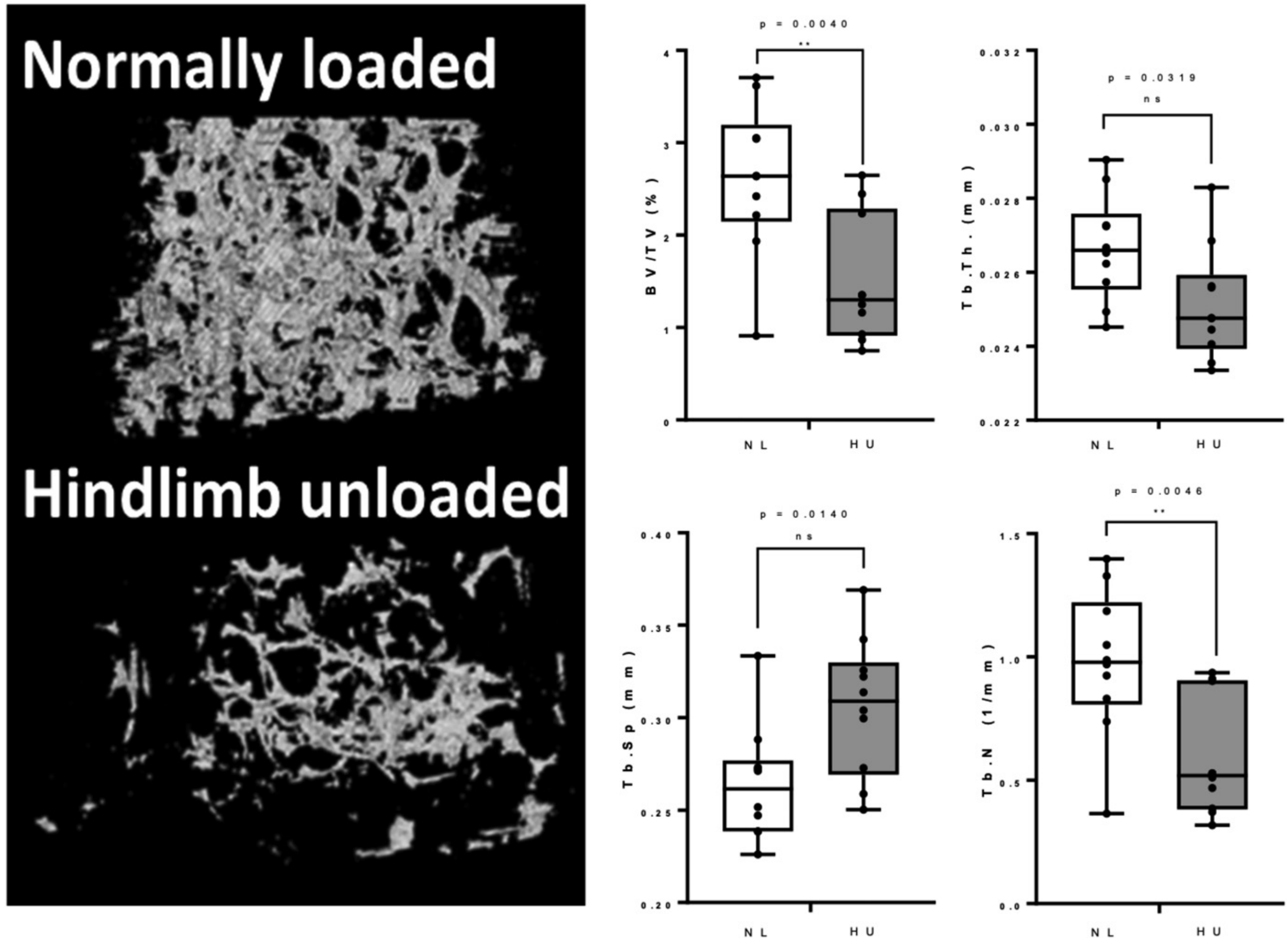


**Fig. 3.** The bone volume/trabecular volume, trabecular thickness, and trabecular number are shown in the HU animals compared to NL. Data shown are median levels ± the max/min levels and individual measurements (dots) to illustrate the data spread.

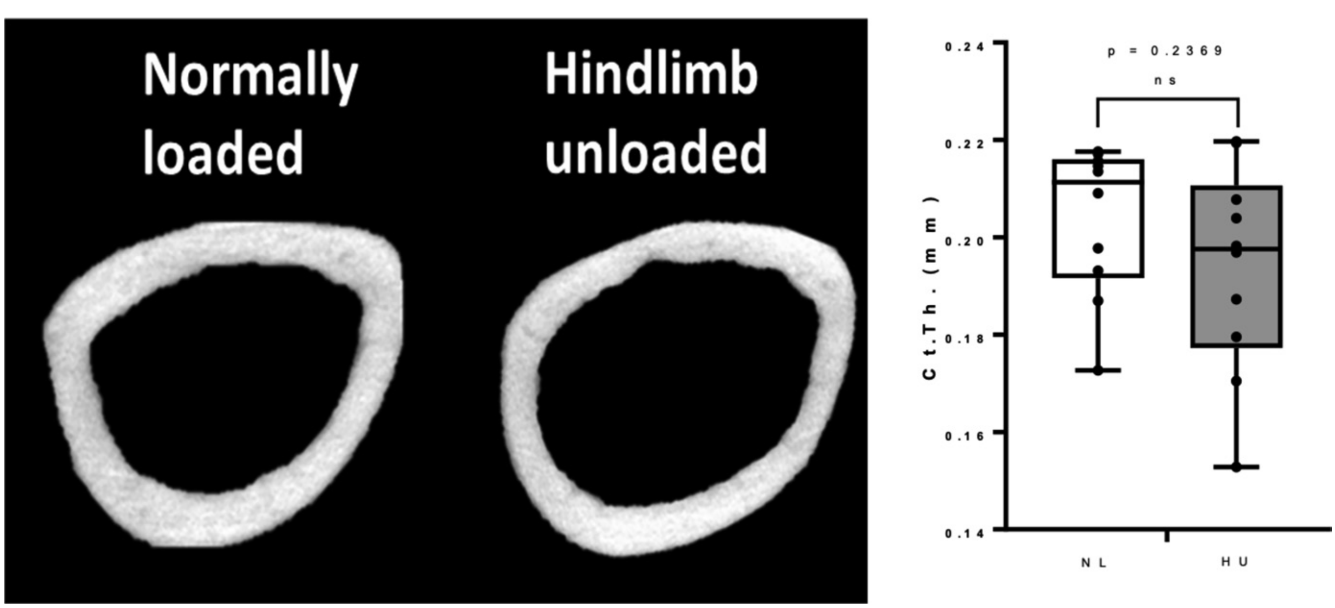


**Fig. 4.** Cortical bone levels in HU compared to NL are shown. Data shown are median levels ± the max/min levels and individual measurements (dots) to illustrate the data spread.

serotonin levels in NL animals. The HU cage may cause a stress response as the floor of the cage is a grate structure, which poses challenges to normal ambulation in the mice. Additional research comparing serotonin levels under conditions of HU and NL to a baseline would be beneficial to explore if unloading is the primary contributor to elevation of serotonin in space, as well as to define how severely unloading compounds serotonin increases due to other stresses. A longer 60-d duration of unloading would also resolve if the plasma serotonin concentration of the HU animals continues to outpace the NL condition. Other stress-inducers in space, including radiation exposure and circadian dysregulation, have established patterns of serotonin disruption that lead to muscle loss, depression, nausea, and vomiting. Combined with the physical and mental stresses of spaceflight, this may additively increase serotonin in plasma and result in significant bone mineral density loss.

An additional next step for investigating if serotonin and bone mineral density loss are causally linked would be to determine if selective 5-HT blockers are able to slow or diminish the bone loss observed in the HU model. A successful outcome would support use in human microgravity trials to determine the effectiveness of a targeted pharmaceutical intervention of the 5-HT related bone loss mechanisms.

New discoveries about gut-derived 5-HT are frequently made as more research is directed to understanding its role in calcium regulation. Much is yet to be learned and 5-HT blockers may have additional protective benefits to biological systems known as key risk factors for extended space travel. It is thus plausible that hypercalcemia in microgravity is the result of the effects of elevated 5-HT release on 5-HT3 and 5-HT1b receptors. We can postulate a mechanism for this. The immediate effects of entry into microgravity environments lead to central nervous system misinterpretation of sensory information, leading to space motion sickness that can potentially jeopardize astronaut performance.[21] Most astronauts overcome the initial nausea in a few days, but occasional bouts do return. If the emetic response could be blocked, it may be possible to reduce other issues relating to hypercalcemia, such as neurological and musculoskeletal dysfunction.[22] It is well known that the 5-HT3 blockers are effective mitigations for radiation-induced nausea and vomiting on Earth. It is also relevant to point out that bone loss is associated with 5-HT elevating compounds like fluoxetine and other SSRI drugs.[23] The 5-HT3 antagonists like ondansetron carry fewer and less severe side effects than bisphosphonates as a potential regulator of bone loss, or the other antiemetic agents promethazine and scopolamine that are currently in use by NASA. These effects point to the contention that 5-HT blockers may be useful in targeting specific 5-HT pathways to help mitigate serotonin mediated microgravity challenges to astronauts. The actions of serotonin are widespread and touch on many physiological functions, in addition to bone loss, that are important in spaceflight.

Another key player in calcium homeostasis is melatonin, an active metabolite of 5-HT that is also produced in the pineal gland and retina. Exogenous melatonin can cause fatigue and act as a chronobiotic to reset circadian rhythms.[24] Elevated levels of 5-HT from continued, periodic nausea could lead to elevated melatonin in cells that can produce melatonin from 5-HT. Moreover, it is possible that the persistent fatigue experienced by astronauts in space is a consequence of elevated melatonin from elevated 5-HT. Fatigue from motion sickness is called sopite syndrome and can also be due to elevated melatonin, which would require elevated serotonin. Calcium extraction by melatonin is evidenced by the calcification of the pineal gland seen in patients over the age of 40, conveniently serving as a biomarker for radiology. It follows that melatonin would be able to extract calcium from other tissue like bone and prior studies have shown elevated melatonin levels can cause bone loss.[25] Melatonin and 5-HT's roles extend beyond calcium regulation, encompassing glucose metabolism, circadian rhythms, and immune function, underscoring the importance of melatonin in maintaining overall physiological balance.

In this study, we used an accepted animal model of microgravity-induced bone loss to demonstrate the correlation between hyperserotonemia and corresponding loss of trabecular and cortical bone architecture representative of many bone loss conditions, including osteopenia or early osteoporosis. These results argue that targeting specific serotonin systems with pharmaceuticals could help mitigate bone loss and other pathophysiological challenges, including nausea, fatigue, and muscle dysfunction induced by microgravity, that threaten astronaut safety and effectiveness, particularly for long duration missions.

## ACKNOWLEDGMENTS

*Financial Disclosure Statement:* The authors have no competing interests to declare.

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# Promethazine Effects on Motion Sickness During Altered Gravity Induced by Parabolic Flight

Renee Abbott; Madison M. Weinrich; Nathan W. Keller; Traver J. Wright; Bonnie J. Dunbar; Pierre Denise; Deanna M. Kennedy; Ana Diaz-Artiles



**INTRODUCTION:** Astronauts commonly experience space motion sickness, which can impair astronaut performance and safety. Pharmaceuticals are frequently used to reduce space motion sickness symptoms but have not been extensively studied in partial gravity. In this research effort, we investigated the impact of oral promethazine on motion sickness during parabolic flight.

**METHODS:** We collected motion sickness scores from 12 subjects (6 women) during parabolic flight. Each subject participated in two flights—one 0-G flight and one partial G flight—experiencing 10 parabolas at 0 G, 0.25 G, 0.50 G, and 0.75 G. Half of the subjects, counterbalanced by gender, were given 25 mg of oral promethazine before flight and the other half were given a placebo. Motion sickness scores were collected preflight/postflight and during flight.

**RESULTS:** Pensacola Motion Sickness Questionnaire scores for the placebo group increased from 2.0 (1.55) preflight to 9.17 (5.42) postflight for the 0-G flight, but not for the partial G flight. Subjects in the placebo group reported motion sickness for 51.8% of parabolas compared to 12.6% of parabolas for the promethazine group. All placebo subjects reported some level of motion sickness during flight, while four of the six subjects who received promethazine reported no motion sickness at all.

**DISCUSSION:** Promethazine was effective at mitigating motion sickness symptoms in both 0 G and partial G. Microgravity conditions (0 G) may be more provocative than partial gravity, possibly due to the greater magnitude of sensory conflict. Further research should continue to investigate motion sickness as a function of hypogravity level.

**KEYWORDS:** partial gravity, microgravity, space motion sickness, human spaceflight.

**Abbott R, Weinrich MM, Keller NW, Wright TJ, Dunbar BJ, Denise P, Kennedy DM, Diaz-Artiles A. *Promethazine effects on motion sickness during altered gravity induced by parabolic flight*. Aerosp Med Hum Perform. 2025; 96(11):976–984.**

Space motion sickness (SMS) is a common neurovestibular condition experienced by approximately 50–80% of astronauts upon initial exposure to the space environment.[1] Symptoms, including nausea, malaise, increased salivation, cold sweats, stomach awareness, gastrointestinal motility changes, and vomiting, typically emerge within the first few hours of microgravity exposure and persist for 2–3 d.[2] However, in some cases, symptoms have been reported to last beyond a week.[3] Some individuals can adapt and perform tasks while experiencing SMS, but severe cases can be debilitating,[4] posing a significant concern if astronauts must complete critical tasks such as extravehicular activity, vehicle control, or landing maneuvers during or shortly after gravitational transitions.

Two primary theories have been proposed to explain SMS: the fluid shift theory and the sensory conflict theory. The fluid shift theory suggests that the redistribution of bodily fluids in microgravity alters vestibular system responses, though empirical evidence for this hypothesis remains limited.[5] Notably, Graybiel and Lackner[6] did not find increased susceptibility to provocative motion during head-down tilt, a

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This manuscript was received for review in March 2025. It was accepted for publication in August 2025.

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DOI: https://doi.org/10.3357/AMHP.6669.2025

commonly used analog for spaceflight-induced fluid shifts. The more widely accepted sensory conflict theory posits that SMS arises when sensory inputs, such as those from the otolith organs, semicircular canals, visual system, and proprioceptors, are incongruent and do not align with previously stored neural patterns due to the altered gravity environment.[7]

Pharmaceutical interventions are the primary treatment for SMS. Numerous antimotion sickness drugs have been evaluated in both flight and ground-based studies.[8] Among these, promethazine and scopolamine are among the most effective options. Promethazine has demonstrated efficacy in laboratory, clinical, and field studies, including parabolic flight.[9] Historically, intramuscular injections of promethazine have been the pharmaceutical countermeasure of choice to mitigate SMS.[10] However, promethazine can induce undesirable side effects such as drowsiness and impaired sensorimotor coordination and perception.[8,11]

Notably, motion sickness and promethazine have primarily been studied in terrestrial analogs and microgravity (0 g) environments during spaceflight or parabolic flight and less is known about promethazine's impact on motion sickness in partial gravity environments (i.e., greater than 0 g but less than 1 g). With NASA's current plans for future exploration missions, astronauts may have to complete mission critical tasks at 0.16 g on the Moon and 0.38 g on Mars. Thus, it is critical to characterize motion sickness in partial gravity as well as microgravity.

Spaceflight analogs are often used to investigate SMS and countermeasures as opportunities for spaceflight studies are scarce. Common ground-based analogs include rotary chair testing and centrifugation.[8] While these methods are accessible and frequently used, they lack the fundamental absence of a gravitational vector, a key characteristic distinguishing SMS from terrestrial motion sickness. Parabolic flight provides a more adequate analog by generating short periods of microgravity that more closely replicates the spaceflight environment.[12]

Given the impacts of motion sickness on spaceflight operations, this study aims to expand our understanding of the effects of promethazine—the primary SMS countermeasure currently used by astronauts—on motion sickness symptoms over a range of hypogravity levels (0 G, 0.25 G, 0.50 G, 0.75 G) during parabolic flight. In this exploratory analysis, we seek to characterize the time course of motion sickness development and its potential variation across different gravity levels. We hypothesize that motion sickness will increase as gravity level decreases, deviating further from Earth's 1 g and resulting in more sensory conflict. Since antimotion sickness medication is commonly used in parabolic flight investigations,[13] it represents a frequent confounding factor. Typically, subjects are given the choice of opting in/out of using medication before each flight, which introduces variability that can obscure experimental outcomes. Considering the scientific interest in understanding the effects of promethazine under partial gravity conditions, we chose to control for medication in the context of a bimanual coordination parabolic flight study by allowing only half of the subjects to take antimotion sickness medication.

## METHODS

### Subjects

Potential subjects were screened using the Motion Sickness Susceptibility Questionnaire (MSSQ)[14] to exclude individuals with extreme susceptibility to motion sickness (>95$^{th}$ percentile), as this could interfere with their ability to complete the experiment. The MSSQ evaluates how often an individual has experienced nausea or sickness during various modes of transportation or entertainment, such as cars, aircraft, and swings. Total MSSQ scores were converted to percentiles, where values greater than 50% indicate that an individual is more susceptible to motion sickness than half of the general population. Additionally, preference was also given to subjects with prior parabolic flight experience without antimotion sickness medication. Three subjects in the placebo group and four subjects in the promethazine group had prior parabolic flight experience without antimotion sickness medication.

A total of 12 subjects (6 women/6 men; 40.2 ± 8.7 yr old) in good general health participated in the study, and they were divided into a placebo group (3 women/3 men) and a promethazine group (3 women/3 men). All but two men (one in the placebo group and one in the promethazine group) had previous experience with parabolic flight. This study was approved by the NASA Johnson Space Center Institutional Review Board (STUDY00000329), the Texas A&M University Institutional Review Board (STUDY2024-0425), and the Comité de Protection des Personnes Nord Ouest II (Avis no. 22.04602.000171). All procedures complied with the Declaration of Helsinki. Written informed consent was obtained from all subjects before data collection.

### Procedure

This study was conducted during the 82$^{nd}$ European Space Agency parabolic flight (PFC82) campaign in June 2023 aboard the Airbus A-310 Zero-G aircraft. The campaign spanned 4 flight days, consisting of: 1) one microgravity (0 G) flight with 31 parabolas organized into 3 sets (the first set contained 11 parabolas, while the remaining 2 contained 10 each); 2) 3 partial gravity flights, each with 1 set of parabolas at 0.25 G, 0.50 G, and 0.75 G (see **Fig. 1**). Subjects were placed into one of three flight groups: flight group A (subjects A, D, G, J); flight group B (subjects C, F, H, I); and flight group C (subjects B, E, K, L). The sequence of partial gravity levels varied across the 3 d to minimize order effects. For example, flight group C experienced 0.75 G for parabolas 0–10, 0.25 G for parabolas 11–20, and 0.50 G for parabolas 21–30.

Each parabola consisted of an initial hypergravity phase at 1.8 G during the pull-up maneuver (∼20 s), followed by a microgravity or partial gravity phase, and concluded with another 1.8 G hypergravity phase during the pull-out maneuver (∼20 s). The duration of the reduced gravity phases varied depending on the gravitational condition: 0-G and 0.25-G phases lasted approximately 20 s, while the 0.50-G and 0.75-G phases lasted 40 s and 50 s, respectively. The average acceleration measured during the 0-G phases was 0.016 G.

Each subject experienced at least 10 parabolas at each gravity level (0 G, 0.25 G, 0.50 G, 0.75 G). Subjects took part in 2 flights: 1 microgravity flight with a single set of 10 parabolas (or 11, if they were part of the first set) and 1 partial gravity flight consisting of all 31 parabolas. Since there was only one microgravity flight, all subjects completed a single set of 0-G parabolas on that day, while the remaining two sets were allocated to other studies. Each flight lasted approximately 3 h.

Subjects were evenly divided into a control group and a promethazine group, with an equal number of men and women in each group. Medications were administered in a double-blind fashion by medical staff at approximately 07:00 on the morning of each flight. The control group received a placebo, while the promethazine group received 25 mg of oral promethazine, which has a peak plasma concentration between 2–3 h after administration.[15] The first set of parabolas began around 10:00, the second set at 11:00, and the third set at 12:00, approximately 3–5 h after promethazine/placebo administration.

During the microgravity or partial gravity phase and for 15 s into the subsequent hypergravity phase, subjects also performed bimanual coordination tasks while seated in modified commercial airline seats. Subjects were seated in the upright position with arms at their sides and elbows bent at a 90° angle. Through force sensors placed under their wrists, subjects controlled a cursor on a screen—the cursor moved horizontally when force was applied with the right limb and moved vertically when force was applied with the left limb. Subjects were instructed to perform different coordination patterns by tracing a template shape on the screen with their cursor. A head-mounted display was used to provide visual feedback and minimize external distractions. Researchers instructed subjects to keep their heads still throughout the experiment. Motion sickness assessments were conducted before and after each parabolic flight, as well as after each individual parabola.

**Materials**

To assess motion sickness before, during, and after each flight, three validated surveys were administered: the Motion Sickness Assessment Questionnaire (MSAQ),[16] the Pensacola Motion Sickness Questionnaire (MSQ),[17] and the Misery Scale (MISC).[18] Both the MSAQ and MSQ were completed under 1-g conditions before and after each subject's two flights. The MSAQ asked subjects to rate how accurately 16 statements (e.g., I feel sick to my stomach) described their experience on a scale from 1 (not at all) to 9 (severely). From these responses, four subscales—central, gastrointestinal, peripheral, and sopite-related—as well as an overall motion sickness score were calculated, expressed as the percentage of the total possible points. As the response scale is anchored at 1 instead of 0, the minimum possible MSAQ score is 11.11 (no motion sickness) and the maximum possible MSAQ score is 100 (severe motion sickness). Similarly, the MSQ contained 28 items measuring various motion sickness symptoms, such as nausea and headache, with subjects rating the severity of each symptom on a scale from 0 (none) to 3 (severe). A total MSQ (ranging from 0–84) was calculated as the sum of all responses. The change in

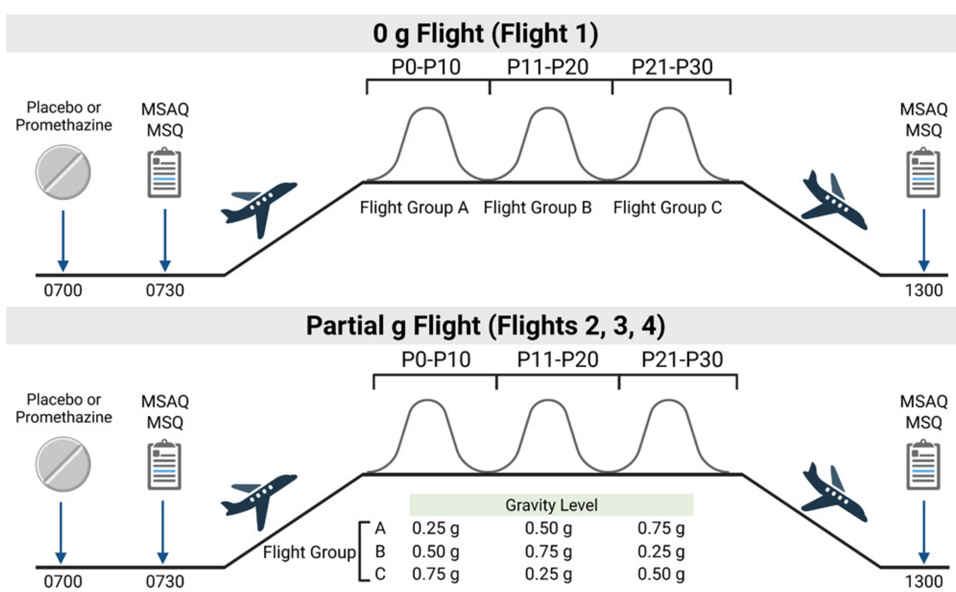


**Fig. 1.** Overview of experimental procedure. Each flight group contained four participants (two women/two men). Subjects received either a placebo or 25 mg of oral promethazine in the morning before each flight, counterbalanced by gender. They completed the Motion Sickness Assessment Questionnaire (MSAQ) and the Pensacola Motion Sickness Questionnaire (MSQ) preflight and postflight. All flight groups participated in the same 0-G flight, with flight group A (subjects A, D, G, J) reporting MIsery SCale (MISC) scores immediately after parabolas 0–10, flight group B (subjects C, F, H, I) for parabolas 11–20, and flight group C (subjects B, E, K, L) for parabolas 21–30. On the partial G flights, one flight group participated in the experiment during the 31 parabolas (e.g., 11 parabolas at 0.25 G, 10 parabolas at 0.50 G, and 10 parabolas at 0.75 G) and they also reported their MISC scores after each parabola. On the partial G flights, the gravity levels (0.25 G, 0.50 G, 0.75 G) were presented in a randomized order. Created in BioRender. Abbott, R. (2025); https://BioRender.com/b21p866.

motion sickness scores (MSAQ and MSQ) before and after the parabolic flights (i.e., Δ motion sickness score) was also calculated by subtracting preflight scores from postflight scores.

Finally, during the flight, subjects reported their motion sickness levels after each parabola using the MISC, a single-item scale ranging from 0 (no problem) to 10 (vomiting). The datasets analyzed for this study are publicly available and a repository can be found on GitHub (https://github.com/BHP-Lab/BimCoord/tree/main/Parabolic_Flight_Motion_Sickness/Data).

**Statistical Analysis**

Motion sickness data from the MSAQ and MSQ were summarized by group (placebo or promethazine), gravity condition (0 g or partial g), and time point (preflight or postflight). The Shapiro-Wilk test was used to determine normality. Paired *t*-tests (or paired Wilcoxon signed-rank tests for nonnormal data) were used to compare: 1) preflight vs. postflight scores for each group at each gravity condition; and 2) 0-G vs. partial G scores for each group at each time point. In addition, Mann-Whitney *U*-tests were conducted to compare: 1) placebo vs. promethazine groups at each time point (preflight and postflight) in each gravity condition; and 2) change in motion sickness ratings between the placebo and promethazine groups in each gravity condition. A Benjamini-Hochberg false discovery rate correction was implemented to adjust for multiple comparisons. However, due to the very low number of subjects included in the study, we report both the unadjusted and adjusted results. Effect sizes (Cohen's *d* for parametric tests and r for nonparametric tests) are also reported and statistical significance was set at $\alpha = 0.05$. Descriptive statistics in the text are reported as means (SD) and percentages, as appropriate. In the figures, central tendency is represented by the median (50$^{th}$ percentile) due to the mixed distribution of the data (both normal and

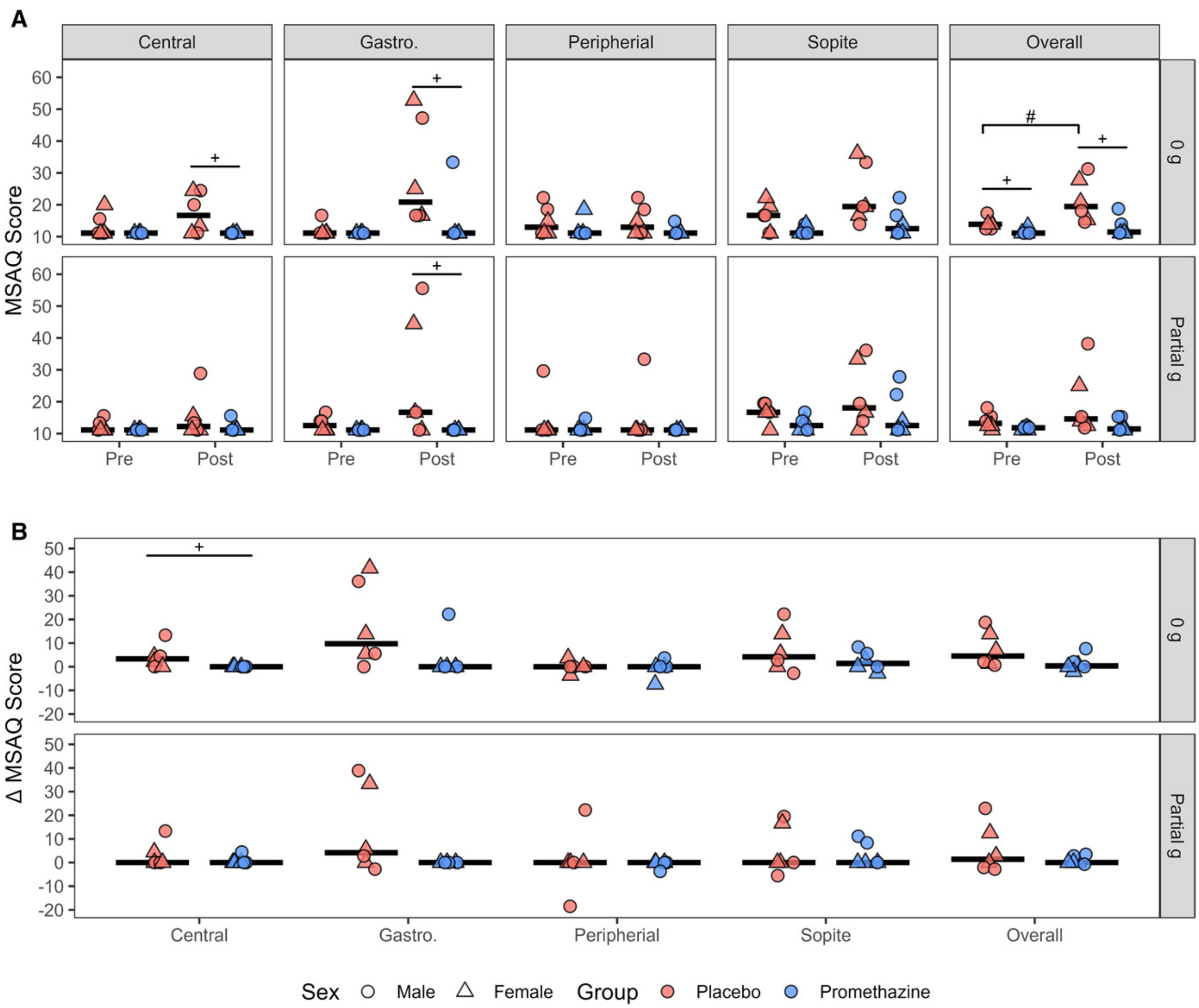


**Fig. 2.** MSAQ Scores for the placebo group (red) and promethazine group (blue) separated by flight day. A) Preflight and postflight MSAQ scores for the 0-G and partial G flights. B) Change in MSAQ scores calculated as postflight–preflight. Individual subjects are shown as points, and the median (50% quantile) is shown with a solid black line. $^{+}P \leq 0.05$ unadjusted, $^{\#}$approaching significance ($P = 0.063$ unadjusted).

nonnormal). All statistical analyses were conducted using R (version 4.4.2, The R Project).

## RESULTS

**Figure 2A** shows MSAQ individual subscales and overall scores preflight and postflight for the 0-G flight and partial G flight separated by group (placebo vs. promethazine). A paired *t*-test indicated that overall MSAQ scores for the placebo group tended to increase from 14.0 (1.78) at preflight to 21.3 (6.83) at postflight with a large effect size [$t(5) = 2.39$, $P = 0.063$, $p_{adj} = 0.49$, $d = 0.97$] on the 0-G flight day, but not on the partial G flight day [$t(5) = 1.34$, $P = 0.24$, $p_{adj} = 0.56$, $d = 0.55$]. MSAQ central, gastrointestinal, peripheral, and sopite subscales were not significantly different between preflight and postflight for either group for either gravity condition. Overall MSAQ scores and the central, gastrointestinal, peripheral, and sopite-related subscales were not significantly different between the two gravity conditions (0 G vs. partial G) for either group at either time point according to paired *t*-tests and Wilcoxon signed-rank tests.

A Mann-Whitney *U*-test indicated that the placebo group had significantly (unadjusted *P*-value) higher MSAQ scores than the promethazine group for the following measures: central 0 G postflight [$U = -2.19$, $P = 0.028$, $p_{adj} = 0.11$, $r = 0.66$], gastrointestinal 0 G postflight [$U = -2.26$, $P = 0.024$, $p_{adj} = 0.11$, $r = 0.68$], overall 0 G preflight [$U = -2.55$, $P = 0.011$, $p_{adj} = 0.11$, $r = 0.76$], overall 0 G postflight [$U = -2.34$, $P = 0.019$, $p_{adj} = 0.11$, $r = 0.69$], and gastrointestinal partial G postflight [$U = -2.19$, $P = 0.028$, $p_{adj} = 0.11$, $r = 0.66$].

Δ MSAQ scores, calculated as postflight–preflight, are shown in **Fig. 2B**. Positive values indicate that motion sickness was greater after the parabolic flight than before the parabolic flight. A Mann-Whitney *U*-test indicated that Δ MSAQ central was significantly greater (unadjusted *P*-value) for the placebo group than the promethazine group, but only for the 0-G condition [$U = -2.19$, $P = 0.028$, $p_{adj} = 0.28$, $r = 0.66$]. Similarly, Δ MSAQ gastrointestinal was generally higher for the placebo group than the promethazine group for the 0-G condition [$U = -1.88$, $P = 0.059$, $p_{adj} = 0.29$, $r = 0.57$].

MSQ scores generally tended to increase from preflight to postflight across both groups (see **Fig. 3A**). A paired *t*-test test indicated that the MSQ scores significantly increased from 2.0 (1.55) preflight to 9.17 (5.42) postflight for the placebo group in the 0-G condition [$t(5)=3.19$, $P = 0.024$, $p_{adj} = 0.048$, $d = 1.30$]. MSQ scores also significantly increased from 0.67 (0.82) preflight to 4.33 (2.25) postflight for the promethazine group in the partial G condition [$t(5)=5.50$, $P = 0.002$, $p_{adj} = 0.01$, $d = 2.24$]. MSQ scores preflight or postflight were not significantly different between the 0-G and partial G flights for the placebo or promethazine group according to a paired *t*-test. According to a Mann-Whitney *U*-test, MSQ scores in the 0-G condition postflight were significantly higher (unadjusted *P*-value) for the placebo group than the promethazine group [$U = -2.18$, $P = 0.029$, $p_{adj} = 0.12$, $r = 0.65$].

Δ MSQ scores, calculated as postflight–preflight, are shown in **Fig. 3B**. There was no significant difference in Δ MSQ score between the placebo and promethazine group for the 0-G [$U = -1.54$, $P = 0.124$, $p_{adj} = 0.25$, $r = 0.47$] or partial G [$U = -0.57$, $P = 0.572$, $p_{adj} = 0.572$, $r = 0.18$] conditions.

MISC scores for each subject over the course of the 0-G flight and the partial G flight are shown in **Fig. 4**. Note that during the 0-G flight, subjects only reported MISC scores for 1 set of 10 (or 11, if subjects participated in the first set) parabolas. The median MISC score across all gravity levels was 1 (range = 0–5) for the placebo group and 0 (range = 0–4) for the promethazine group. Median MISC scores for the placebo group at each gravity level were 1 (range = 0–5) at 0 g, 0 (range = 0–2) at 0.25 G and 0.50 G, and 1 (range = 0–4) at 0.75 g. Median MISC scores for the promethazine group at each gravity level were 0 (range = 0–4) at 0 G, 0 (range = 0–1) at 0.25 G, 0 (range = 0) at 0.50 G, and 0 (range = 0–1) for 0.75 G.

Motion sickness was reported (i.e., MISC score ≥1) at least once by all subjects in the placebo group. In contrast, four of six

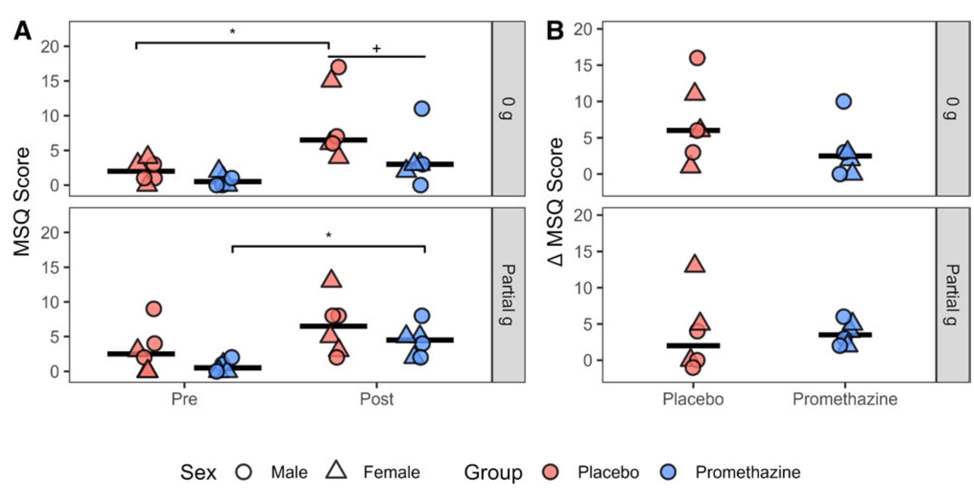


**Fig. 3.** MSQ Scores for the placebo group (red) and promethazine group (blue) separated by flight day. A) Preflight and postflight MSAQ scores for the 0 G and partial G flights. B) Change in MSQ scores calculated as postflight–preflight. Individual subjects are shown as points, and the median (50% quantile) is shown with a solid black line. *$P \leq 0.05$; +$P \leq 0.05$ unadjusted.

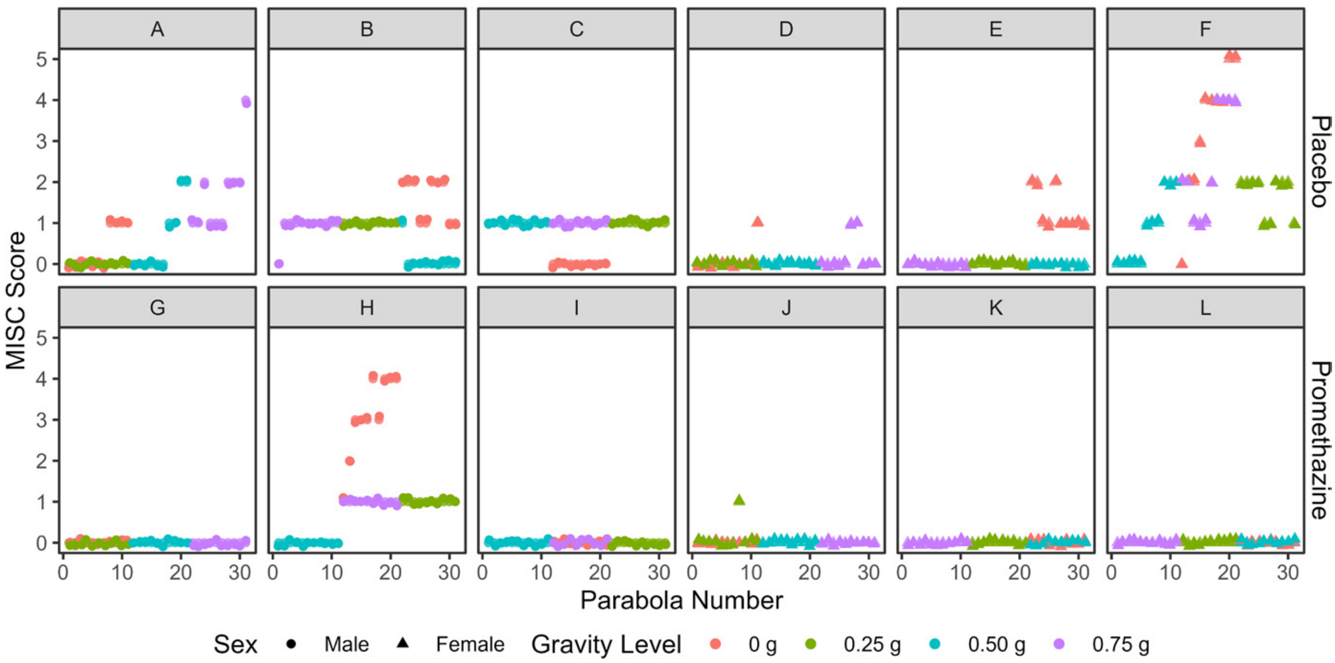


**Fig. 4.** MISC scores, ranging from 0 (no problem) to 10 (vomiting), reported by each subject (A–L) after each parabola. The placebo group is displayed in the top row and the promethazine group is displayed in the bottom row. Women (D, E, F, J, K, and L) are shown as triangles. Colors correspond to the gravity level of the parabola completed immediately before reporting MISC score.

subjects in the promethazine group experienced no motion sickness symptoms at all during flight, and subject J in the promethazine group only reported after one single parabola. Four subjects in the placebo group and one in the promethazine group (subject H) reported MISC scores greater than 1 at some point during their flights. None of the 12 subjects reported any nausea during flight (i.e., MISC score ≥6). The highest MISC score was 5, indicating severe symptoms except nausea, reported by subject F (from the placebo group) during the 0-G flight. On average, placebo group subjects reported motion sickness (MISC score ≥1) in 51.8% of parabolas, compared to only 12.6% of parabolas in the promethazine group.

MISC scores remained at or below 1 during the first 10 parabolas for all subjects except subject *F* (from the placebo group), who also reported the most severe motion sickness symptoms overall. The highest MISC scores for each subject occurred in the second half of the flight (parabolas 16–31). This suggests that motion sickness severity often increased over the duration of the flight, likely because of the prolonged exposure to a provocative environment. On average, motion sickness was reported with slightly higher frequency during the 0-G flight (55.9% of parabolas in the placebo group and 16.7% in the promethazine group) than during the partial G flight (50.5% of parabolas in the placebo group and 11.3% in the promethazine group). MSSQ percentiles were normally distributed for each group and the average MSSQ percentile for the placebo group (5.5 ± 5.2) was not significantly different than the promethazine group (21.8 ± 21.7) [independent samples *t*-test with unequal variance; $t(5.5) = -1.79$, $P = 0.13$].

## DISCUSSION

Motion sickness scores generally increased from preflight to postflight for both groups, with more pronounced changes observed in the placebo group. Most subjects who received promethazine were remarkedly absent of any motion sickness symptoms preflight, during flight, or postflight. While results were inconsistent regarding changes in motion sickness between the two groups, postflight motion sickness scores were higher in the placebo group compared to the promethazine group across several measures. Even though this study has several limitations, further discussed later in this section, and conclusions should be drawn with caution, the data presented offer valuable insights due to the scarcity of knowledge regarding motion sickness in partial gravity.

The MSAQ provides a multidimensional assessment of motion sickness, providing a more complete representation of the subjects' state. The gastrointestinal subscale, encompassing symptoms like queasiness and nausea, was the most affected, with two placebo subjects and one promethazine subject reporting moderate to severe gastrointestinal symptoms postflight. Central subscale scores, which include symptoms such as feeling disoriented, dizzy, and lightheaded, also increased postflight for the placebo group and less so for the promethazine group. Thus, promethazine appears to alleviate motion sickness symptoms, particularly in the gastrointestinal and central subscales, likely due to its role as a central nervous system depressant. It antagonizes histamine and acetylcholine—two of the three neurotransmitters (histamine, acetylcholine, and noradrenaline) associated with motion sickness. Additionally, promethazine exhibits antidopaminergic properties.[15] Its antimotion sickness effects are believed to result from the blockage of central acetylcholine/muscarinic receptors, while its antiemetic properties may stem from dopaminergic receptor inhibition in the chemoreceptor trigger zone of the medulla, a key neural structure involved in motion sickness.[19] Furthermore, promethazine's H1 receptor blockade contributes to reducing symptoms such as nausea and vomiting.[15] Plasma concentrations of promethazine were not measured in this study, but given the approximately 12–15 h elimination half-life of oral promethazine,[15] future work incorporating pharmacokinetic data could clarify whether temporal variations in drug levels influence motion sickness symptoms across the duration of the flight.

The MSAQ also includes sopite-related symptoms, which are often overlooked yet can persist for hours or days even in the absence of nausea. Sopite syndrome, first described by Graybiel and Knepton, is characterized by yawning, drowsiness, lack of motivation, and social withdrawal.[20] Drowsiness, a common symptom of motion sickness, likely contributed to the relatively high incidence of sopite-related symptoms in both groups. Additionally, drowsiness is a known side effect of promethazine and it is used as a sedative at higher doses. Due to its sedating properties, promethazine is often combined with stimulants to counteract its effects.[10] However, in the present study, we did not find any significant difference in sopite-related symptoms between the placebo and promethazine groups. Furthermore, there was no difference in preflight sopite symptoms between the 0-G and partial G flight; thus, sopite symptoms did not appear to carry over from prior flights in this instance.

While direct comparisons between the 0-G and partial G flight conditions did not yield significant differences in motion sickness scores, significant differences between the placebo and promethazine groups as well as between preflight and postflight were more frequent in the 0-G flight. This suggests that microgravity may be more provocative than partial gravity. According to Oman's model, susceptibility to motion sickness is influenced by the amount of sensory conflict, among other factors.[7] The greater magnitude of acceleration changes in the 0-G flight compared to the partial G flight likely led to greater sensory conflict and, consequently, increased motion sickness. The variation in exposure to each hypogravity level is another factor to consider. Hypogravity exposure during each parabola for 0.50 G and 0.75 G was approximately double the duration for 0 G and 0.25 G. This extended exposure to a provocative environment with conflicting sensory stimuli may have intensified motion sickness at higher hypogravity levels. Furthermore, the cumulative exposure to each gravity level differed: ~3.3 min for 0.25 G, ~6.6 min for 0.50 G, ~8.3 min for 0.75 G, and ~10.3 min of cumulative exposure to 0 G. The extended cumulative exposure to 0 G may have contributed to the increased incidence of motion sickness after the 0-G flight. However, the cumulative exposure to partial gravity conditions as a whole (~18.3 min) was almost double the exposure time on the 0-G flight. Despite this, the cumulative exposure to 0 G appears to be more provocative than the cumulative exposure to the partial gravity levels investigated. These results highlight the need to examine whether the larger gravitational transition from 0 g to Martian gravity may induce greater motion sickness compared to the transition from 0 g to lunar gravity.

Parabolic flight is an invaluable tool for hypogravity research. However, no analog can fully replicate spaceflight conditions. The hypergravity periods preceding and following the hypogravity phases are an inherent constraint and confounding factor of parabolic flight. Previous research has shown that head movements during the hypergravity periods of parabolic flight alone can induce motion sickness, with sensory conflict induced by an excess in otolith signals.[21] To mitigate this, we instructed participants to remain seated and minimize head movements. However, increased motion-sickness severity as the flight progressed could have been driven by the provocative stimulus from both the hypogravity and hypergravity periods as well as the transition between hyper- and hypogravity, resulting in greater motion sickness overall.

Subjects had significantly lower MSSQ percentiles (mean ± SD = 13.6 ± 17.3) than the general population (mean = 50). All subjects scored below the 58th percentile, with 9 out of 12 subjects scoring at or below the 20th percentile. Similarly, Golding found that parabolic flight subjects had lower-than-average motion sickness susceptibility scores (MSSQ percentile = 27.4 ± 28.0), likely because individuals prone to motion sickness avoid highly provocative environments such as parabolic flight.[13] Our subjects had even lower MSSQ scores than those in Golding's study, likely due to our recruitment criteria: we specifically selected individuals with prior parabolic flight experience, particularly without the use of antimotion sickness medication, ensuring they could complete the bimanual coordination task even without treatment. Additionally, motion sickness susceptibility was not significantly different between the placebo and promethazine groups, simplifying motion sickness comparisons between the two groups.

It should be noted that there is no significant correlation between those who experience motion sickness in parabolic flight vs. orbital flight.[22] However, parabolic flight induces periods of 0 G and partial gravity in a way that other spaceflight analogs cannot. Changes in torsional eye position, likely due to a loss of compensation for otolith asymmetry in altered gravity environments, have been found during both parabolic flight[23] and orbital flight.[24] Furthermore, torsional offsets in parabolic flight have been proposed as a means to predict SMS[25] and warrants further investigation. Thus, while generalizations from parabolic flight to orbital flight are limited, this similarity may provide a unique link between motion sickness in parabolic flight and orbital flight that has not been shown in other analogs.

There are several limitations to this study. A potential confounding factor is that subjects took part in an additional experiment during one set of parabolas on the 0-G flight day. Thus, we did not have any control over the subjects' activities during those parabolas. When subjects were not participating in an experiment on the 0-G flight, they were instructed to stay seated and avoid any provocative movements that could elicit motion sickness. The sequence of the additional task and the task itself could have influenced in-flight and postflight motion sickness. While we cannot completely disentangle sequence effects, all subjects remained onboard for the entire 0-G flight and the gravitational profile and cumulative effects were the same for all subjects. Additionally, we could not measure motion sickness throughout the entire 0-G flight, limiting our ability to make direct comparisons of the evolution of motion sickness in flight between the partial G and 0-G days. Additionally, promethazine has been shown to exhibit a strong placebo effect,[26] which may confound motion sickness assessments. It is also important to note that the route of administration in this study differs from spaceflight operations (i.e., oral vs. intramuscular). Oral promethazine has lower bioavailability (~25%)[15] due to hepatic first-pass metabolism. While this difference may affect the magnitude of physiological responses, the present findings still provide valuable insights into the drug's effects and support its continued evaluation as a countermeasure. Another limitation of this study is the small sample size, a common constraint in parabolic flight experiments due to limited space on board. However, this reduces the statistical power and generalizability of our results. Similarly, the small sample size prevented statistical analysis of sex differences. The information is still reported, as it may prove useful for future investigations. The small sample size also prevented the use of parametric statistical methods, introducing the limitations associated with nonparametric approaches. Thus, we reported both unadjusted and adjusted statistical results. We acknowledge that the risk of false positives increases with multiple comparisons and adjusted analyses did not retain statistical significance. Due to the small sample size, these results are exploratory and replication with sufficiently powered studies are needed to validate these findings. Nevertheless, we believe that these exploratory data constitute a unique normative dataset that can contribute to future research efforts.

This study enhances our understanding of motion sickness and its modulation by the antimotion sickness drug promethazine across different hypogravity levels in parabolic flight. Our results suggest that motion sickness tends to increase as hypogravity level decreases, deviating further from the 1 g experienced on Earth. However, promethazine effectively mitigated most motion sickness symptoms across all gravity conditions. While this study has limitations that inhibit its generalizability, including a small sample size and the use of parabolic flight rather than orbital flight, it serves as a foundation for future investigations. Further studies are needed to corroborate these findings and explore the relationship between promethazine, motion sickness, and sensorimotor performance. Ultimately, this research effort can contribute to the development of guidelines and countermeasures for SMS in future space exploration missions.

## ACKNOWLEDGMENTS

This work was supported by the NASA Human Research Program, Grant Number: 80NSSC20K1499 and by a NASA Space Technology Graduate Research Opportunity (grant number 80NSSC21K1263). The authors would like to acknowledge NASA, Novespace, and the European Space Agency for their invaluable support in making this experiment possible. Special thanks go to Alexandra Jaquemet (Novespace) for her technical guidance during the design and execution of the experiment and to Neil Melville for his support and expertise throughout all phases of the project. We also extend our gratitude to Herve Normand and Marion Hay for their support with the IRB procedures. Finally, we thank all the subjects and collaborators who contributed to the success of this study.

*Financial Disclosure Statement:* The authors have no competing interests to declare.

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# Optimizing Muscle Activation in Cadets Using Electromyography Biofeedback During Anti-G Training

Renato Massaferri; Adriano Percival Calderaro Calvo; Andre Brand Bezerra Coutinho; Thiago Teixeira Guimarães; Paulo Farinatti



**INTRODUCTION:** Effective execution of the anti-G straining maneuver (AGSM) is essential for pilots to maintain consciousness under high gravitational forces ($+G_z$). This study evaluated whether electromyographic (EMG) biofeedback enhances muscle activation patterns during AGSM training in novice cadets.

**METHODS:** There were 58 Brazilian Air Force cadets (age: 25 ± 1 yr) who performed two AGSM sessions involving sustained submaximal isometric contractions of the gastrocnemius, vastus medialis, and rectus abdominis muscles, synchronized with rhythmic breathing every 3 s. Subjects completed trials under counterbalanced visual EMG feedback conditions (real-time visualization vs. no visualization) and were randomly assigned to verbal feedback conditions (instructor guidance vs. no guidance). EMG signals were recorded at 1500 Hz and normalized to each subject's peak amplitude during the AGSM trials.

**RESULTS:** Muscle-specific responses to feedback were observed. Verbal feedback enhanced gastrocnemius activation but reduced vastus medialis activation. Combined visual and verbal feedback produced the highest activation in the rectus abdominis. Visual feedback alone had minimal effect across all muscles. Despite submaximal instructions, brief peak activations were sufficient for normalization.

**DISCUSSION:** EMG biofeedback facilitated motor learning of AGSM by selectively improving activation in targeted muscles. However, effects varied by muscle group, suggesting the need for tailored instructional strategies. Although task-based normalization offers ecological validity, it may limit comparisons with MVC-based protocols. Incorporating EMG biofeedback may enhance AGSM training, particularly in novice populations or settings without centrifuge access.

**KEYWORDS:** electromyography, biofeedback training, high-G environments, neuromuscular control, anti-G straining maneuver.

**Massaferri R, Calvo APC, Coutinho ABB, Guimarães TT, Farinatti P. *Optimizing muscle activation in cadets using electromyography biofeedback during anti-G training*. Aerosp Med Hum Perform. 2025; 96(11):985–992.**

Effective training in the anti-G straining maneuver (AGSM) is essential for pilots and crew operating high-performance aircraft. This training enables them to withstand increased gravitational forces ($+G_z$), reducing the risk of $+G_z$-induced loss of consciousness (G-LOC)—a condition that occurs when excessive acceleration prevents sufficient oxygen from reaching brain tissues. Under high-G conditions, blood is rapidly displaced toward the lower extremities due to the hydrostatic force of acceleration, resulting in a substantial drop in cerebral perfusion pressure. This hemodynamic shift compromises oxygen delivery to the brain despite adequate systemic oxygenation. Simultaneously, the heart struggles to maintain sufficient blood flow against the gravitational gradient, further reducing systemic arterial pressure. If not counteracted, this cascade can lead to visual disturbances and, ultimately, loss of consciousness.[1,2]

The AGSM is a physiological countermeasure designed to prevent this hemodynamic collapse. It combines sustained isometric contractions of the lower body—primarily the calf, thigh, and abdominal muscles—with cyclical forced exhalations against a closed glottis (typically every 3 s). The muscle strain increases peripheral vascular resistance, reducing venous

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This manuscript was received for review in May 2025. It was accepted for publication in August 2025.

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DOI: https://doi.org/10.3357/AMHP.6714.2025

pooling in the lower limbs, while the respiratory component elevates intrathoracic pressure, enhancing cardiac output and arterial pressure. Together, these mechanisms help preserve cerebral perfusion and prevent G-LOC during high $+G_z$ exposure.[3,4]

Electromyography (EMG) offers a promising approach for quantifying muscle activation during AGSM, providing an objective measure of muscular activation. Implementing EMG-based AGSM training—without the use of a centrifuge—presents a cost-effective alternative to traditional ground-based AGSM training methods focused on technique improvement. It is important to clarify that this approach is not intended to replace centrifuge-based training but rather to complement it, particularly by offering enhanced feedback for neuromuscular control and technique refinement. Previous studies have demonstrated EMG's utility in assessing muscle fatigue during simulated air combat maneuvers[3] and in evaluating AGSM techniques.[5] Additionally, research suggests that lumbar support may enhance AGSM effectiveness by influencing muscle activity, as measured by EMG.[6] Notably, electromyographic activity in the gastrocnemius muscle has been identified as a potential early indicator of G-LOC[7,8] and a strong correlation between muscular contraction and $+G_z$ tolerance has been established.[9]

When AGSM training is applied to inexperienced individuals, such as cadets, the pedagogical focus should prioritize motor control development over maximal performance. Motor learning literature emphasizes that the early stages of skill acquisition benefit from strategies aimed at improving neuromuscular coordination and sustained muscle engagement, rather than maximum contraction efforts.[10,11] This approach is particularly relevant for AGSM, a complex task requiring simultaneous isometric contractions and respiratory maneuvers.[12,13]

This study aimed to evaluate EMG as a training tool for improving AGSM technique. We hypothesized that the provision of verbal feedback, visual feedback, or both would produce significant differences in EMG-measured activation of key muscle groups (medial gastrocnemius, vastus medialis, and rectus abdominis) during AGSM execution among novice cadets. Specifically, we expected that feedback conditions would lead to higher or more stable muscle activation compared to conditions without feedback. By integrating EMG visual biofeedback into AGSM training, this study sought to enhance motor learning and optimize technique. Specifically, we compared the impact of AGSM training with EMG biofeedback to training without it, focusing on differences in muscle activation levels.

## METHODS

### Subjects

There were 63 male Brazilian Air Force (FAB) cadets, all in their third year of training—the stage at which flight instruction begins at the FAB Academy—initially recruited for this study. There were 5 subjects excluded from the final analysis due to incomplete EMG data or technical problems during data acquisition, resulting in a final sample of 58 cadets (25 ± 1 yr; 75.8 ± 4.2 kg; 178.1 ± 3.8 cm) (**Fig. 1**). All cadets had previously completed physiological training at the Aerospace Medicine Institute and volunteered for participation. Eligibility criteria required subjects to be medically cleared through

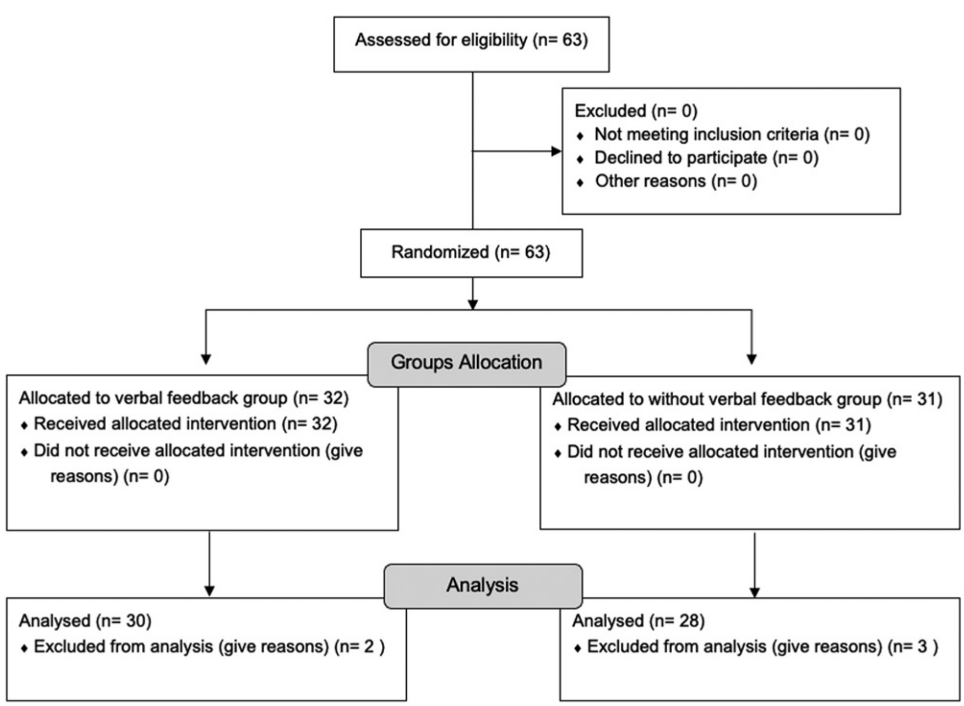


**Fig. 1.** Subjects flow diagram. Subjects were randomized into two groups: with or without verbal feedback. Final analyses included 30 subjects in the verbal-feedback group and 28 in the no-verbal-feedback group.

the institution's annual health assessment, while individuals with musculoskeletal injuries that could compromise performance were excluded. This study was approved by the Research Ethics Committee of the Hospital de Força Aérea de São Paulo (Approval Number 4.349.491), and all subjects provided written informed consent in accordance with the Declaration of Helsinki.

**Procedure**

To assess the impact of different feedback types on EMG activity in the thigh, calf, and abdominal muscles during AGSM training, subjects completed three 30-s sessions, with the first serving as a familiarization trial and the remaining two used for analysis, following a mixed-design approach (between- and within-subject factors) (**Fig. 2**). All AGSM trials were performed in a controlled laboratory setting, without exposure to actual G-forces or centrifuge-based simulation. Subjects remained seated while executing the simulated AGSM synchronized with rhythmic breathing.

It is important to highlight that this AGSM training represented the first practical experience for all subjects. The protocol was designed with an instructional focus, prioritizing the acquisition of the motor skill necessary to properly activate and sustain the contraction of the target muscle groups, rather than maximizing force output.

Visual feedback involved real-time monitoring of EMG signals displayed on a monitor positioned approximately 1.5 m in front of the subject at eye-level during the AGSM trials. The EMG amplitude envelope (smoothed rectified signal) was shown in microvolts, allowing subjects to visually track their muscle contraction levels and adjust them in real time to maintain stable and continuous activation, as instructed. In contrast, verbal feedback consisted of instructor-provided guidance immediately after each trial. The instructor displayed the subject's EMG signal on the same monitor and provided individualized feedback, highlighting strengths and areas for improvement with the goal of enhancing performance in the subsequent attempt.

Subjects performed the AGSM under two within-subject conditions in a counterbalanced order: one with real-time EMG visualization and one without visual feedback. Additionally, they were randomly assigned to one of two between-group conditions: receiving verbal feedback from an experienced AGSM instructor or not receiving any instructor input. This design allowed for a comprehensive evaluation of the effects of visual and verbal feedback on muscle activation during AGSM training. Fig. 2 summarizes the experimental design.

Each AGSM training session lasted 30 s, during which subjects performed sustained isometric contractions of the thigh, calf, and abdominal muscles, synchronized with forced breathing every 3 s. A standardized instructional cue was provided to all subjects before the trials: "You need to contract the muscles of your thighs, calves, and abdomen at a submaximal and continuous level throughout the entire maneuver. Simultaneously, you must perform breathing cycles every 3 s, consisting of a forced exhalation, against a closed glottis, followed by a quick inhalation, without releasing the muscle tension at any point. Because the session lasts 30 s, avoid very intense contractions to prevent premature fatigue and ensure you can sustain the maneuver for the full period." The breathing sequence involved an initial inhalation to approximately 70% of perceived lung capacity, followed by a rapid exhalation and subsequent inhalation every 3 s to maintain lung volume throughout the session. The primary objectives of the AGSM were to: 1) generate and sustain muscle tension; and 2) increase intrathoracic pressure. This physiological mechanism mitigates blood pooling in the lower extremities under high $+G_z$ forces, thereby preserving cardiac output and central perfusion, ensuring pilots remain conscious and maintain optimal operational performance.

EMG data were collected from the gastrocnemius, vastus medialis, and rectus abdominis muscles using a Noraxon DTS system (Noraxon USA Inc., Scottsdale, AZ, USA) at a sampling rate of 1500 Hz, following the SENIAM guidelines.[14] The experimental procedure comprised two 30-s AGSM sessions, separated by a 1-min rest period. EMG signals were digitally processed using a 4$^{th}$-order Butterworth band-pass filter (10–500 Hz) with a 60-Hz notch filter and harmonics to minimize noise.

Muscle activation was analyzed using the windowed normalized area under the curve (nEMG) method, employing 1-s intervals with 50% overlap. EMG amplitude was normalized to the peak activation recorded during each subject's AGSM trials (self-normalization method, nSELF). For each muscle, EMG amplitude was normalized to the highest value observed during either of the two 30-s AGSM trials—whichever



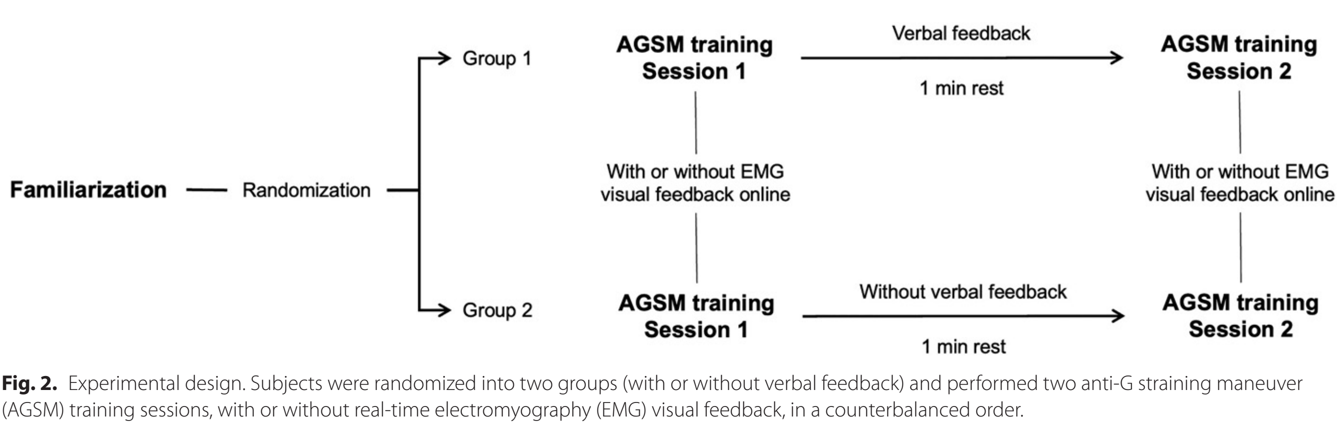


**Fig. 2.** Experimental design. Subjects were randomized into two groups (with or without verbal feedback) and performed two anti-G straining maneuver (AGSM) training sessions, with or without real-time electromyography (EMG) visual feedback, in a counterbalanced order.

exhibited the greatest voltage. These peaks typically occurred within the initial 5–10 s of the first trial, when subjects were more attentive and less fatigued. Due to the novelty of the task and the subjects' limited prior experience with AGSM, fluctuations in neuromuscular control were common, occasionally resulting in brief peaks in EMG amplitude suitable for normalization.

This approach was adopted considering the intraindividual comparison design and the complexity of the AGSM, which involves simultaneous contractions of multiple agonist and antagonist muscle groups coordinated with breathing patterns. Performing isolated MVIC tests for each muscle was deemed impractical and not representative of the specific motor demands of AGSM, particularly for novice subjects.

EMG data were normalized using a self-referenced approach, in which each subject's highest EMG amplitude recorded during the AGSM trials was used as the reference value. This method, while less common than maximal voluntary isometric contraction (MVIC) normalization, was selected for its feasibility and ecological validity within the intrasubject design of this study. Although Slungaard et al.[15] successfully applied MVC-based normalization in aerospace research, our approach is supported by EMG methodological literature recommending task-specific normalization for complex motor tasks.[16,17] This processing strategy offers high sensitivity in detecting activation patterns during AGSM and is particularly useful for identifying reductions in muscle activity that may precede pilot G-LOC.[7] All EMG normalization was performed during postprocessing. An illustrative example of the processed EMG signal from a single subject is shown in **Fig. 3** to demonstrate the typical temporal pattern and peak selection used for normalization.



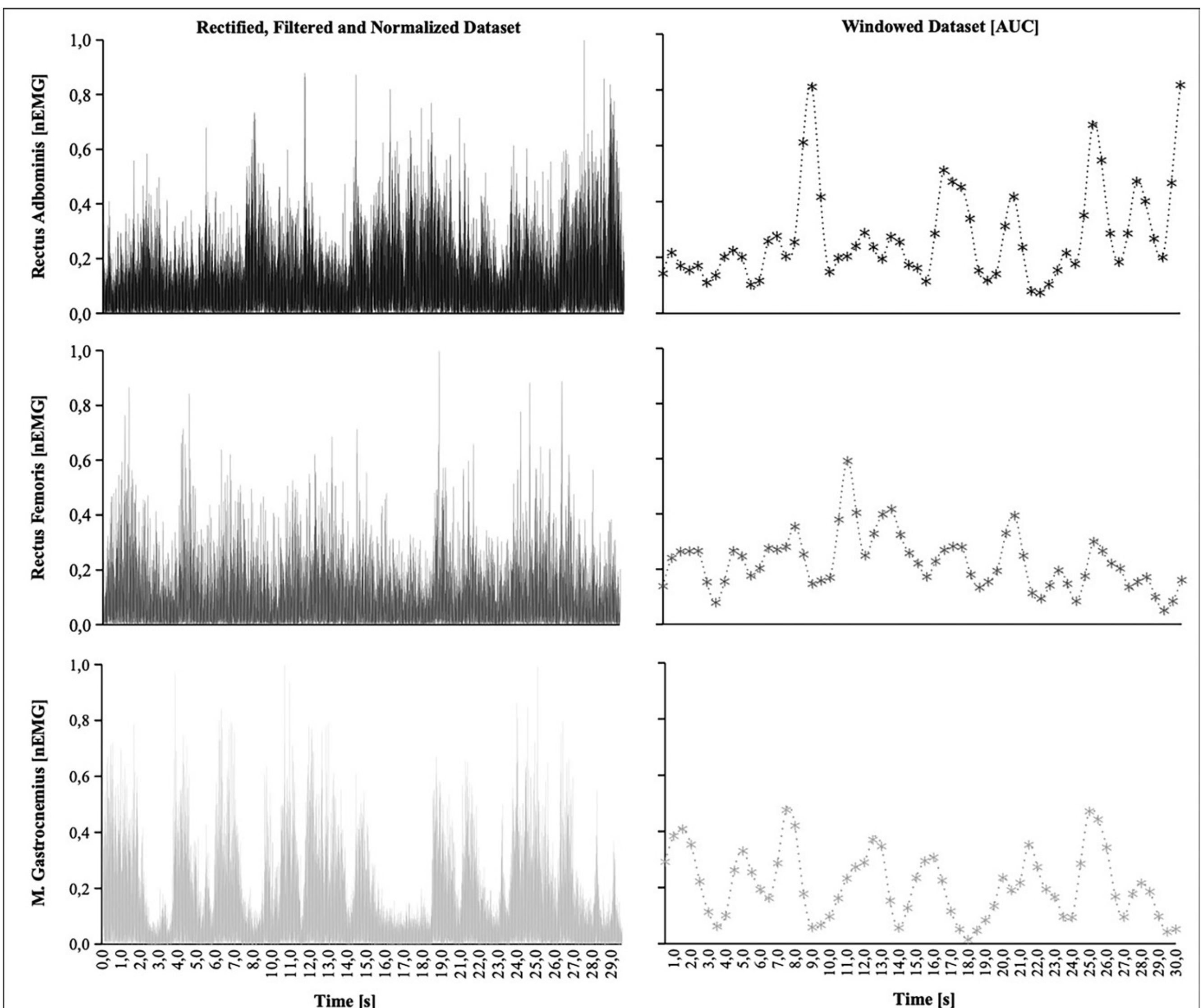


**Fig. 3.** Example of a processed electromyography (EMG) signal from a single subject during anti-G straining maneuver (AGSM). The trace illustrates the temporal pattern of activation and highlights the peak amplitude used for normalization. This example supports the rationale for the task-specific normalization strategy. All data were collected in a controlled laboratory setting, without exposure to G-forces. AUC = area under the curve.

**Statistical Analysis**

Sample normality was assessed using skewness and kurtosis. A two-way repeated measures ANOVA (2 × 2) was conducted separately for each muscle to analyze changes in normalized EMG (nEMG) during AGSM exercises, with verbal feedback and real-time visual feedback as factors. When significant interactions or main effects were detected, simple main effects analyses were performed as follow-up tests. Effect sizes were reported using partial eta-squared ($\eta^2_p$) and classified as small (0.01–0.04), medium (0.06–0.14), or large (≥0.14). Additionally, $\eta^2_p$ values of 0.01–0.039 were interpreted as instructional effects, while values ≥0.039 indicated desirable learning effects. Statistical analyses were conducted using JASP software (Version 0.18.1; University of Amsterdam, Netherlands), with significance set at $\alpha = 0.05$. Post hoc power analysis ($1-\beta > 0.8$) was performed using G*Power (Version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Germany).

## RESULTS

**Fig. 4A** presents data of medial gastrocnemius activation. For the calf muscle, no significant main effect of visual feedback on muscle activation was observed ($F(1, 1730) = 0.613$, $P = 0.434$, $\eta^2p = 0.000354$), indicating that real-time EMG visualization alone did not influence activation levels. In contrast, the main effect of verbal feedback was significant ($F(1, 1730) = 19.393$, $P < 0.001$, $\eta^2p = 0.011$), suggesting that instructor guidance played a role in modulating muscle activity. Additionally, a significant interaction between visual and verbal feedback was found ($F(1, 1730) = 8.335$, $P = 0.004$, $\eta^2p = 0.005$), indicating that the presence of verbal feedback influenced the effect of visual feedback conditions differently. Post hoc analyses revealed that, within the verbal feedback group, the "without visual" condition resulted in significantly greater muscle activation compared to all other conditions ($P \leq 0.05$).

**Fig. 4B** presents the results for the vastus medialis activation. The main effect of visual feedback ($F(1, 1730) = 1.220$, $P = 0.270$) and the interaction between visual and verbal feedback ($F(1, 1730) = 0.511$, $P = 0.475$) were not statistically significant. However, the main effect of verbal feedback was statistically significant ($F(1, 1730) = 17.761$, $P < 0.001$, $\eta^2p = 0.006$), indicating that instructor guidance independently reduced muscle activation, while visual feedback alone or combined had no additional significant effects.

**Fig. 4C** depicts data obtained for the rectus abdominis muscles. The main effect of visual feedback was significant ($F(1, 1730) = 4.696$, $P = 0.030$, $\eta^2p = 0.003$), suggesting that real-time EMG visualization contributed to increased muscle activation. The main effect of verbal feedback was also significant ($F(1, 1730) = 18.019$, $P < 0.001$, $\eta^2p = 0.006$). Additionally, a significant interaction was observed ($F(1, 1730) = 4.548$, $P = 0.033$, $\eta^2p = 0.003$), indicating that the effectiveness of visual feedback was influenced by the presence of verbal guidance. Post hoc comparisons revealed that conditions involving both visual and verbal feedback led to significantly higher activation compared to conditions without any feedback ($P \leq 0.05$).

## DISCUSSION

The present study investigated the impact of visual and verbal feedback on EMG activation during the AGSM among cadet aviators. Results indicated muscle-specific responses, with

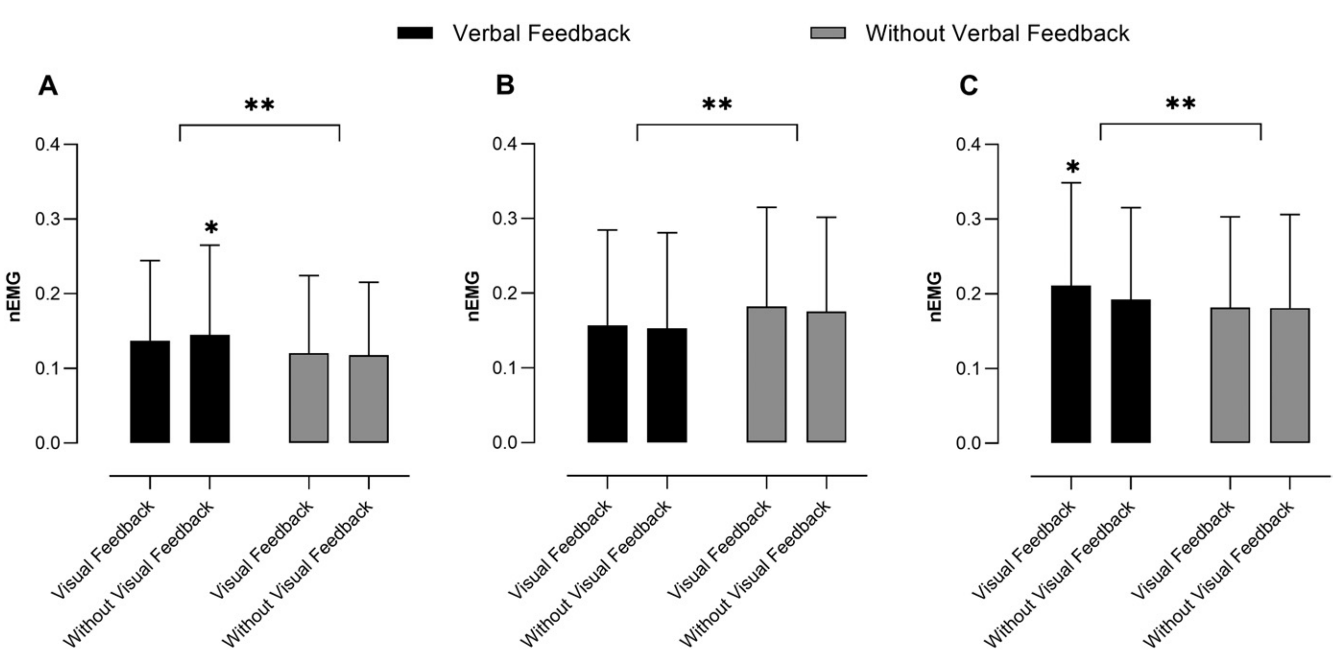


**Fig. 4.** EMG activation during the anti-G straining maneuver (AGSM) in different feedback groups (verbal or without verbal) and conditions (visual or without visual): A) medial gastrocnemius muscle, B) rectus femoris muscle, and C) rectus abdominis muscle. **: significant difference between groups (verbal vs. without verbal) ($P \leq 0.05$); *: significant difference vs. visual in verbal group ($P \leq 0.05$).

significant interactions showing higher activation in the medial gastrocnemius and rectus abdominis muscles under certain feedback conditions. When analyzed separately, verbal feedback had a greater effect size ($\eta^2_p = 0.011$) compared to visual feedback ($\eta^2_p \leq 0.003$). Specifically, in the medial gastrocnemius, verbal feedback alone without visual feedback led to the greatest muscle activation, exceeding all other conditions. In contrast, instructor guidance (verbal feedback) independently led to a significant reduction in vastus medialis activation ($\eta^2_p = 0.006$), while visual feedback alone or combined with verbal guidance showed no additional significant effects.

These findings suggest that verbal feedback consistently influenced muscle activation, whereas visual feedback alone had a limited effect. Interestingly, the condition without visual feedback combined with verbal instructions generated higher gastrocnemius activation than all other conditions, indicating a possible interference or attentional distraction caused by simultaneous visual EMG monitoring. Interaction effects observed in the calf and abdominal muscles suggest that verbal feedback enhances the effectiveness of visual feedback, while the vastus medialis activation decreased specifically due to instructor guidance. Our results emphasize the importance of biofeedback in modulating muscle activation differently across muscle groups, particularly highlighting its effectiveness in the gastrocnemius and abdominal muscles, and its distinct, inhibitory influence on vastus medialis activation.

The significant effect of verbal feedback on gastrocnemius activation suggests that verbal guidance enhances motor learning and neuromuscular control specifically for this muscle during AGSM. However, this effect was not consistent across all muscles, as verbal feedback was associated with a reduction in vastus medialis activation, suggesting that the influence of feedback was muscle-specific rather than universal. The unexpected finding that visual feedback diminished the beneficial effect of verbal cues in the gastrocnemius muscle might be explained by cognitive overload or divided attention when visual EMG feedback is presented concurrently with instructor guidance. This result reinforces previous studies that have identified the gastrocnemius as an important muscle involved in AGSM execution and as a potential early indicator of G-LOC vulnerability in other contexts.[8] It also suggests caution when implementing combined feedback modalities, highlighting the need for further research on optimal feedback strategies. This concurs with research suggesting that EMG biofeedback can serve as a foundation for developing predictive algorithms for pilot safety in high-G conditions.[7]

Similarly, the rectus abdominis showed enhanced activation when both feedback modalities were combined, highlighting its role in sustaining intrathoracic and intra-abdominal pressure—essential for maintaining arterial pressure and cerebral perfusion during AGSM. This finding suggests that feedback-driven training may improve AGSM efficacy by reinforcing the respiratory and pressure-generation components critical to G-protection.[5] The abdominal muscles play a fundamental role in AGSM execution, contributing to core stabilization and intra-abdominal pressure generation, both of which are essential for sustaining high-G conditions. Our findings agree with previous studies emphasizing lumbar support and core engagement in enhancing AGSM performance,[6] reinforcing the premise that multichannel feedback systems optimize motor learning and neuromuscular coordination.[18]

It is important to clarify that the relatively low mean normalized EMG values observed—ranging between approximately 0.1–0.2—do not reflect poor performance but rather the specific instructional strategy adopted. Subjects were explicitly instructed to perform submaximal yet continuous contractions throughout the 30-s AGSM trials, prioritizing muscle activation control and breathing coordination over maximal effort. This approach aligns with motor learning principles for complex isometric tasks,[10,11] particularly when training novice populations, where the focus is on motor control and fatigue management rather than maximal neuromuscular output. Moreover, this study used a submaximal version of the AGSM to maintain sustained contractions over 30 s. Future research should investigate the effectiveness of EMG biofeedback during full-intensity AGSM, where real-time muscle activation data may more clearly identify underperforming muscle groups and optimize training.

While task-specific peak normalization ensures ecological validity and practicality during complex maneuvers like AGSM, it may introduce variability due to differences in subject engagement and motor control. In contrast, MVC normalization offers greater standardization across individuals and studies but lacks task specificity in highly coordinated motor tasks. These differences should be considered when interpreting our findings. An illustrative example of a processed EMG trace from a single subject is presented in Fig. 3 to highlight the temporal variability and support the normalization strategy adopted. Although self-normalization to peak EMG during task execution provides practical feasibility and task-specific comparability, this method is less common than normalization to maximal voluntary contraction (MVC normalization; %MVC) and may hinder cross-study comparisons. Future studies should incorporate MVC-based normalization protocols when experimental conditions allow, to improve generalizability and interpretation.

In contrast, instructor guidance (verbal feedback) significantly reduced vastus medialis activation, while visual feedback alone or combined showed no additional significant effect. This finding may reflect a neuromuscular redistribution strategy resulting from verbal instructions directing attention toward activating less intuitive muscle groups. Previous studies indicate that quadriceps activation during sustained acceleration is relatively stable,[19] and according to motor control literature,[20] verbal cues emphasizing specific muscle groups can lead to selective recruitment patterns, thereby reducing activation in muscles that are naturally recruited with less effort. Further research should explore whether alternative biofeedback strategies, such as prolonged training or higher-intensity contractions, could enhance quadriceps recruitment during the AGSM maneuver.

Our findings corroborate previous research demonstrating the benefits of EMG biofeedback in neuromuscular training.[18,21]

Studies on motor learning suggest that real-time feedback enhances skill acquisition, particularly when combined with verbal instruction.[22] However, it is important to note that the benefits of EMG biofeedback observed in this study were muscle-specific and context-dependent. While it enhanced activation in key muscles like the gastrocnemius and rectus abdominis, it produced no improvement—or even a reduction—in vastus medialis activity. This suggests that EMG biofeedback can be an effective tool when targeted toward muscle groups that benefit from enhanced activation during AGSM, but it may require adapted strategies for muscles where feedback could inadvertently lead to reduced engagement. The results also support the notion that multichannel feedback systems optimize training outcomes by addressing both conscious and subconscious motor control mechanisms.[23]

Additionally, the interpretation of effect sizes ($\eta^2$p) in this study was framed according to the educational approach proposed by Hattie.[11] Effect sizes between 0.01–0.039 represent "instructional effects," meaning moderate but relevant contributions to skill acquisition, while values above 0.039 are considered "desired learning effects," indicating stronger, meaningful improvements. This framework provides an educationally grounded interpretation of how different feedback modalities influenced AGSM learning in this sample of novice participants.

The integration of EMG biofeedback into AGSM training presents a valuable opportunity to improve pilot performance. By tailoring feedback strategies to specific muscle groups, instructors can refine training protocols to enhance muscle activation patterns critical for high-G tolerance.[9] Such approaches align with previous findings highlighting the effectiveness of physiological training in Brazilian Air Force cadets, reinforcing the operational importance of optimized AGSM techniques.[24] Consistent use of EMG biofeedback technology allows instructors to swiftly detect and rectify technical deficiencies, enhancing muscle awareness and control, which are essential factors for optimal performance in high-stress, high-G environments. In consequence, they would be able to promote more efficient technique development, optimizing AGSM performance, and reducing the risk of G-LOC.

Despite its contributions, this study presents certain limitations. First, the absence of direct centrifuge testing precludes definitive conclusions regarding the impact of feedback-driven muscle activation on actual G-tolerance. Second, as the sample consisted exclusively of cadet aviators, the findings may not generalize to experienced pilots or broader populations exposed to high-G environments. Third, the long-term retention and durability of biofeedback training effects remain unknown, requiring further investigation into whether the observed neuromuscular adaptations persist under operational stressors or over extended periods. Additionally, the EMG analysis was limited to the gastrocnemius, rectus abdominis, and vastus medialis. While the hamstrings and gluteal muscles are biomechanically relevant to AGSM, they were excluded due to high susceptibility to movement artifacts in the seated position, which compromised signal reliability. Future studies should consider strategies to include these muscle groups. Finally, conducting the study in a controlled, simulated environment may not fully replicate the physiological and psychological challenges encountered in real-world high-G conditions. Future research should include centrifuge testing to directly assess how biofeedback-enhanced muscle activation influences actual G-force endurance. Additionally, further studies are needed to explore the effectiveness of alternative biofeedback strategies to enhance quadriceps activation during AGSM. Finally, the selective influence of verbal feedback observed in the current study suggests that future AGSM training protocols should strategically emphasize or de-emphasize specific muscle groups to optimize performance outcomes.

Our findings suggest that combining verbal and visual feedback enhances muscle activation in key muscle groups involved in AGSM, particularly in the gastrocnemius and abdominal regions. However, quadriceps activation significantly decreased in response to verbal feedback, indicating that instructional strategies must account for muscle-specific recruitment patterns influenced by verbal cues. Although the study has limitations, particularly the absence of direct G-tolerance assessment, the results strongly support the integration of EMG biofeedback into AGSM training programs. Future research should further explore the direct effects of feedback-enhanced muscle activation on G-force endurance and its adaptability in real-world high-G conditions.

## ACKNOWLEDGMENTS

*Financial Disclosure Statement:* The authors have no competing interests to declare.

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# Evaluation of a Bone Conducted Vibration Device Designed for Motion Sickness Mitigation

Frederick R. Patterson; Alexandra Kaplan; Darci Gallimore; Sarah Sherwood; Dain Horning; Richard V. Folga

**INTRODUCTION:** Historical and modern science has produced many remedies for motion sickness; however, few if any of these remedies have demonstrated successful mitigation without producing negative side effects. The purpose of this study was to determine if a newly created commercial bone conducted vibration (BCV) device could reduce motion sickness symptoms in a simulated visual and provocative motion flight environment.

**METHODS:** Subjects ($N = 12$) passively experienced two 30-min, auto-pilot simulated flights in a motion-based simulator while wearing a BCV device during experimental or placebo conditions. Trial condition presentations were counterbalanced to control potential order effects with a minimum of 1 d between trials. During each trial, subjects completed a tracking task and verbally reported subjective motion sickness ratings every 2 min. After completion of each trial, a Motion Sickness Assessment Questionnaire (MSAQ) was administered.

**RESULTS:** No significant differences in overall MSAQ scores were observed between experimental (29.3 ± 19.4) and placebo (31.1 ± 17.4) BCV conditions. Significant differences in motion sickness scores were observed between the first (34.0 ± 17.6) and second (26.3 ± 18.4) trial sessions.

**DISCUSSION:** The commercial BCV device did not affect the presence or absence of motion sickness during placebo or experimental conditions and had no effect on tracking task performance. During the second trial session, MSAQ scores were lower and time to nausea and failure were longer; however, observed increases in motion tolerance during the second trial sessions likely resulted from sensory adaptation and appeared to be unrelated to the BCV device.

**KEYWORDS:** airsickness, spatial disorientation, vestibular, human factors, cockpit design.

**Patterson FR, Kaplan A, Gallimore D, Sherwood S, Horning D, Folga RV. *Evaluation of a bone conducted vibration device designed for motion sickness mitigation*. Aerosp Med Hum Perform. 2025; 96(11):993–999.**

With today's modern military operations, motion sickness continues to have a negative impact on both training and operational readiness at sea, on land, and in the air; consequently, the Department of Defense has continued to seek easy to use cost-effective remedies that do not have adverse side effects. Among the more recent attempts to develop an effective antimotion sickness remedy is a bone conducted vibration (BCV) device created by Otolith Laboratories.[1–3] This device, referred to as the Otoband, has a small, low-voltage bone conduction transducer that uses an elastic band to hold it in place on the skin surface behind the ear, over the mastoid process. By generating low frequency vibrations, this noninvasive device creates vibration stimulation that reportedly transfers sensations of both linear and angular acceleration to the vestibular system.[4] Developers of this technology believe creating incongruent randomized vibration signals, within the vestibular system, will cause the brain to disregard sensory signals from the inner ear and thereby reduce motion sickness susceptibility. Unlike similar external vestibular stimulus methods, such as galvanic vestibular stimulation, the Otoband BCV technology has been reported as having no adverse side effects.[5] However, since peer-reviewed published data validating the airsickness mitigation benefits of

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This manuscript was received for review in April 2025. It was accepted for publication in August 2025.

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DOI: https://doi.org/10.3357/AMHP.6694.2025

Otolith Laboratories' Otoband is limited, the purpose of this research was to conduct an independent test and evaluation of the device to determine its effectiveness.

For over two millennia, motion sickness associated with traveling in vehicles has been reported as a common and debilitating occurrence.[6] As early as 800 B.C., the Greeks identified wave motion as the cause of seasickness and, by 300 A.D., Chinese medical records documented riding in carts induced an illness known as cart sickness. In addition to inconveniencing vehicular passengers, historical records cited by Huppert indicate motion sickness has also played a critical role in decisive military operations. In 1588, a Spanish Armada intending to invade and conquer England encountered rough weather off the coast of Britain as they came under attack by English ships. Unfortunately for the Spanish, their leader Don Alonzo Perez de Guzman el Bueno was known to be extremely susceptible to seasickness, as were many of his embarked soldiers. Historians have surmised that during the ensuing sea battle, the Armada leader's illness contributed to his poor tactical decisions that led to the Spanish defeat. Several hundred years later (1798–1799), Napoleon's army also encountered tactical problems from motion sickness during their invasion of Egypt. After disembarking from their ships, the French ground forces transitioned their primary mode of overland transportation from horse to camel and soon discovered that "… soldiers who were susceptible to motion sickness" could become "seasick" on this "ship of the desert" and "unable to engage in battle."[7]

During ancient times, Western medical advice for mitigation of motion sickness included a variety of recommendations such as: "fasting or specific diets, pleasant fragrancies, medicinal plants like white hellebore (containing various alkaloids), or a mixture of wine and wormwood." Early Eastern medicine gave more earthy suggestions that involved, "…swallowing white sand-syrup, collecting water drops from a bamboo stick, or hiding earth from the kitchen hearth under the [patient's] hair".[7] Although modern medicine has provided more effective treatments for mitigating motion sickness, such as anticholinergics (scopolamine) or antihistamines (Dramamine), the undesirable side effects of these drugs has led to a reemergence of noninvasive anecdotal remedies. Similar to examples from the past, current unvalidated motion sickness treatments include a variety of approaches ranging from acupressure constricting wrist bands to motion sickness glasses.[8,9] Despite the beneficial claims made by manufacturers of these present-day antimotion sickness devices, many of their claims have proven to be highly exaggerated and demonstrably false.[10]

Although multiple theories exist to explain the underlying causes of motion sickness, the most widely accepted explanation is the sensory conflict theory proposed by Reason and Brand in 1975.[11–13] This theory suggests all types of motion sickness can occur when an individual is exposed to a mismatch of spatial sensations (afferent neural transmission) generated from visual, vestibular, or proprioceptor organs. The spatial conflict theory further explains that motion sickness responses are often triggered when the human brain senses conflicting sensory organ information. As an example, if a person in a moving vehicle is looking outside, they would experience optical visual flow of the scenery and at the same time sense vehicle motion from their vestibular and proprioceptor systems. Under these circumstances, they would experience three sources of congruent spatial information telling them they were in motion. In contrast, if a person in a moving vehicle has no outside view (no optical flow), their vestibular and proprioceptive systems would still send signals indicating they were in motion; however, their visual system would send conflicting (incongruent) sensations indicating they were stationary, thereby creating sensory conflict.

Scientists have further theorized that sensory conflict and motion sickness may have an evolutionary link to nausea and vomiting encountered with air, sea, and car travel. When early human ancestors were foraging for food, they may have occasionally consumed readily available plant material containing neurotoxins (i.e., nightshade, hemlock, jimson weed, etc.). If this did occur, consumption of these types of plants would initially create sensory conflict by disrupting the human sensory system, prior to the poison causing fatal circulatory collapse. In the event poisonous plants were ingested by the evolving human species, there would have been considerable natural selection pressure promoting evolution of a rapid vomiting response as a means of removing the substance from the body. Reason suggested that modern humans have retained this sensory conflict/vomiting response, and similarities that exist between ingesting neurotoxins and experiencing incongruent visual-motion sensations is what causes the brain to trigger nauseogenic motion sickness.[13]

The primary goal of this study was to evaluate the effectiveness of Otolith Laboratories' BCV device in mitigating motion sickness during provocative motion flight simulations in the Disorientation Research Device (DRD) located at the Naval Medical Research Unit (NAMRU-D), Dayton, OH. The hypothesis for this experiment was: therapeutic BCV exposure (independent variable) will affect onset time, frequency, and magnitude of airsickness symptoms (dependent variables) measured by self-reporting scores of the Motion Sickness Assessment Questionnaire (MSAQ), the Baxter Retching Faces (BARF) scale, time to nausea, and Target Tracking Task performance (TTT).

## METHODS

The protocol for this study was approved by the NAMRU-D Institutional Review Board (IRB) in compliance with all applicable federal regulations governing the protection of human participants (IRB approval #NAMRUD.2020.0008).

### Subjects

A total of 12 healthy adults (mean age = 28.83 ± 4.01) consisting of 5 men and 7 women participated in this study. All subjects were recruited through flyers, online announcements, or by word of mouth and subjects who completed the study received compensation. Subjects self-reported normal or corrected-to-normal vision and had no history of neurological, vestibular, or other medical diagnoses.

Prior to enrollment, subject candidates confirmed eligibility by completing the Motion Sickness Susceptibility Questionnaire (MSSQ) and verbally answering screening questions over the phone. The MSSQ was used to assess individuals' experiences with motion sickness (i.e., nausea, vomiting) in nine different types of transport or entertainment (i.e., vehicles, swings, fair rides, etc.) before the age of 12 and within the last 10 yr.[14] Subjects rated their frequency of motion sickness for each experience using a 5-point Likert scale from 0 (never) to 4 (always). The MSSQ score is calculated as the total summed symptom rating scaled by the number of transport/entertainment types experienced, and is considered a reliable measure of motion sickness susceptibility during provocative motion stimulation. Only individuals with MSSQ scores greater than or equal to 45.5 were included to ensure enrollment of subjects with moderate to severe motion sickness susceptibility (mean = 144.87 ± 44.56, range 84.15–209.88).

Prior to starting their first trial session, subjects provided written informed consent with a witness present and were instructed to refrain from taking any type of motion sickness medication prior to participating in either the first or second trials. Female subjects were screened for pregnancy using either a validated pregnancy questionnaire or a urine pregnancy test.[15] Any female subject candidates with indications of potential pregnancy were excluded from the study as a safety precaution.

### Equipment

Subjects were equipped with a comfortable but snug-fitting standard military helmet with the Otolith Laboratories' BCV device modified to fit inside the right helmet earcup, behind the ear, and over the mastoid bone skin surface. This allowed the device, when activated, to provide localized mastoid vibrations to stimulate the vestibular system.[3] Helmet fitting and device placement was done by the same researcher for every subject to ensure reliable placement. The placebo device consisted of an Otolith Laboratories' BCV power source and bone conduction transducer fixed on top of the helmet in a holding bracket. This provided diffuse vibrations to the entire head and avoided direct stimulation of the vestibular system. The amplitude of the experimental device was 1.47 times greater than the placebo with average amplitudes of 16.9 $ft \cdot s^{-2}$ (5.15 $m \cdot s^{-2}$) compared to 11.5 $ft \cdot s^{-2}$ (3.51 $m \cdot s^{-2}$), respectively.

This study incorporated motion and visual flight stimuli using the NAMRU-D DRD motion platform. The DRD has six bidirectional axes degrees of freedom: two linear (heave and horizontal) and four rotational (roll, pitch, yaw, and planetary), all on a bidirectional rotating platform (planetary axis) that provides an acceleration field for the occupant capsule.

A standardized DRD motion profile for inducing motion sickness was initially evaluated for inclusion with the study protocol;[16] however, after running several test subjects, it was determined the standard profile was not provocative enough for the goals of this study. Subsequently, a rated U.S. Navy test pilot flew and recorded a DRD simulated T-6A Texan aircraft (Laminar X-Plane software) flight profile that consisted of increasing orders of magnitude for pitch, wingover, and near stall maneuvers. This series of aerobatic type maneuvers, coupled with decreasing time between maneuvers, produced a more provocative motion-sickness effect that was considered suitable for evaluating the motion-sickness mitigation capabilities of the BCV device. The revised DRD motion path and synchronized flight simulation consisted of an ellipse pattern, with a maximum achievable distance of ±12.5 ft (3.8 m) in the forward/backward directions and ±7.0 ft (2.1 m) laterally. In this motion space, the maximum achievable acceleration was 1.2 $G_z$ for less than a half second. The DRD angular velocities were created using only the roll and pitch gimbal axes, with the maximum angular positions limited to ±60° for roll and ±45° for pitch. Maximum angular velocity was limited to $30° \cdot s^{-1}$. These parameters were combined with motion washout to provide subjects with angular rate cues, as opposed to the sustained angular displacements and rates experienced in real world flight environments.

### Procedure

Subjects underwent a simulated flight session during two separate counterbalanced visits: once with a BCV placebo and once with the BCV experimental device. To conceal the identity of the experimental and placebo devices, subjects were deceptively informed that the purpose of this study was to determine whether optimum placement of the BCV device was on top of the helmet or in the right ear cup. Each study session was approximately 90 min with a maximum of 30 min spent on each flight simulation trial and a minimum of 1 d between each trial session. After providing consent, subjects completed health screening and demographics questionnaires and were escorted to the DRD control room for fitting with a helmet equipped with a BCV experimental or placebo device. After donning the BCV equipped helmet, subjects were led to the DRD capsule and briefed on egress and emergency procedures before being strapped into the capsule seat with a five-point harness. They were then given instructions on how to report BARF ratings and how to perform the TTT during their flight session.

The BARF scale is a pictorial scale originally validated for measuring nausea in children.[17] Subjects were presented with six faces and asked to rate their nausea on a scale of zero (neutral face) to 10 (vomiting face). BARF scores were averaged to create mean BARF scores for each subject's session. Cronbach's alphas for the placebo and experimental conditions were 0.95 and 0.96, respectively. Time to onset of nausea was determined by the time at which subjects reported a BARF rating greater than or equal to one. The session ended when a subject exceeded a BARF score of four or finished the 30-min flight session, whichever came first.

In accordance with the Navy DRD protocol, subjects were informed flight sessions would end if they reached a BARF score of 5 or greater (to avoid potential emesis, per DRD protocol) and were told they could stop the flight simulation session if they felt sick, or for any other reason. A baseline BARF rating was obtained before the start of capsule motion, after which, subjects began their 30-min flight simulation trial. Throughout the flight, subjects verbally reported their BARF ratings every 2 min.

Throughout each flight, subjects used an F-16 type force stick to perform the TTT.[18] This task consisted of 4-min epochs of continuously centering an on-screen reticle within a diamond-shaped, moving target. The reticle and diamond shape target were overlaid on the flight simulation background, which consisted of Pensacola, FL, moving scenery as it would be viewed from a cockpit at 5000 ft (1524 m) above mean sea level altitude. TTT data were collected using an in-house developed research operator station. Tracking task performance was quantified in terms of throughput, which was defined as the number of "hits" divided by the time available to complete each TTT session, where a hit was considered to occur whenever the distance between the center of the target diamond and reticle (i.e., TTT distance) was less than 50 pixels.[19] When TTT distance was less than 50 pixels, the center of the diamond fell within the inner circle of the reticle. Data at the start of each TTT session was excluded by finding the first point at which the TTT distance value was less than or equal to the session mean following a 10-s buffer. This was done to exclude large spikes that sometimes occurred at session starts due to temporary distraction while reorienting to the TTT. Subjects typically refocused on the TTT quickly following task pauses, resulting in a small difference in discretionary time across BCV conditions (M = 0.58 s, SD = 1.94 s). A custom MATLAB script was written to process the TTT data.

After each 4-min TTT session, there was a 4-min rest interval. During these rest periods subjects were instructed to remain looking forward at the screens; to ensure compliance, a video camera and recorder were used to monitor the subjects' gaze direction.

After completion of each trial session, subjects were escorted from the capsule and asked to complete the MSAQ.[20] The MSAQ assesses four dimensions of motion sickness symptoms: gastrointestinal (e.g., I felt sick to my stomach); central (e.g., I felt faint like); peripheral (e.g., I felt sweaty); and sopite-related (e.g., I felt tired/fatigued). Subjects rated 16 items using a scale from one (not at all) to nine (severely). MSAQ scores were summed for each dimension and were used in a formula for each subscale, where Rating = (Sum of each subclass symptom rating)/[(number of the questions related to the corresponding subclass) × 9]. Overall MSAQ scores were calculated as: score = (sum of all items/[(number of all questions) × 9] × 100. Cronbach's alphas were 0.94 for both the placebo and experimental conditions.

At the end of the first test session, subjects were reminded not to take any over-the-counter nausea medications prior to the next session. After the study was completed, subjects were debriefed by a researcher on the true purpose of the study, the nature of the deception, and the reasoning and need behind the deception. Subjects were allowed to ask questions and were asked for permission to use their data for the study analysis.

### Statistics Analysis

This was a counterbalanced, placebo-controlled study with repeated measures. Based on existing literature and information provided by the BCV device manufacturer, the power analysis for this protocol assumed an effect size of 0.45, which led to an original sample size estimate of 24 subjects. However, after observing no significant changes between the control and experimental conditions during trials for the first 12 subjects, exposing additional subjects to the nauseogenic effects of the protocol was deemed inappropriate under IRB guidelines. Subsequently, only data from the first 12 subjects was used for this study.

## RESULTS

On average, 6.58 ± 16.59 d elapsed between subjects' test sessions, with one outlier having 59 d between sessions. After removing this outlier, the average days between sessions were 1.81 ± 1.78 d and 58.33% ($N = 7$) of the subjects completed their sessions with a 1-d interval. Per DRD protocol, flight sessions were ended if subjects reached a BARF score of 5 or more. This protocol resulted in five of the first session flights ending before 30 min and one of the second session flights ending before 30 min. On average, elapsed times for the first and second sessions were 24.88 ± 7.57 min and 29.17 ± 2.89 min, respectively.

To examine whether the experience of motion sickness symptoms differed between the placebo and experimental flight sessions, paired-samples *t*-tests were conducted to compare overall MSAQ scores across BCV conditions. The results indicated there was no significant MSAQ difference between the BCV experimental and placebo conditions (**Table I**). For this study, order effect was not considered a definitive factor for measuring BCV effectiveness; however, since order effects were mentioned in a previous study that examined Otolith Laboratories' BCV device

**Table I.** Paired Samples *t*-Test Results for MSAQ Scores Across BCV Conditions and Study Visits.

| MSAQ CATEGORY | BCV CONDITIONS (EXPERIMENTAL vs. PLACEBO) | | | | | BCV TRIAL SESSIONS (TRIAL 1 vs. TRIAL 2) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | M | SD | t(11) | P | Hedge's g | M | SD | t(11) | P | Hedge's g |
| Overall | 1.8 | 15.12 | −0.41 | 0.34 | −0.08 | −7.7 | 12.95 | −2.06 | 0.03* | −0.36 |
| Gastro | −10.42 | 21.9 | −1.71 | 0.06 | −0.44 | −9.49 | 21.57 | −1.57 | 0.08 | −0.39 |
| Central | 2.41 | 13.52 | 0.62 | 0.28 | 0.11 | −4.63 | 12.87 | −1.25 | 0.12 | −0.21 |
| Peripheral | 0 | 24.31 | 0 | 0.5 | 0 | −12.96 | 20.19 | −2.22 | 0.02* | −0.54 |
| Sopite | −0.46 | 17.99 | −0.09 | 0.47 | −0.02 | −6.02 | 16.87 | −1.24 | 0.12 | −0.24 |

**P*-values indicating significant differences between first and second trials.

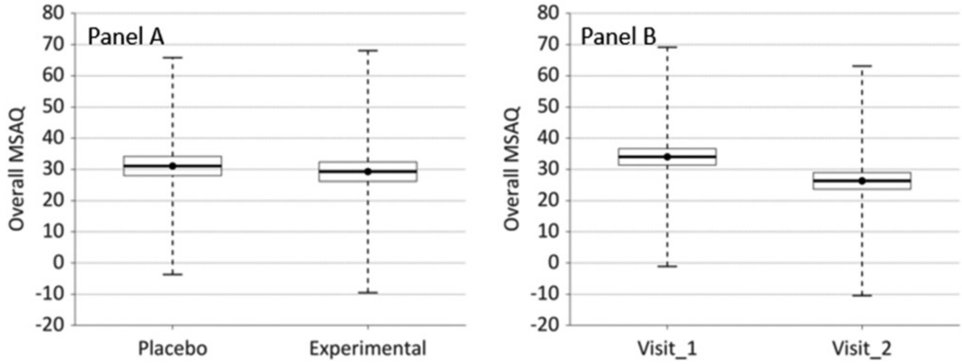


**Fig. 1.** Overall MSAQ means by BCV condition and visit number. Heavy lines with dots represent means. Boxes represent within subject standard error. Whiskers represent M ±2·SD. (All mean plots follow the same format.)



with a Head Mounted Display Virtual Reality system, an exploratory analysis was conducted to evaluate possible differences in MSAQ scores across study visits.[21] Since onset of nausea caused the first trial sessions of this study to end early for five subjects and only one subject's trial ended early for the second session, there was a reduction in homogeneity of variance between the first and second trial sessions. Subsequently, a simple *t*-test analysis was considered a viable exploratory option for evaluating order effects instead of analysis of variance. The paired *t*-test comparing order effect revealed significant differences in overall and peripheral MSAQ subscales scores between the first and second trials, with lower scores appearing during the second trial session (Table I, **Fig. 1**).

Using a BARF rating score of 5 for terminating DRD sessions led to a pattern of missing data across time, which contravened the visit order counterbalancing scheme. To compensate for the missing data, BARF sessions were matched within each subject by including only sessions up to the minimum session number across conditions. BARF ratings were then averaged within each condition for each subject. Paired *t*-tests across BCV conditions and visit number were conducted to compare average BARF ratings and a survival analysis was conducted to compare time to failure. For BARF rating averages across BCV experimental and placebo conditions, paired *t*-tests revealed no significant difference [$t(11) = -0.78$, $P = 0.22$, g = −0.25]. For BARF rating averages across visit numbers, the paired *t*-test revealed a significant difference [$t(11) = -4.24$, $P < 0.01$, g = −0.99], with lower BARF ratings occurring during the second trial sessions (**Fig. 2**).

For time to nausea across BCV conditions, the paired *t*-test and Wilcoxon signed-rank test revealed no significant differences [respectively, $t(11) = 0.078$, $P = 0.47$, g = 0.016, and Z = 19, $P = 0.72$]. Comparing time to nausea for trial sessions one and two, paired *t*-test revealed a significant difference [$t(11) = 2.72$, $P = 0.01$, g = 0.46], with longer times during the second trial sessions. The Wilcoxon signed rank test also revealed a significant difference with the increasing time to nausea during the second trial sessions [Z = 44, $P = 0.008$] (**Fig. 3**).

The BARF scale failure criterion of 5 resulted in only three subjects reaching failure in both the placebo and experimental conditions (one subject reached failure in both conditions). Consequently, for the purposes of survival analyses, the failure criterion was lowered to a BARF rating of four, which led to 9 out of 12 subjects reaching failure in the placebo condition, and 5 out of 12 subjects reaching failure in the experimental condition. Nonfailure cases were considered right censored. For failure time by BCV condition, the survival analysis revealed a nonsignificant difference between placebo and experimental conditions (Wilcoxon Chi-squared, $P = 0.28$). For failure time by visit number, the survival analysis indicated a significant difference (Wilcoxon Chi-squared, $P = 0.04$), with lower probability of failure during the second trial session.

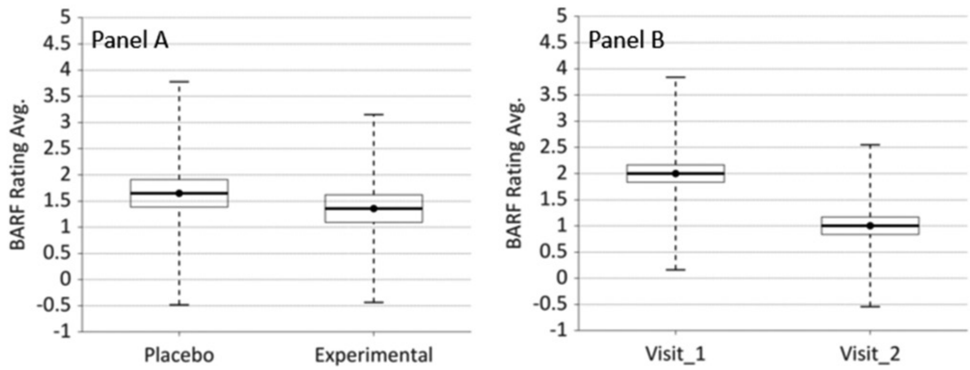


**Fig. 2.** BARF rating means by BCV condition and visit number.

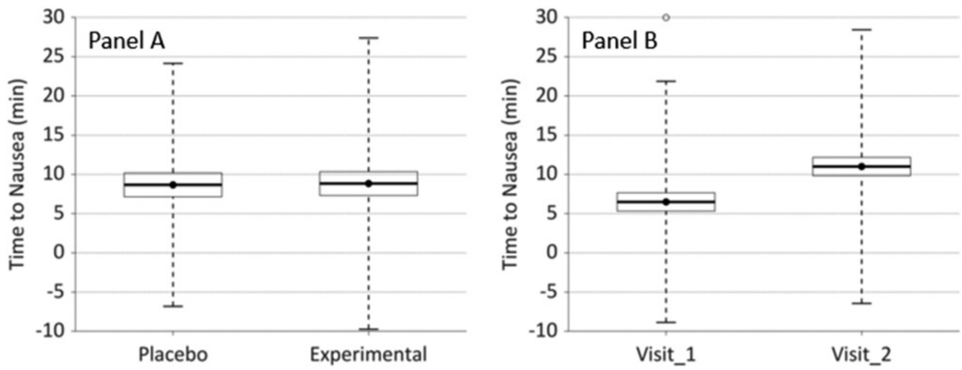


**Fig. 3.** Time to nausea means by BCV condition and visit number.

Paired samples *t*-tests for TTT performance between the placebo and experimental BCV conditions also revealed no significant difference [$t(11) = 0.16$, $P = 0.44$, g = 0.01] and, for throughput by visit number, the paired samples *t*-test indicated no significant difference [$t(11) = 1.23$, $P = 0.12$, g = 0.11].

## DISCUSSION

The results of this evaluation indicate the tested BCV device did not have a significant impact on motion sickness. These findings are consistent with a similar study that determined BCV intervention did not mitigate head-mounted display virtual reality cybersickness.[21] In both studies, the order effect was the only factor that reduced motion sickness, which suggests subjects most likely acclimated and adapted to the nausea-inducing motion stimulus after repeated trials. This study appears to further confirm previous research documenting natural acclimatization to motion environments is the most effective motion-sickness mitigation strategy, regardless of any BCV intervention.[13] Although future BCV designs may offer some potential to expand human compatibility with adverse motion environments, more research is needed to quantify and qualify health risks associated with this technology. For several decades the U.S. Army Research Laboratory has been evaluating commercially available BCV devices and reported:

> "… state-of-the-art bone conduction systems and bone conduction literature are not easily available due to their commercial limitations, trade restrictions, and military applications. However, there is still a scarcity of information about bone conduction in open literature and in trade magazines. In addition, information available in popular media outlets (e.g., TV, Internet, trade magazines) about the capabilities and physiological basis of bone conduction communication is frequently far from scientific scrutiny and leads to misinformation."[22]

Unfortunately, credible health risk assessments for BCV therapeutic uses are limited, even though there is an abundance of research documenting interference with the normal function of the inner ear can have a profound negative impact. Researchers have demonstrated: "… Low Frequency Noise (LFN), defined as broadband noise with dominant content of low frequencies (10–250 Hz) differs in its nature from other environmental noises at comparable levels."[23] Consequently, "… LFN at moderate levels might adversely affect visual functions, concentration, continuous and selective attention, especially in the high-sensitive to LFN subjects."[23] Since the BCV device tested with this study reported using LFN vibrations of 50 Hz with a power level of 98 dB, the existing medical research suggests this range of stimulation could increase health risks.

A more encompassing concern that exists with BCV technology is the "shotgun" approach used to stimulate the inner ear by sending vibrations through the mastoid bone. Vibrations intended for stimulation of vestibular organs (semicircular canals and otoliths) also simultaneously stimulate the cochlea of the inner ear hearing system. An unintended consequence of this collateral stimulation is it bypasses the middle ear acoustic reflex, which is a protective mechanism that reduces transmission of harmful vibrational energy to the cochlea.[24] Such transmission also causes a second physiological anomaly to occur when the ear canal is closed or occluded by earplugs or sound attenuation ear cups. In this situation, BCV vibrations sent through the mastoid bone generate airborne sound pressure waves within the external canal and thereby induce oscillation of the tympanic membrane and ossicles. Unfortunately, this indirect BCV stimulation of the external and middle ear has been found to increase transmission of low frequency (LF) mechanical energy to the cochlea by up to 40 dB.[25] Since BCV devices intended for reducing motion sickness are designed to produce continuous external LF vibrations between 10–50 Hz with 100–150 dB of acoustic power, adding an additional 40 dB of LF power to the inner ear may significantly increase risk of hearing loss and interference with normal vestibular function.[4]

Recent auditory research has also discovered that low frequency 30-Hz sound at 120 dB for 90 s "… induces slow oscillations of cochlear compression and gain, subsequently causing several measures of cochlear activity to cycle through phases of increased and decreased sensitivity [aka: bounce pattern].”[26] This slow oscillation of the homeostatic control mechanism within the cochlea has been suggested as the source of the bounce pattern during exposure to moderately loud LF vibrations. Based on this observed physiological phenomenon, researchers have suggested if this control mechanism fails to operate correctly, and disturbances of cochlear homeostasis are not rectified, hearing may become impaired and vestibular function could be compromised by formation of endolymphatic hydrops and finally Ménière's disease.[26] Since commercially available BCV devices are known to use LF vibrations that exceed 120 dB for periods extending well beyond 90 s, there exists the possibility that unrestricted use of these devices could incrementally create irreversible cochlear and vestibular damage.

Although this study found the tested commercial BCV device was ineffective for mitigation of motion sickness, applications for commercial use of BCV technology are continuing to expand. Based upon the documented potential risks associated with exposure to low frequency sound vibrations (20–200 Hz) with moderate (80 dB) to high (150 dB) energy levels, further research is needed to make an accurate health risk assessment of BCV stimulation. Establishing safe finite conditions for BCV exposure in civilian and military environments will help mitigate any potential hazards related to hearing loss, induced vertigo, or decreased cognitive function caused by this emerging technology.

## ACKNOWLEDGMENTS

We would like to thank Charles Weisenbach and Andrew Spencer for their dedicated assistance with collection and storage of the subject data. We would also like to thank Charles Powell for his extensive programming/software support and the entire DRD support team that monitored and ensured the safety of subjects during multiple motion-based trials in the DRD.

*Financial Disclosure Statement:* The authors have no competing interests to declare.

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# Spine Surgery in Space

Dion Birhiray; Abdullah Ghali; Trey Philipp; Srikhar Chilukuri; Benjamin Fiedler; Jad Lawand; Lorenzo Deveza



**INTRODUCTION:** Prolonged exposure to microgravity alters spinal biomechanics, increases disc herniation risk, and complicates perioperative care. With commercial and deep-space missions on the horizon, the need for in-orbit surgical capability has gained prominence as a safeguard for astronaut health.

**METHODS:** A narrative review of PubMed, EMBASE, and Google Scholar through November 2024 identified human, animal, and in vitro studies addressing spinal physiology, pathology, or surgical feasibility in actual or simulated microgravity. Studies unrelated to the spine or lacking English full text were excluded.

**RESULTS:** Of 988 records, there were 85 that met inclusion criteria. Across study types, microgravity consistently produced spinal elongation, disc swelling, vertebral bone loss, and muscle atrophy, leading to elevated postflight spinal morbidity. Although no spine operations have been reported in orbit, analog studies describe key intraoperative challenges, including fluid containment, sterility, imaging, anesthesia, and hemodynamic control. Promising countermeasures encompass bisphosphonates, resistive exercise, robot-assisted instrumentation, and teleoperation. These data offer a generalizable framework for perioperative planning during long-duration missions.

**DISCUSSION:** Existing evidence clarifies physiological and logistic barriers to operative care. Targeted musculoskeletal countermeasures, coupled with tele-robotic and augmented-reality platforms, provide a realistic pathway to safe spine surgery during future long-duration missions. Further translational research and on-orbit validation are essential before clinical deployment.

**KEYWORDS:** spine surgery in microgravity, orthopedic challenges in microgravity, astronaut spinal health, microgravity-induced physiological changes.

**Birhiray D, Ghali A, Philipp T, Chilukuri S, Fiedler B, Lawand J, Deveza L. *Spine surgery in space*. Aerosp Med Hum Perform. 2025; 96(11):1000–1007.**

The pursuit of space exploration exemplifies humanity's quest for knowledge, driven by the desire to unlock the secrets of the universe and expand our understanding beyond Earth's confines. Space agencies such as NASA, the European Space Agency, and Roscosmos (the Russian Space Agency) have historically led numerous expeditions into space, ranging from Earth orbits to manned and unmanned missions to the Moon, Mars, and beyond. These missions have provided crucial insights into the cosmos, the origins of celestial bodies, and the possibility of extraterrestrial life.

A defining characteristic of space travel is microgravity, in which gravitational forces are significantly reduced compared to those on Earth.[1–3] This environment enables weightlessness, leading to profound physiological changes.[1] While early studies during the initial stages of space exploration investigated these phenomena, much remains to be discovered about how prolonged exposure to microgravity triggers various adaptations in bone density, muscle mass, cardiovascular function, and fluid distribution.[2,4,5]

The biomechanical challenges presented by microgravity significantly increase the risk of spinal injuries for astronauts. Factors such as spinal elongation, fluid shifts, and altered muscle function can predispose them to conditions like disc herniation, spinal stenosis, and vertebral fractures, which pose potential threats to mission objectives and crew safety.[6–8] Due to the potential for injury under these conditions, understanding the effects of microgravity on spinal anatomy and biomechanics is crucial for precise preoperative planning. Surgeons must consider how altered gravitational forces might impact

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This manuscript was received for review in January 2025. It was accepted for publication in July 2025.

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DOI: https://doi.org/10.3357/AMHP.6637.2025

surgical outcomes, including spinal stability, implant efficacy, and tissue healing processes.[3]

In addition to surgical considerations in microgravity, postoperative recovery and rehabilitation strategies must be adapted to account for the impact of microgravity on tissue healing and functional recovery.[7,9] Implementing comprehensive monitoring and rehabilitation programs postsurgery is essential to optimize surgical outcomes and reduce the risk of complications during missions.[7] Given these complexities, advancing our understanding of spinal health after prolonged exposure to microgravity and developing tailored surgical strategies is critical. Addressing these challenges will enhance the safety and effectiveness of space missions, protecting and improving the health and well-being of astronauts.

With the exponential growth of technological capabilities making space travel more accessible, space exploration is projected to become more frequent in the near future. This narrative review aims to examine the impact of microgravity on spinal health and evaluate current and future strategies for managing spine-related issues during and after space missions.

## METHODS

The studies included in this review were identified through comprehensive searches of electronic databases, including PubMed, EMBASE, and Google Scholar, and by examining the reference lists of relevant articles. Databases were searched from inception up to November 2024 with all field search terms, including: "spinal surgery and astronauts," "spaceflight and spine surgery," "paraspinal muscle alterations and microgravity," "spine health and microgravity," and "spaceflight and surgery." Inclusion criteria encompassed publications (articles, reviews, NASA reports) that specifically addressed spinal physiology or spine surgery in actual or simulated microgravity. We included human studies and relevant animal or in vitro studies that offered insight into human spinal responses to microgravity. Exclusion criteria ruled out works not focused on the spine, spine surgery, or surgery in space (e.g., studies solely on other organ systems or general space medicine topics without a musculoskeletal or surgical context) and articles without available English full text. Relevant references cited in selected publications were reviewed and incorporated when appropriate.

## RESULTS

Our search identified 988 records, of which 85 publications met all inclusion criteria and were analyzed qualitatively. No study reported a spine operation performed during spaceflight; all clinical surgical experience remains Earth-based.

### Microgravity-Induced Spinal Changes

Across the 32 biomechanical papers, prolonged weightlessness was consistently associated with spinal elongation (astronauts gain ~3–5 cm in height), intervertebral disc swelling, paraspinal muscle atrophy, and reduced bone density in vertebrae.[10–12] A large retrospective cohort further documented a 4.3-fold increase in herniated nucleus pulposus among astronauts within the first postflight months compared with terrestrial controls.[13] Cephalic fluid redistribution, documented by ultrasound and MRI, straightens lumbar lordosis and adds to disc swelling, reinforcing these structural changes.[10,14]

### Therapeutic Considerations

There were 23 papers which addressed treatment and recovery. Collectively, they show that microgravity impairs wound and bone healing.[15–17] Multimodal countermeasures, such as peri-mission bisphosphonate therapy,[18] targeted nutrition, resistance exercise, and telemetric monitoring, are required to support postoperative recovery. There is a broad consensus that early supervised rehabilitation and continuous physiological surveillance are essential for restoring spinal stability and function.[15,19] Several studies recommend cardiovascular support, including graded re-ambulation, lower-body negative pressure, compression garments, and judicious fluid loading, to counter postflight orthostatic intolerance during early mobilization.[4,19]

### Surgical Feasibility and Technology

A total of 22 publications evaluated surgical feasibility. The literature reflects that no actual spine surgeries have been done in space to date, but there is extensive discussion of potential techniques. All cited environmental hurdles include sterility maintenance, free-floating fluids, and restricted workspace.[20–22] Surgical simulation studies, including animal models on shuttle missions, demonstrate that minor procedures are technically feasible in microgravity (Drudi et al.).[22,23] Most authors identified image-guided robotics, augmented-reality navigation, and telemedicine as critical enablers for future space surgeries.[21,24,25] The spaceMIRA experiment in 2024 provided the first on-orbit demonstration of Earth-controlled robotic surgical tasks, validating the mechanical feasibility of tele-operation in microgravity.[26] Five studies further noted that total intravenous anesthesia and restrained airway management are preferred options to mitigate equipment float and altered pharmacokinetics in weightlessness.[27]

Together, the literature reveals predictable microgravity-induced spine degeneration, highlights targeted countermeasures for postoperative recovery, and suggests that emerging imaging and robotic systems offer a plausible pathway toward safe spine surgery during future long-duration missions.

## DISCUSSION

### Impact of Microgravity on Spine Health

The impact of microgravity on the musculoskeletal system, specifically the spine, is essential for mitigating the adverse effects of space travel on astronaut health and operational efficiency.[28] In microgravity, the absence of Earth's gravitational pull results in diminished axial loading on the spinal intervertebral discs, allowing these discs to expand and contributing to increased spinal length.[29–31] MRI studies have shown that astronauts can experience spinal elongation of up to 5 cm following prolonged spaceflights.[6] This elongation, which leads to a straightening of the natural spinal curvature, is thought to be driven by changes in fluid distribution within the discs, tissue hydration shifts, and microgravity-induced adaptations in spinal biomechanics.[32] Furthermore, microgravity affects the structure and function of intervertebral discs. The reduction in gravitational forces facilitates disc hydration shifts and swelling, resulting in alterations in disc height and mechanical properties.[10] Variations in disc metabolism and nutrient exchange have also been speculated to exacerbate disc degeneration, potentially increasing susceptibility to herniation and degenerative disc disease.[33,34]

CT studies have demonstrated persistent decreases in bone mineral density, paraspinal muscle cross-sectional area, and muscle density in astronauts, even after a year of readaptation to Earth's gravity.[11] This decline was corroborated by Bailey et al., who found reduced flexion-extension range of motion and decreased muscle mass following long-duration spaceflights.[12]

The lack of normal mechanical loading in microgravity also leads to muscle disuse and atrophy, particularly affecting the paraspinal muscles essential for spinal stabilization and posture maintenance, thus increasing the risk of musculoskeletal injuries.[6,35] Concurrently, microgravity disrupts the balance between bone formation and resorption, leading to accelerated bone loss, especially in weight-bearing bones such as the vertebrae. This can result in osteopenia and osteoporosis, conditions characterized by weakened bones and an increased fracture risk. Notably, astronauts often experience significant losses in bone mass while in space, particularly in the hip and spine regions.[36] Understanding these microgravity-induced spinal changes is crucial for surgical planning. Surgeons must anticipate that astronauts might present with degenerative changes or injury postflight, and that bone fragility or muscle atrophy could impact surgical stability and healing.

### Challenges in Spine Surgery After Extended Time in Space

Performing spine surgery on individuals who have spent extended periods in space presents unique challenges that require innovative solutions and adaptations to current guidelines to ensure safe and effective procedures. These challenges stem from logistical constraints, altered biomechanical behavior, and resource limitations inherent to space missions.[6,37]

The rigorous planning and stringent scheduling of space missions offer limited windows for medical interventions, necessitating the alignment of surgical procedures with mission timelines, crew availability, and operational constraints.[27,38,39] The remote nature of space missions, coupled with potential delays in communication with mission control, exacerbates these logistical difficulties, necessitating a higher degree of autonomous decision-making and the possible reliance on telemedicine support.[40]

Prolonged exposure to microgravity significantly affects the biomechanical behavior of the spine, resulting in reduced gravitational loading, changes in tissue properties, and shifts in mechanical responses.[31,41,42] Additionally, deteriorated bone quality increases the risk of complications such as screw loosening or failure of spinal constructs, complicating surgical care. Surgeons may need to adapt their plans to accommodate altered tissue and intraoperative dynamics.[43] To address these complexities, precise instrumentation, advanced imaging techniques, and vigilant monitoring throughout procedures will be crucial in navigating the challenges posed by the absence of gravitational force.[40,44,45]

Anesthetic management in microgravity presents its own set of challenges. Traditional inhalational anesthesia is problematic in a closed spacecraft environment, as anesthetic gases can diffuse unpredictably and are difficult to scavenge in weightlessness.[22] A more promising approach is total intravenous anesthesia,[22] which avoids gas leakage issues; however, microgravity-induced fluid shifts and reduced blood volume can alter pharmacokinetics and drug efficacy. Securing the airway for general anesthesia requires restraining both the patient and the equipment to prevent movement and ensure stability. Endotracheal intubation must be performed with the patient and operator securely anchored to prevent the tube from dislodging. Special endotracheal tube holders are necessary to keep the tube in place during surgery. Regional anesthesia (nerve blocks) can mitigate some risks by avoiding intubation and minimizing cardiovascular depression; however, performing these blocks in microgravity is challenging due to the lack of gravitational reference points and the floating of both the patient and the ultrasound needle, which can complicate needle guidance.[46]

Additionally, microgravity affects intraoperative physiology. Due to the high surface tension of blood, cohesive fluid domes or streams adhere to the wound surface rather than dispersing as free-floating droplets.[47] Although these are typically manageable with sponges and suction, causing minimal obstruction in small surgical fields, larger or arterial bleeds produce high-velocity streams that pose a greater challenge in microgravity and require immediate control.[47] Altered fluid dynamics in microgravity also compromise drainage systems, as standard drains may clog or fail due to surface tension and capillary action resisting fluid flow, necessitating redesigned drainage systems such as shorter, larger-bore tubing or self-contained drainage units .[47] A sealed surgical enclosure has been proposed to further enhance visualization and prevent cabin contamination .[47] Hemodynamic regulation is also more precarious as astronauts often have blunted baroreceptor responses and diminished cardiac output after adaptation to microgravity,[48] raising concern for hypotension when surgical anesthesia is induced. These anesthetic and physiological challenges underscore that developing spine surgery capability for space is not solely about the surgical technique, but also about ensuring the patient's homeostasis can be maintained in a radically altered environment.

The constraints imposed by spacecraft, including limited spatial allowance, weight restrictions, and resource availability, pose substantial logistical challenges for conducting spine surgery.[43] Surgeons must operate within restricted workspaces with minimal access to equipment and supplies, necessitating continued innovation of compact, lightweight surgical instruments and the optimization of surgical workflows.[49,50] Current innovations include the development of an instrument called the spaceMIRA, a microwave-sized device that can mimic human movement using two different robotic arms. In February of 2024, the spaceMIRA successfully remotely simulated several surgical techniques on the International Space Station, representing an advancement in the current standard of surgery in space with implications for future space travel.[26] Further development and implementation of streamlined, space-efficient surgical tools and methods will likely be essential to overcoming the spatial and resource constraints in extraterrestrial environments; however, these advancements may be limited in scope due to costs and the limited demand for innovation.[51]

### Therapeutic Considerations for Spine Surgery

To protect astronauts' bone health during and after space missions, a multidisciplinary approach involving space medicine, biomechanics, and surgical innovation is essential.[20,52,53] Ensuring adequate intake of nutrients such as calcium, vitamin D, and proteins is crucial to counteract the bone demineralization and muscle atrophy induced by microgravity.[20,54] Nutritional strategies should focus on mitigating these effects. Regular exercise regimens, including resistance training, are also essential for stimulating bone growth and muscle strength, thereby reducing the risks of osteoporosis and muscle atrophy prevalent under microgravity conditions. A study by Leblanc et al. supports the peri-mission administration of alendronate and bisphosphonates to attenuate bone loss in the spine, hip, and pelvis, with significant implications for both preventative and surgical care.[18] Additionally, emerging pharmacological agents, such as receptor activator of nuclear factor kappa-B ligand (RANKL) antibodies and proteasome inhibitors, have shown promise in reducing bone resorption and promoting bone formation in microgravity conditions.[55] However, alterations in tissue healing processes due to microgravity-induced changes in cellular behavior[17,56] and reduced mechanical loading may impede surgical site healing.[15,16,57] Minimally invasive surgical approaches, including endoscopic and laparoscopic techniques, are preferred for their reduced tissue trauma and enhanced visualization capabilities.[45,58] The integration of these methods, alongside advanced robotic technologies, offers effective solutions that improve postoperative outcomes and recovery times, which are critical for astronauts fulfilling mission objectives.[40,59,60]

Beyond musculoskeletal rehabilitation, clinicians must manage the broader physiological changes associated with spaceflight during the postoperative period. Fluid shifts due to microgravity, such as cephalic fluid redistribution, can contribute to facial edema and potentially increase intracranial pressure.[14,61,62] When returning to Earth's gravity, this can reverse and lead to orthostatic intolerance. There is also evidence that microgravity may alter the endothelial glycocalyx, the protective carbohydrate layer on blood vessels that regulates permeability.[63] Disruption of the glycocalyx could exacerbate fluid leakage into tissues and impair vascular function during recovery. As a result, astronauts might experience more tissue edema or difficulties in volume regulation after surgery.

Moreover, long-duration missions lead to cardiovascular deconditioning, characterized by reduced plasma volume, cardiac muscle atrophy, and diminished baroreflexes.[48] In the immediate postflight period, astronauts often suffer orthostatic hypotension.[4,48] A postoperative patient with such issues is at risk for fainting or inadequate perfusion of the spinal cord when ambulating. Postoperative care protocols should therefore include cardiovascular support, such as gradual reambulation under monitoring, fluid loading, compression garments, or lower-body negative pressure to counteract orthostatic effects.[4,48] Close monitoring of hemodynamics, in addition to neurological status, is critical.

Effective postoperative care is vital in managing microgravity-induced alterations in the spine and musculoskeletal system. Rehabilitation programs that focus on muscle strengthening, range-of-motion exercises, and proprioceptive training are essential for promoting spinal stability and functional recovery, while mitigating the risk of musculoskeletal deconditioning in astronauts.[64] Continuous monitoring of postoperative outcomes is crucial, as the deconditioned spine and altered physiology may increase the risk of chronic pain, delayed wound healing, and impaired neurological function.[15,19]

Interventions to enhance tissue repair may include optimizing nutritional intake to ensure adequate protein and vitamin levels, coupled with pharmacological agents that promote collagen synthesis and wound healing.[65] Similarly, fluid and blood pressure management, and possibly pharmacological support to protect vascular integrity, are warranted. Employing robust telemedicine support is helpful for effective postoperative recovery management and promptly addressing complications that may arise following space missions.[66]

### Adaptations and Innovations in Spine Surgery for Astronauts in Space

Addressing the challenges of maintaining spinal health in space necessitates the integration of advanced imaging technologies and surgical techniques, including remote surgery, augmented reality, and robotic systems. These innovations are essential to ensure the safety and efficacy of surgical procedures performed on astronauts who may require intervention before returning to Earth. One promising strategy involves using image-guided navigation systems that combine real-time imaging data with precise location tracking to enhance surgical accuracy while minimizing radiation exposure. This is particularly advantageous considering that astronauts are already exposed to elevated baseline levels of radiation, which can exacerbate the residual effects of prolonged space exposure.[67]

MRI offers high-quality three-dimensional visualization of anatomical structures without the use of ionizing radiation. Despite challenges such as strong static magnetic fields and confined spaces, MRI-compatible robotic systems are being developed to assist with intraoperative MRI. This real-time guidance is crucial for patients whose musculoskeletal systems have been affected by long-duration spaceflight.[68] Additionally, intraoperative ultrasound is valuable due to its cost-effectiveness, efficiency, and real-time visualization capabilities. Intraoperative ultrasound is particularly useful for visualizing soft tissues and pathologies during surgery, especially in scenarios involving intradural lesions that microgravity-induced changes may exacerbate.[69,70]

Augmented reality could aid visualization and navigation during spine surgery by allowing surgeons to view three-dimensional anatomical structures directly while observing the surgical field. This technology improves accuracy and reduces operating time, making it particularly beneficial for addressing anatomical changes resulting from prolonged space habitation.[71] This adaptation is particularly relevant for the unique challenges astronauts face after extended missions.[72] Robotic-assisted surgery provides enhanced precision and control, which is crucial for patients who have experienced the musculoskeletal impacts of microgravity.[73] Robotic systems improve surgical accuracy and dexterity, reduce surgeon fatigue, and can incorporate advanced imaging technologies such as intraoperative CT or fluoroscopy for real-time navigation.[21,24,25] Platforms like the da Vinci Surgical System and the Mazor Robotics Renaissance System, which have demonstrated success on Earth, hold promise for adaptation to the unique challenges caused by spaceflight.[40]

**Future Directions and Recommendations for Spine Health**

Interdisciplinary cooperation among neurosurgeons, engineers, and space scientists is crucial for refining surgical techniques and technologies tailored to the needs of astronauts following long-duration space missions. Ground-based analogs, such as bed rest studies or innovative analogs like hyperbuoyancy flotation, can provide insights into spinal unloading and reloading mechanisms.[74] Continued investigation in this focus informs the development and implementation of effective countermeasures to spinal muscle atrophy and spinal instability during space missions. Evaluating the efficacy of regular axial loading exercises is crucial for maintaining spinal health.[53]

Technological innovations, including intraoperative image guidance, robotics, and augmented reality, have significantly enhanced spine surgery on Earth but require rigorous validation for application in space. Investment in advanced neurosurgical technologies, such as machine learning, augmented reality, and virtual reality, is pivotal for enhancing diagnostic accuracy, reducing complications, and improving surgical outcomes. Training programs using these technologies can equip surgeons to address the unique challenges of spine surgery on astronauts, thereby enhancing surgical skills and minimizing the risk of complications. Wearable sensors have been proposed as a solution to monitor spinal and muscle activity under microgravity conditions, providing longitudinal data on the efficacy and reliability of interventions in space.[75,76] Despite extensive advancement of technology, a more intentional evaluation of its use in a microgravity environment is required to mitigate potential risks.[50] Additionally, policies and infrastructure must support the provision of surgical care during and after space missions, ensuring the availability of trained medical personnel, necessary surgical equipment, and telemedicine capabilities for remote guidance and support.[22] Addressing these domains will enable policymakers, space agencies, and healthcare providers to advance spine surgery capabilities for astronauts more effectively, ultimately enhancing their health and safety during and after space missions.[20]

**Ethical and Legal Implications of Space Healthcare**

Legal frameworks and regulatory standards are pivotal in ensuring patient safety, maintaining medical ethics, and addressing liability issues in space medicine. International space law, including key treaties like the Outer Space Treaty and the Agreement on the Rescue of Astronauts, delineates the principles that govern space activities, emphasizing cooperation, mutual assistance, and shared responsibility for astronaut health and safety.[77] However, as surgical interventions in space are contemplated, these regulations will need to evolve to address consent, autonomy, and liability in the off-Earth context.

National space agencies, including NASA, the European Space Agency, and Roscosmos, have formulated specific regulations that govern medical procedures in space.[78] These regulations encompass preflight assessments, in-flight care, and postflight monitoring, including medical standards that exist for low Earth orbit spaceflight. There also exists a medical checklist, written in both English and Russian, on the International Space Station for potential standard medical procedures, as well as a standard of care for the process of stabilizing and transporting a crewmember in case of injury or medical emergency.[79] As of December 2016, NASA's Office of the Chief Health and Medical Officer integrated a NASA procedural requirement (NPR 8900.1B) based on the framework of medical ethics developed by the Institute of Medicine's Aerospace Medicine and Medicine in Extreme Environments Committee in an effort to further expand guidelines governing medical ethics and procedures in space.[78] While the European medical ethics guidelines have not been publicly announced, agencies are striving to collaborate closely with regulatory authorities and medical experts to ensure adherence to safety and ethical standards during spaceflight.[80]

**Spinal Surgery in Space**

While spine surgery in space may be possible in the near future, there remain considerable challenges at present that have been presented by the existing literature. Lajczak et al. highlight several limitations of conventional manual surgical techniques in their review, finding major drawbacks in accuracy, size, and invasiveness of procedures, exposure to radiation, and surgical efficiency.[21] These challenges are further amplified in the setting of microgravity during space missions and may limit the application of conventional means to emergency or extremely narrow circumstances.[20,81] Robotic surgery could reduce these limitations and may be an effective solution for performing spine surgery in space.[21,25]

A unique challenge accompanied by using robotics surgery in space derives from communication delays between Earth and the space crew. Although the speed at which information travels may be negligible in low Earth orbit, missions that span beyond this region are subject to latency or communication delays that range from minutes to hours, compromising the performance of telesurgery and telemonitoring.[40] The limitations of current technology suggest that long-duration space missions may require flight surgeons to accompany the crew to provide definitive care for injuries that exceed the training and technical capabilities of the crew medical officer, a crewmember without a medical background who has received 60 h of medical training.[40,82] Others have proposed artificially intelligent autonomous systems capable of performing a selection of preset surgeries to assist the crew and crew medical officer.[51,60,83] Although the literature on the topic of robotics surgery for space applications has emphasized a completely autonomous system with cognitive capabilities for active decision-making,[51,60,83] a fully autonomous and cognitive system has not received FDA (Food and Drug Administration) clearance nor, to our knowledge, has been developed.[84] Such an ambitious feat is beyond what is capable with today's technology; however, augmenting the surgical methods to accompany human decision-making through the use of preplanned robotics movements may fill the technological gap until these advanced surgical systems are developed. While patient-specific prerecorded surgeries may be feasible, it would require a perfect overlap of the surgical field in the prerecorded robotics surgery and the surgical field erected during the mission. Moreover, it is possible that with high-precision scans of the affected crewmember and an even more robust virtual simulation system, surgeons may be able to perform surgeries on a virtual copy of the patient before sending the virtual recording to the flight crew, who then prepare the surgical robot and the patient to replay the surgery from space as if it was occurring in real-time. This, of course, would require an extensive and highly delicate calibration cycle to minimize the risk of invading unintended tissue or bone during spine surgery.

The spaceMIRA device represents an advancement in the current status of technology and surgical abilities in space.[26] While there were limitations stemming from the signal latency, the spaceMIRA was able to complete several basic surgical tasks. Regarding the future of spinal surgery, a device similar to the spaceMIRA with the additional ability to perform the surgery in augmented reality portrays potential future devices that could be used to perform spinal surgery in space. The spaceMIRA, in this example, would be classified as a remote-controlled robot, in contrast with an on-site-controlled robot that would have to be controlled on the International Space Station.[85] Using remote-controlled robots in surgery provides an opportunity for a myriad of different surgeons to perform a multitude of surgeries, including spinal surgeries, based on the needs of the patient in space. Furthermore, robots are currently in use during spine surgery and relocating a similar robotic device to the International Space Station could provide further opportunities and new directions for spinal surgery in space.

Effective spine surgery during and after space travel requires a comprehensive approach to address the physiological changes induced by microgravity. Prolonged exposure significantly affects bone density, muscle mass, and disc health, necessitating targeted interventions upon return to Earth. A holistic strategy that includes rehabilitation, pharmacological support, and surgical solutions is essential for maintaining spinal integrity. Notably, this review identifies novel methodologies, such as teleoperated robotic surgical systems, advanced imaging guidance, and augmented reality navigation, as promising avenues to enable safe spinal surgery beyond Earth. These technologies, alongside rigorous astronaut training and telemedical support, represent new frontiers in surgery and future directions of study that can mitigate the limitations imposed by microgravity. Continued research and innovation are crucial to overcoming these challenges and ensuring the safety and effectiveness of spine surgeries for astronauts. By developing space-adapted surgical techniques and supportive care protocols, we can protect the long-term health of astronauts. As we venture further into space, our commitment to astronauts' well-being will empower future missions, ensuring that those who lead humanity into the cosmos return intact and thriving.

## ACKNOWLEDGMENTS

*Financial Disclosure Statement:* The authors have no competing interests to declare.

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# A Streamlined Telepresent Video Platform for Aerospace Medicine

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**INTRODUCTION:** Improved video transmission is needed for telemedicine in austere or remote ground, maritime, and aerospace environments. A prototype compression algorithm named "V-CRAMMIT" (patent pending) streamlines medical images, improving bandwidth efficiency. This study evaluated the technology by assessing diagnostic designations made by medical clinicians using uncompressed vs. compressed video.

**METHODS:** An inventory of deidentified videos was selected from a library of recorded MP4 pulmonary ultrasound scans. Videos displayed four lung pathology conditions: Pneumothorax, Pneumonia, Pleural Effusion, and No Finding/No Pathology. Four videos were selected per condition, yielding 16 recordings compressed using V-CRAMMIT. Average file size reduction was 83%. A total of 20 ultrasound clinicians evaluated each video in both uncompressed and compressed format, presented in a randomized 32-trial sequence. In each trial, subjects selected one of the four pathology designations or an "Inconclusive/Unsure" designation. Trials were presented using a mouse interface and virtual dashboard displaying large-format video, the anatomic location of each scan, a replay button, and response buttons for the above designations. Accuracy, response time, and replay frequency were analyzed using repeated-measures ANOVA incorporating Video format (Uncompressed vs. Compressed) and Pathology (four levels) as independent factors.

**RESULTS:** Performance did not differ between video conditions: Uncompressed vs. Compressed trials showed no significant differences in accuracy, response times, or replays. Pathology imposed significant effects for all measures, with subjects making the most accurate (91% correct) determinations in Pleural Effusion cases.

**DISCUSSION:** Streamlined video afforded performance equivalent to standard video and could thus enable improved bandwidth efficiency for remote telemedicine settings.

**KEYWORDS:** video compression, telepresence, bandwidth efficiency, imaging.

**Beer JMA, Ng PC, Wlodarski DC, Tompkins J, Mock J, Mojica A, Clemons M. *A streamlined telepresent video platform for aerospace medicine*. Aerosp Med Hum Perform. 2025; 96(11):1008–1014.**

Telemedicine offers a means to improve medical outcomes and efficiency for providers who have limited resources or are situated in austere environments.[1] In a telepresent medical consultation, audiovisual medical information and guidance are exchanged between a local provider offering patient care and a medical specialist at a physically separate, possibly distant facility possessing greater resources.[2] Using telemedicine can offer new opportunities to deliver guided therapeutic care in remote settings[3,4] and support swifter interpretation of scans in emergency stroke care.[5] Telemedicine may improve logistical efficiency, with one study reporting that the need for medical evacuation in U.S. service personnel deployed in Iraq and Syria decreased 57% following implementation of telemedicine services.[6] This decrease yielded an estimated reduction of 328 evacuations/10,000 personnel/year, with an attendant savings of 1.27M USD/10,000 personnel/year in 2020.

Information exchange in telemedicine may be asynchronous, whereby audiovisual information is recorded and transmitted for evaluation later. Alternatively, when the need for

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This manuscript was received for review in March 2025. It was accepted for publication in July 2025.

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DOI: https://doi.org/10.3357/AMHP.6687.2025

consultation is urgent or specialized, information exchange may be synchronous, whereby communication between point of care and specialist occurs in real time, culminating in the most advanced form of telemedicine, which is a telepresent surgical interface.[7] In both asynchronous and synchronous information exchange, telemedicine depends on bandwidth and information throughput, with network limitations presenting logistical and security constraints. In the Hotker[4] study, failures of operability were attributed to reception conditions and transmission rate 69% and 59% of the time, respectively, and while commercial communication networks may seem to provide an adequate audiovisual platform, they often lose signal during teleconferencing without an obvious cause.[8] In the asynchronous realm, reduced bandwidth can limit the benefits of telemedicine by delaying consultant responses from a domain of seconds to one of hours,[6] while synchronous telemedicine can be hampered critically via latency, video jitter, and interruptions.[7] These findings indicate that video transmission must improve if it is to support triage and consultation in bandwidth-constrained conditions, particularly when synchronous communication is required. This need is expected to grow because future telemedicine requirements may emanate from environments that are progressively more hostile to continuous communication, including combat sites, remote field care locations, and ultimately space. Especially in this last arena, where signal delay and weakness are inherent, the potential consequences of interruption are calamitous and the need for bandwidth efficiency acute.

One way to address bandwidth problems is to reduce the quantity of information transmitted, either in each asynchronous exchange of "record/forward" files or throughout the continuous transmission inherent in synchronous telemedicine. This exploratory study was performed to evaluate the clinical effectiveness of a prototype compression algorithm called "Video-Compression using Robust, Adaptive, Multiple Methods and Innovative Techniques" (V-CRAMMIT) which streamlines video files used for medical imaging, reducing their size to speed transmission. V-CRAMMIT, which is the intellectual property of KBR, Inc., and is pending patent approval, offers the potential capability to transmit streamlined images with a fidelity equivalent to that of uncompressed video, yielding advanced bandwidth efficiency. While these gains had been indicated using engineering metrics, they have not yet been verified with human users, especially clinicians possessing expertise reading medical scans.

Here, V-CRAMMIT was deployed in a paradigm designed to emulate asynchronous delivery of medical video content that could be used for triage and diagnosis. A collection of video recordings of point-of-care ultrasound (POCUS) scans showing four different pulmonary pathology conditions was constructed. Recordings were then compressed using V-CRAMMIT. Clinicians with POCUS expertise reviewed recordings in both standard ("Uncompressed") and V-CRAMMIT ("Compressed") formats and were asked to identify the pathologies shown. The accuracy and speed of their assessments were recorded and compared across video formats and pathology conditions to determine whether V-CRAMMIT afforded equivalent performance. The study tested the hypothesis that the efficiency gains claimed using engineering metrics would generalize to clinical effectiveness: if clinicians identified pathologies as accurately and swiftly when they viewed medical scans in Compressed vs. Uncompressed format, this would indicate enhanced efficiency whereby V-CRAMMIT could support remote triage and diagnosis with a reduced demand for bandwidth. In military medical applications, this could yield a concomitant decrease in vulnerability to detection and attack.

## METHODS

The study protocol was approved in advance by the USAF 59th Medical Wing Institutional Review Board (#FWH20230093E). It was conducted under a waiver from Human Subjects regulation, including required informed consent, because it was determined to impose minimal risk: interventions were not invasive or stressful and datasets and scans were deidentified. The study comprised one test session lasting 30–45 min and was conducted across three sites in San Antonio, TX, including the 59th Medical Wing, University of Texas Health Science Center Emergency Ultrasound Division, and Brooke Army Medical Center.

### Subjects

A total of 20 volunteers (7 women, 13 men), ages 29–63 (mean 37.2 yr, SD 7.7 yr), enrolled following e-mail or verbal recruitment. Pilot data were not available, so $N$ was projected from analysis seeking 89% power to detect a 0.75-SD (moderate) difference between Video conditions (alpha = 0.05, two-tailed). Subjects self-reported as licensed Doctor of Medicine (14), Doctor of Osteopathic Medicine (4), or Physician Assistant (2). All reported proficiency in medical image reading and completion of training or experience in pulmonary POCUS as part of their medical practice. Subjects provided demographic information, including specialty and experience, but names were not recorded. Subjects were not required to show credentials because the study was approved as an exempt procedure. Although the protocol required no informed consent documentation, subjects received a description of the procedure, including emphasis that they could withdraw at any time. Subjects were screened for near visual acuity of 20/30 or better. Of the subjects, 6 wore no vision correction, with 10 wearing spectacles and 4 wearing contact lenses.

Enrollment included an eight-trial practice block to familiarize subjects with the procedure. These trials included two examples of each of the four Pathology conditions described below. All practice videos were Uncompressed, so subjects would train on the format offering the most potential information density. This established "Uncompressed" as the default format against which the Compressed format would be compared. Practice trials depicted different patients from the videos used in the experiment, but otherwise resembled the experimental trials described in the Equipment and Procedure sections.

**Equipment**

V-CRAMMIT comprises an amalgam of video compression and precompression techniques to streamline images and videos while ensuring acceptable visual fidelity and adherence to standards. It optimizes compression by combining lossy and lossless precompression methods. It can be adapted to multiple video or image formats, to various network states (including loading and available bandwidth), and to users' specified display needs, including recipient display characteristics and area-of-interest circling. V-CRAMMIT includes a "Store & Forward" function which stores videos when a transmission network is inoperable or constrained, and automatically transmits when network availability recovers. Here, V-CRAMMIT was used to streamline 16 MP4 video files which were selected as described below. The original files and their streamlined versions comprised "Uncompressed" and "Compressed" stimulus sets, respectively.

A set of video sequences was compiled from a library archive of deidentified POCUS scans recorded and retained at Brooke Army Medical Center as part of a prior observational study of pulmonary case treatments. Patient Personal Identification Information links were destroyed after this earlier study, so the current study was considered secondary data review. Scans had been recorded in MP4 format using a Philips Lumify POCUS scanner (Koninklijke Philips NV, Amsterdam, Netherlands). Video sequences ranged from 3–8 s in duration and were recorded from various thoracic zones which differed in their frontal, lateral, and vertical location. Sequences were selected from this archive for assignment to four pulmonary pathology conditions: three that were judged to present distinctive pathology indicators—"Pneumonia with Consolidation" (PNA/C), "Pneumothorax" (PTX), "Pleural Effusion" (PE)—and one, "No Finding/No Pathology" (NF/NP), included to make clinicians consider the absence of pathology indicators in the scan. Each video was selected to be an exemplar of indicators for one of the pathologies (or their absence in "NF/NP" videos) and was cross-referenced with the original case's accompanying CT and patient release diagnosis (also deidentified) as a criterion to confirm accuracy of the condition assignment and avoid situations where several pathologies were present.

Four different POCUS recordings were selected to represent each pathology condition, forming a stimulus set of 16 videos in Uncompressed format. These videos were postprocessed using V-CRAMMIT to generate a matching set of 16 Compressed sequences. V-CRAMMIT yielded reductions in file size ranging from 76–90% (mean = 83%). The complete set of 32 recordings including both Uncompressed and Compressed versions were intermixed and presented in random order in the test session, with each subject reviewing both versions of each recording. Random presentation was included to negate potential familiarity effects; subjects were just as likely to see the Uncompressed vs. the Compressed version of each patient scan first. The stimulus set was double-blind: no cues regarding the video format were available in any trial to either the subject or the investigator.

The study followed a repeated-measures design with two independent within-subject factors: Video format (Uncompressed vs. Compressed) and Pathology condition (PNA/C vs. PTX vs. PE vs. NF/NP, with each possible combination of factors presented in four different patient scans. The design offered a direct comparison of performance across each matched pair of sequences viewed in the two Video conditions.

The task was presented on a laptop (Dell, Round Rock, TX) using a mouse-actuated dashboard interface displayed on a 1920 × 1200, 60-Hz flat-panel screen (Sceptre, City of Industry, CA). The top portion of the dashboard was occupied by a display area where POCUS videos were presented (**Fig. 1**). The display panel was horizontal (letterbox) in format and occupied the width of the screen. Below the display area, a Play/Replay button was placed for initiating playback. In the lower left portion of the dashboard, a schematic anatomical diagram of the patient's torso was displayed to indicate where the scan had been performed, i.e., which thoracic zone (among zones 1–8) was being shown in the trial. Within this diagram, the scan zone was highlighted with a red circle. Below the Play/Replay button, five response buttons were placed. These included alternatives naming the four pathology conditions and a fifth button labeled "Inconclusive/Unsure" for the subject to indicate lack of clarity or confidence in any of the response choices. To minimize the possibility of anchoring or other positional biases, the response buttons' relative positions were shuffled randomly between trials.

**Procedure**

Subjects were informed that they would review pulmonary scans obtained from various anatomic locations, across a range of magnifications. Instructions named the four possible conditions that might be displayed in each trial, including NF/NP. Instructions stated that the scans would show a variety of appearances, but some trials might resemble one another since the same location could be used for multiple scans.

Upon initiation of the session with the Play/Replay button, the video played the first trial sequence once, after which the subject used the mouse to select the most appropriate response button. Subjects were instructed to treat each trial as an independent evaluation and respond as accurately and swiftly as possible, emphasizing accuracy. Subjects could use the Replay function as many times as desired. Once a response was entered, the next trial began. Accuracy in each trial was recorded as correct or incorrect. "Inconclusive/Unsure" responses were considered incorrect. Response time (RT) was recorded from the onset of the video until the selection of a button. Number of Replays was also recorded.

**Statistical Analysis**

Performance was assessed using Percent Correct, RT, Number of Replays, and frequency of "Inconclusive/Unsure" responses. Dependent metrics were analyzed using JASP Version 0.19.0 (University of Amsterdam, Netherlands). Two-way repeated-measures ANOVA was performed incorporating Video format and Pathology condition as independent factors with two and four levels, respectively. Where main effects emerged from the multilevel Pathology factor, post hoc contrasts were used using Bonferroni correction for

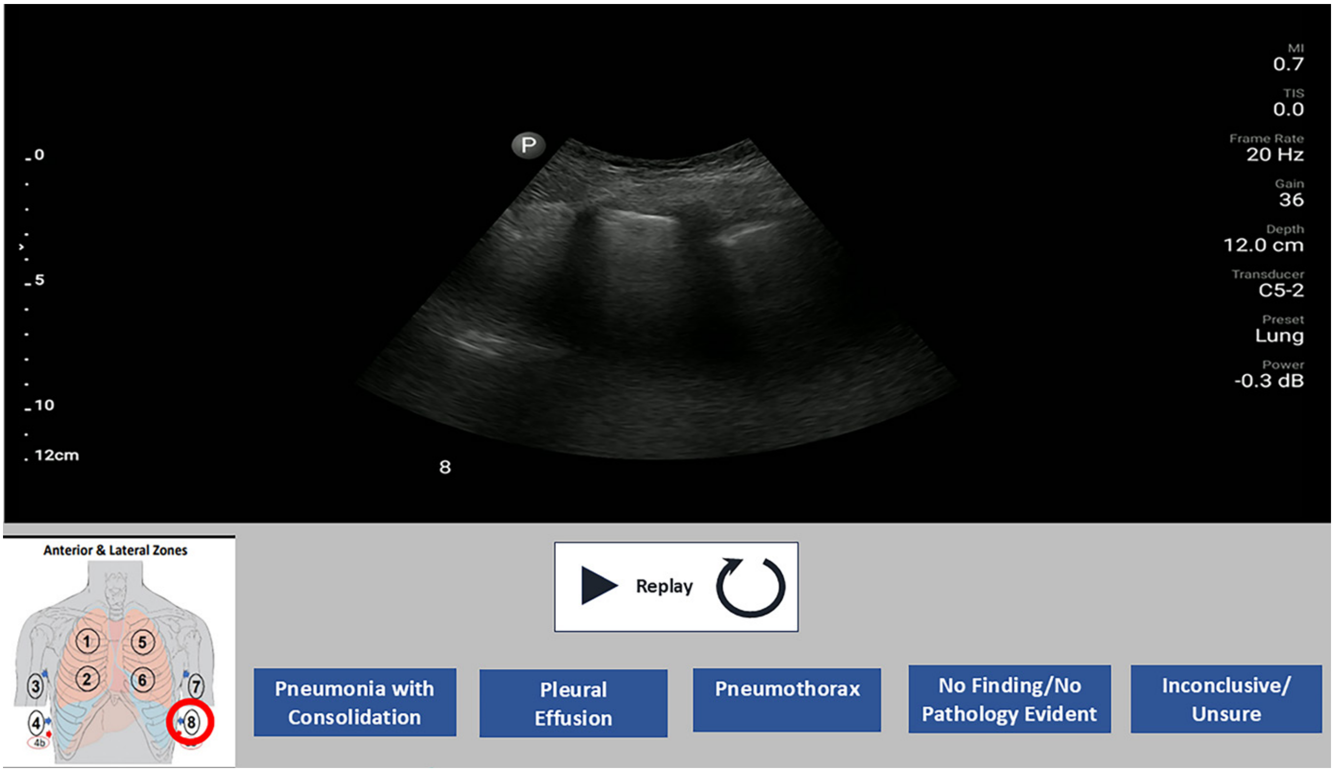


**Fig. 1.** Schematic view of interface dashboard including POCUS display panel, Play/Replay button, anatomical scan diagram (note red highlighting indicating that the scan shows Zone 8), and five response buttons. This view shows only a single frame and hence does not show the dynamic information available in the animated video of the test stimuli.

multiple comparisons. Greenhouse-Geisser adjustment was applied to degrees of freedom when the Mauchly test identified departures from sphericity.

## RESULTS

Video format did not influence Percent Correct significantly [$F(1, 19) = 2.27$, $P = 0.148$]. Pathology influenced Percent Correct [$F(3, 57) = 25.99$, $P < 0.001$] without significant interaction. The highest accuracy was recorded in PE trials, followed by PTX, NF/NP, and PNA/C. Post hoc contrasts identified more accurate designations in PE cases than in all other Pathologies ($P < 0.005$). PNA/C cases were identified less accurately than the other three Pathology conditions ($P < 0.001$), while accuracy did not differ significantly between PTX and NF/NP (**Table I** and **Fig. 2**).

Video format did not influence RT significantly [$F(1, 19) = 0.003$, $P = 0.956$]. Pathology influenced RT [$F(3, 57) = 16.84$, $P < 0.001$] without significant interaction. The longest and shortest mean RTs were recorded in NF/NP and PE trials, respectively. Contrasts identified shorter RTs in PE than in the other three Pathology Conditions ($P < 0.001$), with no significant differences among PTX, NF/NP, and PNA/C.

Video format did not influence Number of Replays significantly [$F(1, 19) = 0.037$, $P = 0.850$]. Pathology influenced Number of Replays [$F(3, 57) = 14.16$, $P < 0.001$] without significant interaction. Subjects used Replay less in PE than in other Pathology conditions ($P < 0.005$), with no significant differences among PTX, NF/NP, and PNA/C.

Video format did not influence number of "Inconclusive/Unsure" responses significantly [$F(1, 19) = 3.065$, $P = 0.096$]. Pathology influenced "Inconclusive/Unsure" responses [$F(3, 57) = 3.9$, $P = 0.013$] without significant interaction. Subjects responded "Inconclusive/Unsure" least frequently in PE, with contrasts identifying the difference with NF/NP as significant ($P = 0.004$).

**Table I.** Analyses of Dependent Metrics.

| | VIDEO FORMAT | | | PATHOLOGY | | | VIDEO FORMAT × PATHOLOGY | | |
|---|---|---|---|---|---|---|---|---|---|
| DEPENDENT VARIABLE | *F* ratio | *P* | $\eta^2$ | *F* ratio | *P* | $\eta^2$ | *F* ratio | *P* | $\eta^2$ |
| Percent Correct | $F(1, 19) = 2.27$ | 0.148 | 0.107 | $F(3, 57) = 25.99$ | <0.001 | 0.578 | $F(3, 57) = 1.415$ | 0.248 | 0.069 |
| RT (All Responses) | $F(1, 19) = 0.003$ | 0.956 | 0.0002 | $F(3, 57) = 16.84$ | <0.001 | 0.470 | $F(2.018, 38.335) = 0.412$* | 0.667 | 0.021 |
| Number of Replays | $F(1, 19) = 0.037$ | 0.850 | 0.002 | $F(3, 57) = 14.16$ | <0.001 | 0.427 | $F(2.063, 39.197) = 0.306$* | 0.745 | 0.016 |
| Unsure Responses | $F(1, 19) = 3.065$ | 0.096 | 0.139 | $F(3, 57) = 3.900$ | 0.013 | 0.170 | $F(3, 57) = 2.298$ | 0.087 | 0.108 |

$N = 20$. Parameters include *F* ratio, exact *P*-value, and effect size. Departures from sphericity (indicated by *) triggered Greenhouse-Geisser correction of degrees of freedom.
RT: reaction time.

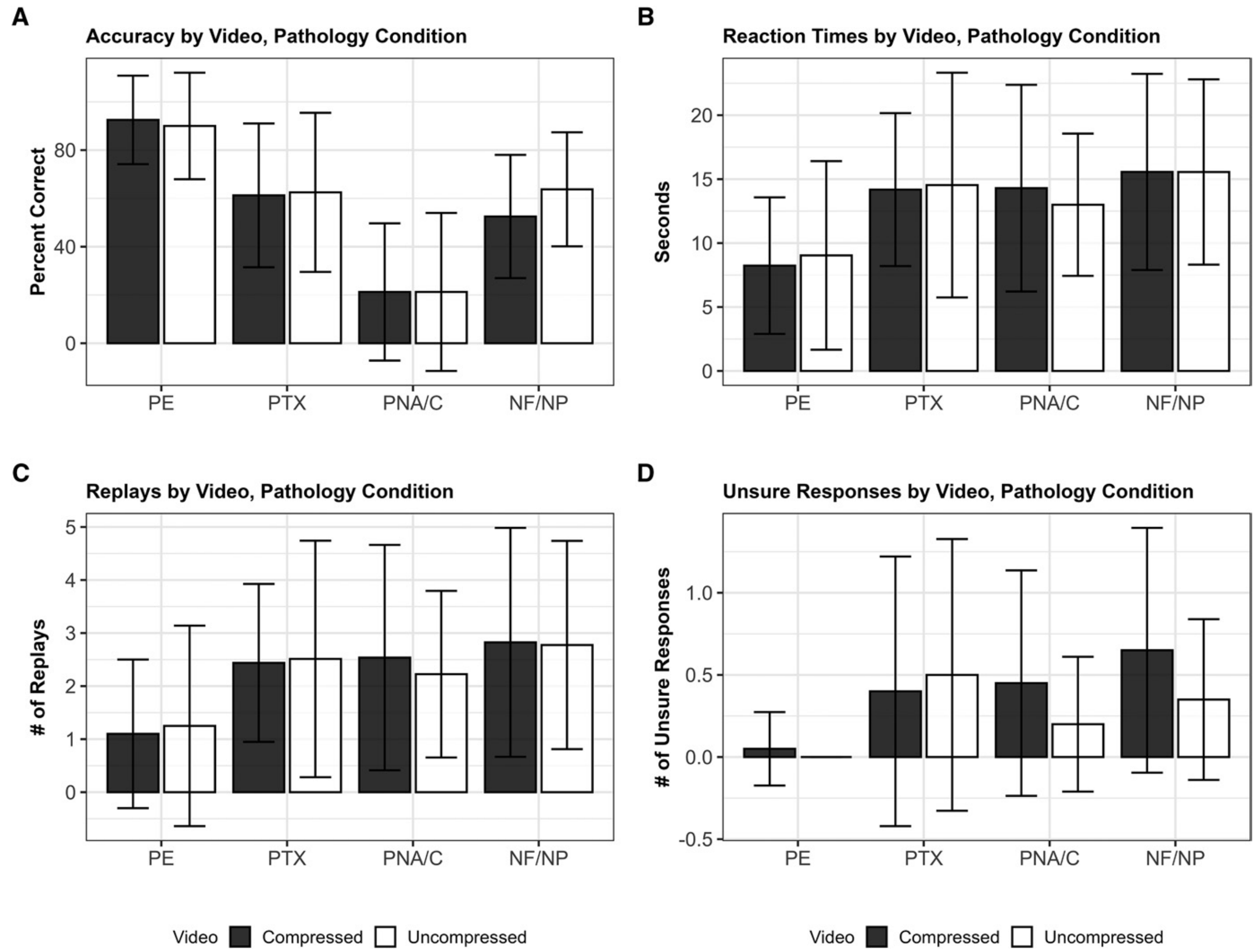


**Fig. 2.** Mean values for A) percent correct, B) reaction times, C) number of replays, and D) frequency of "Unsure/Inconclusive" responses, separated by video format and pathology condition. Error bars represent standard deviations. "PE" = pleural effusion; "PTX" = pneumothorax; "PNA/C" = pneumonia with consolidation; "NF/NP" = no finding/no pathology.

## DISCUSSION

The study compared subjects' designations of lung pathology reviewed using POCUS scans recorded with vs. without video compression. Percent Correct and RT means did not indicate significantly lower accuracy or delayed decisions when using Compressed vs. Uncompressed video. The absence of main effects for Replay and "Inconclusive/Unsure" metrics indicates that subjects were not discernibly less confident reviewing trials displaying Compressed videos either. These findings were observed without significant interaction from Pathology condition, suggesting that video streamlining did not precipitate additional error vulnerability that was specific to any single pathology. Findings are consistent with the hypothesis that, in this context, clinicians designated pathologies as accurately, swiftly, and confidently using streamlined vs. uncompressed video.

The ability to transmit telehealth images efficiently from remote locales, from aerospace or deep space environments, or in deployed austere situations such as military operations or disaster relief, conveys immense potential benefit. This capability expands access to professional medical expertise and thereby improves quality of care in such locales. In addition, the findings indicate a potential security benefit for deployed military medical personnel whose electromagnetic emissions could be exploited by hostile signals intelligence: increased bandwidth efficiency reduces and shortens targeting vulnerability.

The Pathology condition manipulation identified PE as the condition yielding best performance in this environment. With Percent Correct—the most important performance metric since it assesses clinical accuracy—post hoc contrasts suggested that, in this viewing environment, the visual indicators of excessive pleural fluid were particularly salient and unambiguous compared with other conditions. Conversely, the less accurate performance obtained in PNA/C trials indicates that observable markers for this pathology were less salient and reliable here. RT, Replay, and "Inconclusive/Unsure" metrics also indicated that PE trials yielded the fastest, most confident designations.

This paradigm was designed to evaluate the clinical utility of a video algorithm and was not intended to be comparable to a comprehensive medical evaluation in its diagnostic accuracy. Clinical lung ultrasound studies have yielded sensitivity values of 86% for pneumothorax[9] and 93–94% for pneumonia and pleural effusion,[10,11] which are higher than the Percent Correct means obtained in three of our four Pathology conditions. Medical diagnosis is complex and requires more tools than a review of a single scan lasting a few seconds, so it is not surprising that overall accuracy fell below 100%, especially considering that in each trial, subjects must make a speeded multiple-choice categorization without clinical context information. While the review of recorded scans emulated some aspects of an asynchronous medical communique, this passive viewing paradigm limited decision-making since it denied subjects the opportunity to direct the scan. The only aspect of review subjects could control was number of replays, which limited the visibility of markers to what was "canned" in the recording. The solution for this is to afford clinicians the opportunity to request or generate their own exploratory scans and, for this purpose, an enhanced version of V-CRAMMIT is under development to afford continuous transmission of streamlined video for telemedicine in real time.

We note that the lower accuracy in PNA/C trials contrasts with relatively high diagnostic sensitivities recorded in clinical studies.[11,12] It is possible that the scans presented here represented nonoptimal locations for viewing pneumonia markers, or that these markers were particularly vulnerable to the impediment of passive viewing.

A potential limitation of the study concerns the repeated presentation of each case in order to include both formats. This design was used to enable direct comparison of subjects' evaluation of stimuli varying only in Video format, at the cost of potential learning effects, which might have contributed data noise. This was addressed by instructing subjects that they would see multiple scans from the same anatomical zone and by using random presentation order to balance potential learning effects between formats.

While it is not claimed that the lack of significantly reduced accuracy and speed in Compressed trials demonstrates unequivocally that streamlined video yields performance equal to uncompressed video, these initial findings are encouraging and motivate further validation of the V-CRAMMIT algorithm. Follow-on studies should confirm its effectiveness in a larger sample of clinicians and include more rigorous screening for medical specialization. (Although deidentified, self-report-based screening reduced recruiting stress, it might have increased variability in subjects' ultrasound proficiency.) Future investigation should use a variety of image types, including more data-dense formats such as DICOM, where V-CRAMMIT could yield pre-to-post processing file size gains up to 50:1 (compared to the 4:1 ratio obtained here with MP4 files, which already incorporate some compression and might not be clinicians' preferred format). The next planned validation phase will incorporate the streaming application, currently in development, to afford video telepresence in real time. The final empirical goal of this technical development program will be to compare the effectiveness of clinical diagnoses performed using uncompressed vs. compressed video formats in an environment where data bandwidth is explicitly constrained. In this case, streamlined video could offer the potential not merely to match the performance of uncompressed video, but to surpass it.

## ACKNOWLEDGMENTS

This study was completed with the sponsorship of USAF 59th Medical Wing Restoral Program and the logistical support of the Pulmonology Department of Brooke Army Medical Center (BAMC), who provided the archive of POCUS video recordings. It was approved as an exempt protocol by the 59th Medical Wing Institutional Review Board in compliance with applicable regulations governing the protection of human subjects. The authors are grateful to the faculty and fellows of the University of Texas Health Science Center San Antonio Department of Emergency Medicine Ultrasound Division and physicians from the BAMC Anesthesiology Department for their generous participation in the study. Savannah Chavez, M.D. (UT Health Science Center San Antonio) and Kayla Knuf, M.D. (BAMC Anesthesiology Residency Program) were particularly helpful in reviewing the study methods and organizing participation of volunteers from their respective institutions. Robert Gerhardt, M.D. (DHA Director of Trauma and Clinical Care Research – 59th Medical Wing Science and Technology Office) contributed subject matter expertise regarding telemedicine applications and military medicine in austere environments. Brittany Swiger Daley and Marisol Resendiz, Ph.D., facilitated navigation of the POCUS video library at the BAMC Pulmonology Department. Zeynep Deligonul (University of the Incarnate Word School of Osteopathic Medicine) contributed to the cataloguing of video sequences. Samantha Adler, Ph.D., contributed literature research in the proposal phase of the study.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of KBR, the University of Texas Health Science Center, Brooke Army Medical Center, the U.S. Air Force, the Department of Defense, or the U.S. Government. No Federal endorsement of the views, procedures, or products described herein is intended.

The V-CRAMMIT technical concept comprises intellectual property of KBR, the employer of five co-authors of this paper. V-CRAMMIT is currently patent pending.

*Financial Disclosure Statement:* Jeremy Beer, Dan Wlodarski, Jenny Tompkins, Jeffrey Mock, and Andrew Mojica are employed by KBR, which possesses the intellectual property rights to the V-CRAMMIT technical concept. The other authors have no competing interests to declare.

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# Spatial Disorientation Event During Flight Due to Proposed Reverse-Dip Visual Illusion

Idan Nakdimon; Barak Gordon



**BACKGROUND:** Spatial disorientation is a leading nontechnical cause of fatal military aviation accidents, triggered by insufficient or misleading cues mainly from the visual and vestibular systems. Spatial disorientation accounts for 20–38% of fatal military aviation accidents, but case reports describing specific illusions during actual flight are rare.

**CASE REPORT:** On a clear night, an aerial refueling tanker was cruising at 16,000 ft (4877 m), while an F-15I fighter aircraft was 3 mi behind and 971 ft (296 m) below. About 100 s before a near collision, the fighter pilot switched to Air-to-Air mode, displaying the distance and speed difference to the tanker via a Target Designator box on the Head-Up Display. However, the crew did not realize they were accelerating toward the tanker [from 597–663 ft $\cdot$ s$^{-1}$ (182–202 m $\cdot$ s$^{-1}$)] or climbing by 738 ft (225 m). The two aircraft came within 49 ft (15 m) of each other before the navigator noticed the tanker and initiated a roll to the left.

**DISCUSSION:** The dip illusion occurs when a pilot flying in trail attempts to maintain the image of the lead aircraft in a fixed position on the windscreen as separation increases, which can lead to unintentional descent. In this case, we propose a "reverse-dip" illusion. The fighter crew was unaware they were closing in on the tanker, causing the Target Designator box to rise in the Head-Up Display. The pilot instinctively pulled back on the stick to maintain the box's position, resulting in an unintentional climb. Recognizing how such illusions develop in flight is essential to reducing future risks.

**KEYWORDS:** aircrew, aviation accident, formation flying, orientational cues, work overload.

**Nakdimon I, Gordon B. *Spatial disorientation event during flight due to proposed reverse-dip visual illusion*. Aerosp Med Hum Perform. 2025; 96(11):1015–1018.**

Situational awareness for military aircrew involves a correct understanding of various conditions, including the tactical environment, location, weather, weapon capabilities, and is affected by the aircrew member's mental state and spatial orientation. When a pilot loses awareness of their position, attitude and motion relative to the Earth's surface, this leads to spatial disorientation (SD), a specific form of situational awareness loss.[1] During flight, the spatial orientation of an aircrew is primarily influenced by the interplay between the visual, vestibular, and proprioceptive systems, with the visual and vestibular systems being the dominant contributors.[2,3] Insufficient or misleading cues perceived by these two systems can create illusions that may lead to SD events during flight.[4]

SD events can be classified into several types. First, based on the physiological mechanism that causes the event, whether it results from a visual illusion, a vestibular illusion, or insufficiently perceived orientational cues due to the aircrew's attention being focused on other aspects of the flight rather than the aircraft's spatial position.[1] Second, based on the component of the aircraft's spatial location that is misperceived by the aircrew, whether it is the aircraft's attitude, its position (including altitude), or its change in motion.[1] Third, the recognition status of the event during its occurrence. Type 1 is an unrecognized event, where there is a discrepancy between the aircrew's perceived spatial location and the actual location of the aircraft. This is the most common type of recognition status classification, accounting for 80–85% of cases, and it has the greatest impact on the severity of the event.[5] Type 2 refers

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This manuscript was received for review in February 2025. It was accepted for publication in July 2025.

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DOI: https://doi.org/10.3357/AMHP.6656.2025

to a recognized status, in which the aircrew notices a conflict between their perception of the aircraft's spatial state and what the flight instruments indicate. Type 3 is incapacitation, in which the illusion is so severe that the aircrew is unable to correct the aircraft's spatial position due to overwhelming sensory sensations.[1]

SD is the main nontechnical cause of fatal military aviation accidents. Several studies and reports have examined this issue in the U.S. Air Force, U.S. Navy, and Royal Air Force. Between 1983–2017, SD was identified as the primary cause in 20–38% of all fatal military aviation accidents.[2,3] This data correlates with the numbers from the Israeli Air Force (IAF), where SD was responsible for 27% of fatal accidents between 2000–2024. In addition to fatal aviation accidents, there have also been several severe, nonfatal incidents attributed to SD.

Most studies investigating SD have been surveys that assess the incidence of accidents and the rates at which pilots report experiencing disorientation, or experiments using flight simulators to induce various illusions. However, there are very few case reports that describe the occurrence of a specific illusion during actual flight, explain the flight conditions that triggered it, and analyze the underlying mechanisms. One such example, which took place in a simulator rather than in a real flight, is "The Giant Hand Illusion experienced on a simulator".[6] In the present case report, we describe an unusual visual illusion that occurred during flight.

## CASE REPORT

At 19:30 on a clear night in May 2019, a Boeing 707 acting as an aerial refueling tanker took off and established a cruising altitude of 16,000 ft (4877 m) above mean sea level. The crew, following standard training protocols, was positioned to await contact from multiple fighter aircraft, which were required to approach and establish communication before the refueling procedure could begin.

At 20:13, approximately 7 min before the near collision, an F-15I took off with a highly experienced crew for a refueling training mission. The F-15I, operated by the IAF, is a dual-seat ground attack aircraft based on the F-15E, a U.S. multirole strike fighter derived from the McDonnell Douglas F-15 Eagle. The IAF operates the F-15I with unique avionics systems.

Starting 2 min after the F-15I took off and continuing for the following 3 min, the crew attempted to repair a failure in the navigation pod. During this time, the crew experienced communication overload on the radio channel and had difficulty determining the spatial location of the refueling aircraft. Despite several attempts to locate it using the Global Positioning System, the lack of clarity created an unusual workload that impaired the crew's ability to perform necessary pre-refueling tasks. As a result, the pilot failed to switch the avionics master mode from Navigation to Air-to-Air mode, as required prior to refueling. At 20:18, the fighter aircraft's crew noticed the refueling tanker crossing in front of them in the opposite direction and subsequently performed a turn to follow it at the required distance.

According to IAF standard practice for refueling missions, the fighter aircraft is required to maintain a horizontal distance of 3 mi and a vertical distance of 1000 ft (305 m) behind and below the refueling tanker. The separation must be maintained until radio communication contact is established and the tanker crew gives approval to initiate the refueling procedure. At 20:19, approximately 100 s before the near collision, the fighter aircraft was 3 mi behind the refueling tanker, at an altitude of 15,030 ft (4581 m), which is 970 ft (296 m) below the refueling aircraft, and traveling at a speed of 350 kn ($180 \text{ m} \cdot \text{s}^{-1}$).

At that point, the fighter pilot switched the master mode to Air-to-Air mode, which enabled the display of the distance to the refueling tanker and the speed difference between them. This data was simultaneously presented on the Head-Up Display using the Target Designator (TD) box feature. The TD-box is a graphical display that shows target information, including not only the location of the target but also its relative motion. As a result, the TD box moves along the pilot's Head-Up Display field of view, representing the location and motion of the refueling tanker.

At this stage, the fighter aircraft's crew was attempting to communicate with the refueling tanker's crew. However, the refueling tanker crew was listening to a different radio channel than the one briefed to the fighter aircraft crew before the flight. As a result, they did not receive any response to their transmissions. Both the pilot and the navigator were therefore occupied with trying to find the correct radio channel. During this time, the fighter aircraft crew did not notice the trend of their aircraft closing in on the refueling tanker. In the 60 s before the near collision, the fighter aircraft accelerated from 354–393 kn ($182–202 \text{ m} \cdot \text{s}^{-1}$) without the crew's awareness. This acceleration caused the aircraft to close the distance to the tanker and triggered an unrecognized ascent, with its altitude increasing from 14,930 ft (4551 m) to 15,670 ft (4776 m) in the same 60-s window, an unintentional climb of 740 ft (225 m). The combination of both the accelerating closure and altitude climb caused the two aircraft to come within 197 ft (60 m) horizontally 2 s before the near collision, while the pilot estimated the distance to the tanker to be 1.5 mi (2414 m) and the navigator believed it was 3 mi (4828 m). At that point, the tanker crew gave the fighter aircraft permission to initiate the refueling procedure. The fighter aircraft's navigator saw the lights of the refueling tanker 1 s later and initiated a roll to the left, which occurred while the aircraft were only 49 ft (15 m) apart, as shown in **Fig. 1**.

## DISCUSSION

Dip illusion is a relatively common visual illusion in aviation, particularly during formation flying at night. In two separate surveys conducted by the U.S. Air Force and the Royal Netherlands Air Force, 22–38% of the pilots reported experiencing this illusion during flight.[7,8]

In their book *Fundamentals of Aerospace Medicine*, Davis et al. define this illusion as follows:

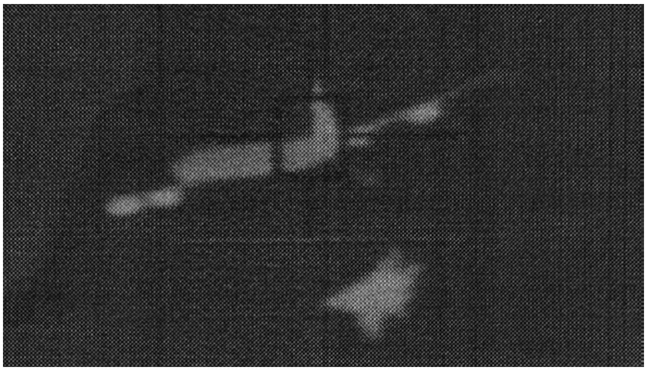

**Fig. 1.** The distance between the aircraft at the near collision event. The F-15 is below the refueling tanker. The distance between the two aircraft was 15 m.

*It occurs during formation flying at night, when one aircraft is in trail behind another. The pilot in trail places the image of the lead aircraft in a particular position on the windscreen and keeps it there. If the pilot is told to 'take spacing' (separate) to 10 km (5 nautical miles), for every 1 degree below the lead, the pilot is lower by 1.7% of the distance behind the lead. Therefore, if the pilot is 2 degrees below lead and keeps the image of the lead aircraft at the same spot on the windscreen all the way back to 10 km, the trailing aircraft will descend to 350 m (1100 ft) below the lead aircraft. In the absence of ambient visual orientation cues, the pilot cannot detect this large loss of altitude unless he or she monitors the flight instruments and may inadvertently 'dip' far below the intended flight path.*[1]

The near collision began with the aircraft crew not realizing they were getting closer to the refueling tanker, which likely resulted from the cumulative effects of high workload throughout the flight. This led the fighter crew to be unaware of their increasing velocity, indicative of degraded situational awareness. As a result, the crew did not know they were closing in on the refueling tanker. To keep the TD box in the same position relative to the windscreen, the pilot may have instinctively and unintentionally pulled back on the stick. While this action keeps the TD box steady, it also results in the aircraft climbing, leading the crew to believe they were maintaining a vertical distance of 1000 ft (305 m) from the tanker, when, in reality, they were closing the gap, as illustrated in **Fig. 2**.

We propose a subtype of the dip illusion, which will be referred to as the "reverse-dip" illusion. In the classical dip illusion, the aircraft descends due to the intended fixation of the position of the leading aircraft on the windscreen during increased distance between the aircraft. In "reverse dip", due to the same intention to fix the position of the leading aircraft on the windscreen (in our case the TD box) during decreasing distance between the aircraft, the trailing aircraft ascends (**Fig. 3**).

When examining the various classifications of SD events in this specific case, it can be categorized as a visual illusion that caused SD in the crew's perception of their position. The crew misperceived their own absolute altitude, inadvertently climbing from their assigned 15,000 ft (4572 m). This unrecognized climb led to a significant reduction in the intended vertical separation of 1000 ft (305 m) between the two aircraft. As the crew remained unaware of the deviation, the event fits the criteria for a Type 1: Unrecognized Event. This status held until 2 s before the near collision, when the navigator finally saw the refueling tanker and maneuvered the aircraft to avoid the collision by moving the stick.

It is crucial to understand the factors that contributed to the occurrence of this event: A) refueling during flight is a highly complex task that demands intense concentration; B) nighttime flight reduces the availability of visual cues necessary for proper orientation; C) work overload decreases the ability to follow the proper procedures for the primary flight tasks, thus increasing the likelihood of mistakes that can affect spatial orientation; and D) undefined and overlapping crew roles led both aircrew members to focus on resolving the radio channel issue, rather than having one of them monitor the flight



A B

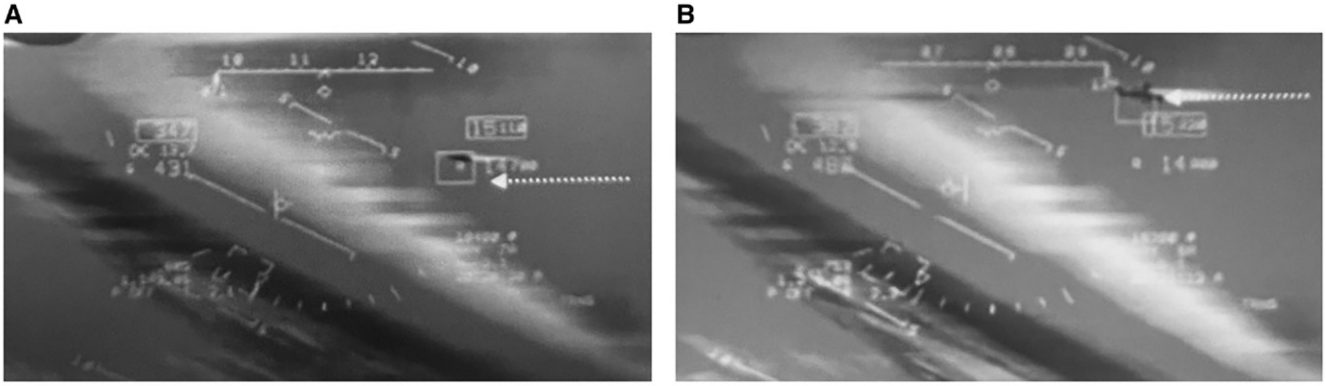

**Fig. 2.** Comparison of the TD-box's location on the Head-Up Display 40 s vs. 15 s before the near-collision. The TD-box is marked with a dotted arrow. A) Left image: the box is located near the lower altitude indicator; B) Right image: the box is located above the higher altitude indicator. The two altitude indicators are fixed in the Head-Up Display image.

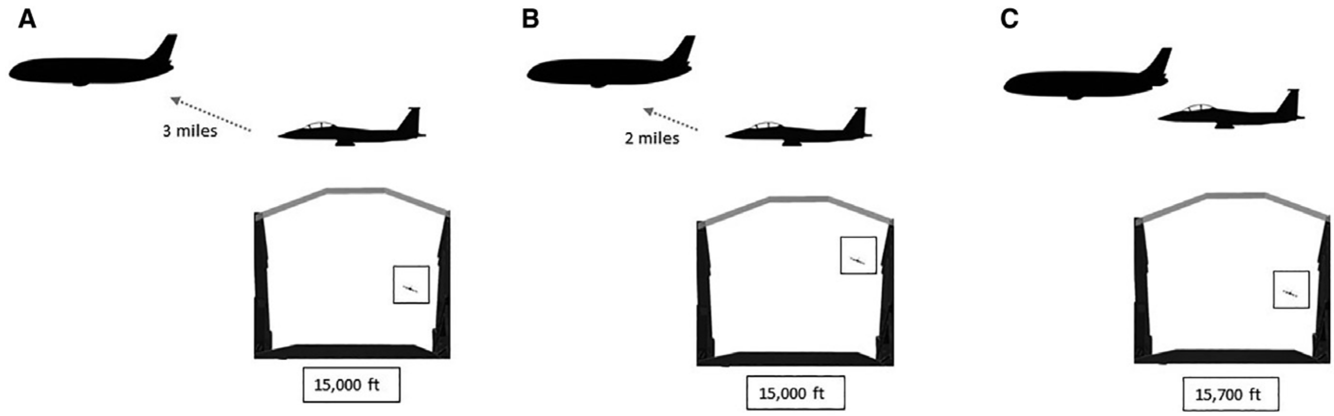


**Fig. 3.** Illustration of the Reverse-Dip Illusion. A) The F-15 is 3 mi behind the tanker, at an altitude of 15,000 ft (4572 m). The TD-box is located in the middle of the F15's windscreen. B) As the F-15 approaches the tanker, the TD-box moves higher in the windscreen. C) To return the TD-box to its original position on the windscreen, the F-15 pilot makes small adjustments to the stick, which brings the TD-box back to its original spot, but also causes the aircraft to ascend.

conditions. By understanding these factors as risk elements for SD events, we can better mitigate the risk of recurrence in the future. To that end, clearer procedural guidelines may be warranted for night aerial refueling. In dual-seat aircraft, one crewmember should be explicitly responsible for monitoring key flight parameters and calling them out at regular intervals. In single-seat aircraft, pilots should be trained to integrate routine instrument cross-checks even under high workload. These practices could reduce the likelihood of SD events and help counteract the conditions that lead to them.

## ACKNOWLEDGMENTS

*Financial Disclosure Statement:* The authors have no competing interests to declare.

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# Revisions to Spacecraft Maximum Allowable Concentrations for Acetaldehyde

Edward Spencer Williams; Cynthia Marie Tapia; Valerie Ryder



**INTRODUCTION:** Spaceflight Maximum Allowable Concentrations (SMACs) were previously developed for acetaldehyde in 1994. Acetaldehyde is commonly detected at low levels on the International Space Station, and at higher concentrations it might be expected to cause respiratory and eye irritation. Since 1994, numerous exposure studies in human volunteers and laboratory animals have deepened our understanding of potential effects associated with exposure to acetaldehyde vapor.

**METHODS:** A comprehensive literature search was conducted using principles of systematic review to identify toxicological data on acetaldehyde published since 1994. This search was supplemented by the use of summary sources for setting other safety values (i.e., safety values from the U.S. Environmental Protection Agency, occupational limits, etc.).

**RESULTS:** There were 13 primary toxicology studies identified in this exercise, prompting a re-evaluation of SMACs for all durations. Though the toxicity of acetaldehyde has traditionally been understood as a function of the metabolism of ingested ethanol, scientific publications after 1994 greatly increased our understanding of the toxicological effects of inhaling acetaldehyde vapor. In particular, the development of a physiology-based pharmacokinetic model generated data that was critical to the development of updated SMAC values.

**DISCUSSION:** The availability of newer data enabled the generation of SMACs for acetaldehyde that are markedly higher than the prior values. The shorter-duration SMACs increased by approximately 10-fold, and the longer-duration SMACs rose by twofold. The proposed values will appropriately protect astronaut health and performance and provide critical information for the design of life-support systems for low Earth orbit and beyond.

**KEYWORDS:** acetaldehyde, SMAC, spaceflight, inhalation toxicology, occupational health.

**Williams ES, Tapia CM, Ryder V.** ***Revisions to spacecraft maximum allowable concentrations for acetaldehyde*****. Aerosp Med Hum Perform. 2025; 96(11):1019–1023.**

Acetaldehyde is a volatile liquid with an odor that is fruity at low concentrations (with an odor threshold of 0.05 ppm) and becomes more pungent as concentrations increase. It is used as a chemical intermediate in the production of pesticides, pharmaceuticals, fragrances, flavors, and plastics. It is also produced naturally as a by-product of fermentation and combustion.[1] Acetaldehyde is frequently detected on the International Space Station at levels as high as 1 ppm (1.8 mg · m$^{-3}$). Historically, the concentration has averaged on the order of 0.1 ppm (0.2 mg · m$^{-3}$), but lower levels have been observed over the last several years. NASA uses Spaceflight Maximum Allowable Concentrations (SMACs) as environmental safety guideline values for crew exposures during spaceflight. The previous SMACs for acetaldehyde were set in 1994.[2] For durations of 1 h and 24 h during an off-nominal event, such as an unexpected hardware leak, concentrations of 12.5 ppm and 5 ppm, respectively, were deemed acceptable, as these levels were unlikely to cause more than minor, reversible effects over that period. Longer-term SMACs (7-d, 30-d, 180-d) were

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This manuscript was received for review in May 2025. It was accepted for publication in August 2025.

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DOI: https://doi.org/10.3357/AMHP.6726.2025

set at 2 ppm, which is not expected to cause any symptoms. A SMAC for 1000-d was not set.

## METHODS

A comprehensive search of the peer-reviewed literature was conducted using principles of systematic review to identify toxicological data on acetaldehyde published since 1994. This search was supplemented by the review and assimilation of summary sources that describe the development of other safety values [i.e., U.S. Environmental Protection Agency's (EPA's) interim Acute Emergency Guideline Levels (AEGLs) and Integrated Risk Information System (IRIS) assessment, occupational limits, etc.].

## RESULTS

The systemic toxicity of acetaldehyde is understood best as a metabolite of ethanol.[1,3,4] Ingested ethanol is metabolized to acetaldehyde, which is then converted to acetate (acetic acid) by aldehyde dehydrogenase (ALDH), which is then further metabolized to acetyl CoA by acetyl coenzyme A synthetase.[5] A genetic polymorphism of ALDH2 creates a well-characterized sensitivity to acetaldehyde; humans with this polymorphism may experience flushing, tachycardia, headache, nausea, and other effects after consuming even small amounts of alcohol. This polymorphism is much more frequent among persons of Asian heritage, appearing in as much as 50% of the population.[1]

Acetaldehyde is very volatile and highly reactive in the environment, and as such the most sensitive toxicological endpoint for acetaldehyde vapor is irritation of the eyes and upper respiratory tract followed by damage to olfactory epithelium.[1] These effects are likely mediated by a combination of general reactivity and mechanosensory effects, macromolecular cross-linking, and the increase in intracellular H+ (proton) levels as a result of ALDH-mediated detoxification of acetaldehyde.[5,6] At lower concentrations, effects are isolated to the upper respiratory areas, but as concentrations rise, effects will begin to occur deeper in the respiratory tract (including bronchiolitis obliterans and bronchoconstriction secondary to the release of histamine).[3] This threshold may be attributable to the capacity of ALDH to detoxify acetaldehyde, which can be saturated in laboratory animals at concentrations somewhere between 100–1000 ppm.[7] The relationship between the irritation effects and the effects on olfactory epithelium is unclear, but it is possible that irritation is a function of H + generation (generated by ALDH), while degeneration of olfactory epithelium is more a function of macromolecular binding by acetaldehyde as ALDH activity is saturated under higher doses.[5–7] A PBPK model for acetaldehyde indicates that the susceptible phenotype should not affect the local/irritation responses that arise after exposure to lower concentrations of acetaldehyde.[5] Interestingly, the model seems to predict that rats are more sensitive to the effects of acetaldehyde than humans, as the human equivalent concentration (HEC) of 50 ppm in rats is 67 ppm in humans. This, however, is contradicted by the analysis described in Dorman et al.[6] in which 50 ppm exposures in rats is projected to have an HEC of 12.5 ppm (using the same PBPK model).

In a study conducted by Silverman et al.,[8] groups of 12 volunteers (both male and female, but numbers not specified) were exposed to acetaldehyde vapor for 15 min at nominal concentrations of 25, 50, and 200 ppm. Several volunteers "strenuously objected" to the vapor at 25 ppm due to eye irritation, and the majority developed eye irritation at 50 ppm (though exposure concentrations were not analytically confirmed). Subjects reported nose or throat irritation at 200 ppm, and some experienced erythematous eyelids and bloodshot eyes at that concentration. However, a majority of the subjects declared that they would be willing to work an 8-h shift at 200 ppm acetaldehyde.

In a separate study, 14 healthy male volunteers were exposed to a series of irritating components of smog, including acetaldehyde.[9] The volunteers did not report eye irritation at 134 ppm acetaldehyde after 30 min, though it was reported after exposure to other aldehydes. Mild respiratory tract irritation was reported, however.

Muttray et al.[10] exposed 20 healthy male volunteers (age 20–35) to 50 ppm acetaldehyde for 4 h. The subjects were monitored for numerous clinical parameters and asked to provide subjective levels of irritation via questionnaire. On a scale of 0–5, the median score for subjective symptoms of irritation was 0. The study also did not detect any changes in expression of inflammatory markers or physiological functions of the upper respiratory tract.

Cassee et al. examined the irritation effects of three aldehydes (formaldehyde, acrolein, and acetaldehyde) individually and as mixtures.[11,12] Male Wistar rats were exposed to these aldehydes for 30 min to establish an irritation potency via decreases in breathing frequency,[11] and for 1 or 3 d to determine the effects on nasal epithelium.[12] Formaldehyde and acrolein were determined to be approximately 300 times more potent as irritants,[11] as measured by RD50 (i.e., 50% reduction in breathing frequency). Acetaldehyde caused minimal changes in nasal epithelium after up to 1500 ppm and 18 h of cumulative exposure; there is some dispute as to whether the effects were more significant after 18 h vs. 6 h. The authors note that the toxicological relevance of the observed effects at 18 h is "somewhat doubtful," as similar effects are observed in control animals.[12] When developing their interim AEGL-2 (acute emergency guideline level above which health effects are expected to occur in the general population), the EPA judged that these findings indicated that olfactory degradation is duration-dependent and not solely concentration-dependent. As a result, the AEGL-2 values were time-scaled from 6 h, with 1500 ppm as the point of departure.[1]

To determine the toxicological importance of the ADLH2 polymorphism, Oyama et al.[13] exposed wild-type and ALDH2 knockout mice to 125 and 500 ppm acetaldehyde for 14 d ($24 \text{ h} \cdot \text{d}^{-1}$). As expected, the ALDH2 knockout mice exhibited increased sensitivity to acetaldehyde exposure, with more frequent and more severe damage to the respiratory tract at both dose levels. This study served as the basis for the 24-h Emergency Exposure Guideline Level (EEGL) set by the U.S. Navy [125 ppm as the point of departure, including two uncertainty factors of 3 to account for extrapolation from LOAEL to NOAEL (lowest and no observed adverse effects level) and from mice to humans; final value 12.5 ppm].[3]

In a subacute study ($6\ h \cdot d^{-1}$, $5\ d \cdot wk^{-1}$, 4 wk), groups of 20 rats were exposed to 401, 941, 2217, or 4975 ppm acetaldehyde.[4] Growth retardation was noted in the 941 ppm exposure group and above, as well as histopathological changes in the nose. Tracheal and lung lesions were observed in the two highest exposure groups. A follow-up study used concentrations of 110, 150, or 500 ppm for 4 wk, with damage to olfactory epithelium noted at the 500 ppm dose level.[4] In a similar study, rats exposed to 243 ppm for 5 wk ($8\ h \cdot d^{-1}$, $5\ d \cdot wk^{-1}$) showed inflammatory reaction in the nasal cavity and perturbations of the olfactory epithelium.[14] A NOAEL of 390 ppm was identified in a 90-d study in hamsters exposed to 390, 1340, and 4560 ppm (390 h of cumulative exposure),[15] with similar findings of growth retardation, ocular and nasal irritation, and damage to nasal epithelium.

In rats exposed for up to 65 d ($6\ h \cdot d^{-1}$, $5\ d \cdot wk^{-1}$) to concentrations up to 1500 ppm, no effects were seen on weight gain and there were no other signs of systemic toxicity.[6] However, the study did observe inflammation, growth perturbations in respiratory epithelium, and loss of olfactory neurons at concentrations greater than 150 ppm, with an identified NOAEL of 50 ppm.

Woutersen et al.[16] exposed rats for 28 mo ($6\ h \cdot d^{-1}$, $5\ d \cdot wk^{-1}$) to acetaldehyde at 750, 1500, or 3000 ppm. Growth retardation and degeneration of the olfactory nasal epithelium was observed, along with nasal carcinomas and adenocarcinomas. The EPA has designated acetaldehyde as a probable human carcinogen, with sufficient evidence in animals based on this study and others.[4] The International Agency for Research on Cancer (IARC) concluded that acetaldehyde contributed to esophageal cancers observed in humans who were deficient in ALDH2, and its likely mode of genotoxicity is via sister chromatid exchange and/or the formation of stable DNA-protein crosslinks.[2]

Most safety values for acetaldehyde were developed before the 1994 SMAC was established (**Table I**). The EPA developed a reference concentration (RfC) using the Appleman et al. studies in rats.[4] This value included an overall uncertainty factor of 1000 to account for inter- and intraspecies differences, as well as extrapolation from subchronic data to a chronic application.[4] The EPA classifies acetaldehyde as a probable human carcinogen (B2) and developed an inhalation unit risk of $2.2 \times 10^{-6}$ per $ug \cdot m^{-3}$. As a result of this designation, the U.S. National Institute of Occupational Safety and Health (NIOSH) requires that concentrations of acetaldehyde be kept to the lowest feasible concentration (LFC). In 1968, the U.S. Occupational Safety and Health Administration (OSHA) promulgated a Permissible Exposure Limit (PEL) of 200 ppm ($360\ mg \cdot m^{-3}$). A revised PEL of 100 ppm with a Short-Term Exposure Limit (STEL) of 150 ppm was proposed in 1989 but was never adopted. The American Conference of Government Industrial Hygienists' (ACGIH's) Threshold Limit Value (TLV) is currently set at 25 ppm ($45\ mg \cdot m^{-3}$).

**Table I.** Terrestrial Safety Values for Acetaldehyde.

| ORGANIZATION | VALUE | ppm | $mg \cdot m^{-3}$ | DATE |
|---|---|---|---|---|
| EPA | p-$RfC_{chronic}$ | 0.005 | 0.009 | 1991 |
| OSHA | PEL | 200 | 360 | 1968* |
| NIOSH | REL | Ca: LFC† | | |
| ACGIH | TLV-C | 25 | 45 | 1993 |
| CDC | IDLH | 2000 | 3600 | 1994 |

EPA: U.S. Environmental Protection Agency. OSHA: U.S. Occupational Safety and Health Administration. NIOSH: U.S. National Institute of Occupational Safety and Health. ACGIH: American Conference of Government Industrial Hygienists. CDC: U.S. Centers for Disease Control and Prevention. PEL: Permissible Exposure Limit. REL: recommended exposure limit. IDLH: immediately dangerous to life and health. STEL: Short-Term Exposure Limit. TLV-C: threshold limit value-ceiling.

*OSHA proposed a PEL of 100 ppm and a STEL of 150 ppm in 1989, but these values never came into effect.

†Ca: LFC acetaldehyde has been identified as a potential occupational carcinogen and as such NIOSH recommends that occupational exposures to carcinogens be limited to the lowest feasible concentration.

## DISCUSSION

The prior 1-h SMAC for acetaldehyde was set in 1994 based on the study in human volunteers conducted by Silverman et al.[2,8] To account for the sensitive individuals and duration of exposure, the 1-h SMAC (10 ppm) was based on the LOAEL of 25 ppm reduced by half to reduce the level of overall irritation expected. For the 24-h SMAC (6 ppm), the LOAEL of 25 ppm was divided by an additional factor of 2 for the uncertainty of extrapolating a 15-min exposure value to 24 h. The longer-duration SMACs (7-d, 30-d, and 180-d) were further adjusted by a factor to account for the small number of volunteers, yielding a final value of 2 ppm. A change in the irritancy potential of this level was not expected to change over any of these durations.[2] This study was disregarded by the EPA when setting their AEGLs, as the concentrations were not confirmed analytically and because of a lack of detail regarding protocol and results.[1]

The key study for setting the current 1-h SMAC is Sim and Pattle,[9] the highest NOAEL in humans (**Table II**). After a 30-min exposure to 134 ppm, the volunteers reported no eye irritation and only mild respiratory tract irritation. As noted in the interim AEGL, this study is superior to that of Silverman et al.[8] as the exposure concentration was measured analytically and the exposure methods were better described.[1] Though the exposure duration was only 30 min, extrapolation to an hour is appropriate as respiratory irritation would be driven more by the concentration than by the duration in this scenario (AEGL). Despite its limitations, Silverman et al.[8] does mention that the majority of volunteers in their study felt they would be able to work an 8-h shift at a nominal concentration of 200 ppm, higher than the proposed 1-h SMAC. This is consistent with the paradigm for short-term SMACs for off-nominal situations, in which minor, reversible symptoms are considered acceptable as the crew responds to the event.

**Table II.** Spaceflight Maximum Allowable Concentrations for Acetaldehyde.

| ENDPOINT | EXPOSURE CONCENTRATION (ppm) | SPECIES | UNCERTAINTY FACTORS | | | | SPACEFLIGHT MAXIMUM ACCEPTABLE CONCENTRATIONS (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | NOAEL | DURATION | SPECIES | SPACEFLIGHT | 1 h | 24 h | 7 d | 30 d | 180 d | 1000 d |
| NOAEL irritation, 30 min[12,13] | 134 | Human | 1 | 1 | 1 | 1 | 134 | -- | -- | -- | -- | -- |
| NOAEL, 28 d[14] | 150 | Rat | 1 | 1 | 1 | 1 | -- | 50 | -- | -- | -- | -- |
| NOAEL, 90 d (390 h)[9] | 50 | Rat | 1 | NA | 1 | 1 | -- | -- | 12.5 | | | |
| NOAEC, 90 d (390 h)[9] | 50 | Rat | 1 | 2 | 1 | 1 | -- | -- | -- | 4 | 4 | 4 |
| Previous SMAC values[2] | | | | | | | 12.5 | 5 | 2 | 2 | 2 | NS |

NS: not set. SMAC: Spaceflight Maximum Allowable Concentration. NOAEL: no observed adverse effects level.

In considering a SMAC for 24-h, it is possible that 134 ppm remains appropriate for this duration. However, given a lack of data in human subjects for this duration, the 24-h SMAC is predicated on Muttray et al.,[10] in which human volunteers reported no irritation after 4 h of exposure to 50 ppm acetaldehyde. In the same study, no detectable changes in molecular markers for inflammation were observed. A duration adjustment is not considered necessary, as irritation effects would not be expected to vary greatly at this level between 4–24 h of exposure. This approach is similar to that taken by EPA in developing their interim AEGL-1 values, which they set at 45 ppm at durations from 10 min to 8 h, and which are considered protective of sensitive subpopulations after division of the NOAEL from Sim and Pattle (134 ppm)[9] by 3 to address variability among humans.[1]

Because there are no subchronic human exposure studies, the proposed 7-d SMAC of 12.5 ppm is predicated on the findings of Dorman et al.[6] (Table II). Rats exposed to 50 ppm for up to 65 d (approximately 390 cumulative hours of exposure) displayed no olfactory degeneration, the most sensitive endpoint in the study.[5,6] Relatively minor effects were observed at 150 ppm. The authors estimated that an HEC of 12.5 ppm under continuous exposures would achieve the local concentrations corresponding to a NOAEL in rats (though Teeguarden et al.,[5] using the same model, suggested that the HEC would be 67 ppm). Dorman et al.[6] applied an aggregate uncertainty factor of 30 (presumably 3 for toxicodynamic differences between rats and humans and 10 for differences in sensitivity among human receptors) in proposing a reference concentration (RfC) of 0.42 ppm. This additional uncertainty factor for interspecies variation is deemed not necessary for the astronaut population. The work of Oyama et al.[13] demonstrates that a deficiency in ALDH2 could lead to slightly increased rates and severity of damage at 500 ppm in mice. The difference at 125 ppm is markedly less clear, and the proposed 7-d SMAC is 10-fold lower than that concentration. Further, it appears that mice have a significantly lower baseline capability to metabolize acetaldehyde compared with hamsters, rats, or guinea pigs.[7]

In considering the longer-term SMACs, no studies provide insight into safe levels of exposure beyond 390 h. The only chronic studies available used high concentrations (>750 ppm) as their lowest dose level, and significant increases in hyperplasia/neoplasia were observed in rats (750 ppm) and hamsters (1650 ppm),[4,16] but not observed in hamsters at 1500 ppm.[4] No increases in DNA-protein crosslinking were observed in rats at 50 ppm after 65 d of exposure.[6] This is consistent with the observation that detoxification capacity of ALDH is not saturated at this level.[7] No data is available to characterize the prevalence of ALDH2 polymorphisms in the astronaut community. Thus, the possibility of an ALDH2 polymorphism among Asian astronauts (i.e., from the Japanese Space Agency, JAXA) cannot be discounted. As such, an uncertainty factor of 3 is applied to the $NOAEL_{HEC}$ provided in Dorman et al.[6] for longer durations. This establishes a SMAC of 4 ppm for 30, 180, and 1000 d. The $NOAEL_{HEC}$ developed in Dorman et al.[6] was developed by averaging the tissue concentration over time, in effect correcting for continuous, longer-term exposures. The authors used this HEC to propose an RfC for the general population (with uncertainty factors appropriate to that population, indicating that they viewed further extrapolation for time-dependent effects to be unnecessary). This proposed set of SMAC values is expected to produce no symptoms and no increased risk of carcinogenesis, even with continuous exposure out to 1000 d.

## ACKNOWLEDGMENTS

*Financial Disclosure Statement:* The authors have no competing interests to declare.

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# Carbon Dioxide as a Multisystem Threat in Long Duration Spaceflight

Lorna A. Evans

**BACKGROUND:** Elevated partial pressure of carbon dioxide ($P_{CO_2}$) poses a persistent health challenge during spaceflight. Unlike Earth's environment, the International Space Station experiences $P_{CO_2}$ levels that often exceed terrestrial safety thresholds, creating unique physiological risks for astronauts. In microgravity, localized $P_{CO_2}$ "pockets" can form due to lack of convection, exacerbating hypercapnic symptoms such as headaches, visual disturbances, and cognitive impairments. Moreover, microgravity-induced cephalad fluid shifts amplify the impact of $CO_2$-mediated cerebral vasodilation, contributing to elevated intracranial pressure and potentially exacerbating spaceflight-associated neuro-ocular syndrome. Chronic hypercapnia also raises concerns about bone demineralization and renal stone formation, compounding mission risks. As we move toward longer missions to the Moon and Mars, mitigating $CO_2$-related health effects through engineering controls, physiological countermeasures, and enhanced monitoring is essential. This article discusses current evidence and calls for integrated strategies to safeguard astronaut health and mission success under the compounded stressors of $CO_2$ exposure and microgravity.

**KEYWORDS:** carbon dioxide, microgravity, spaceflight, hypercapnia, astronaut health, long-duration missions, space exploration, International Space Station.

**Evans LA. *Carbon dioxide as a multisystem threat in long duration spaceflight*. Aerosp Med Hum Perform. 2025; 96(11):1024–1026.**

Spaceflight continues to stretch the boundaries of human physiology, exposing astronauts to stressors that test the limits of human health and performance. Among these, elevated partial pressure of carbon dioxide ($P_{CO_2}$) levels within spacecraft habitats, particularly the International Space Station, remain a persistent and underappreciated health concern.

On Earth, atmospheric $P_{CO_2}$ averages around 0.3 mmHg, whereas aboard the International Space Station, concentrations typically range from 2.3–5.3 mmHg, with the highest recorded peak reaching 14.9 mmHg.[1,2] NASA currently sets a 1-h average permissible $P_{CO_2}$ at 3 mmHg; however, astronauts often experience symptoms at levels lower than those known to cause effects under terrestrial conditions.[2,3]

## Physiological Mechanisms of $CO_2$ Response

$CO_2$ is a potent respiratory stimulant and cerebral vasodilator. As it diffuses rapidly across the blood-brain barrier, $CO_2$ acidifies the cerebrospinal fluid by forming carbonic acid, which dissociates into bicarbonate and hydrogen ions.[4] This decrease in cerebrospinal fluid pH activates central chemoreceptors on the ventrolateral medulla, prompting increased ventilation.[4] Peripheral chemoreceptors in the carotid and aortic bodies respond even more rapidly to increased arterial partial pressure of $CO_2$ and acidosis, initiating afferent signals that drive respiratory compensation.[4]

However, this adaptive response has downstream effects. The acidosis induced by $CO_2$ promotes vasodilation via mechanisms involving nitric oxide, second messenger pathways, and ion channel modulation leading to increased cerebral blood flow, which in the closed environment of the cranium can elevate intracranial pressure.[2] Terrestrial studies suggest that every 1-mmHg increase in arterial $P_{CO_2}$ can raise intracranial pressure by 1–3 mmHg, pushing levels toward thresholds associated with neurological compromise.[5] In microgravity, cephalad

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This manuscript was received for review in May 2025. It was accepted for publication in August 2025.

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DOI: https://doi.org/10.3357/AMHP.6716.2025

fluid shifts caused by the absence of gravity further exacerbate this issue by redistributing blood volume to the upper body and brain.

#### Health Effects of Hypercapnia in Space

Fluid redistribution combined with $CO_2$-mediated vasodilation may exacerbate spaceflight-associated neuro-ocular syndrome, characterized by optic disc edema, globe flattening, and visual disturbances.[6] Law et al. reported that each 1-mmHg increase in $P_{CO_2}$ doubles the risk of headache and recommended maintaining 7-d average levels below 2.5 mmHg.[2]

Astronauts' subjective reports align with these findings, linking $P_{CO_2}$ levels between 2.8–5.0 mmHg to symptoms such as headaches, fatigue, blurred vision, poor sleep, and nausea, with symptom severity increasing alongside $P_{CO_2}$ concentration.[2,7] At $P_{CO_2}$ concentrations around 3.5 mmHg, astronauts experienced frontal headaches and chronic cough.[7] A recent study conducted by Cole et al. found a significant link between $P_{CO_2}$ levels and congestion, with congestion incidence doubling for every 1-mmHg increase in $P_{CO_2}$.[8]

The relationship between increased bone resorption when compared to bone formation and the lack of mechanical loading is well-established, as the absence of weight-bearing activities accelerates bone density loss in microgravity. Hypercapnia may exacerbate this by disrupting calcium balance, further promoting bone resorption and increasing renal stone risk.[9] This concern is further supported by new evidence of $CO_2$-associated calciuria and reduced bone density.[9] Although potassium or magnesium citrate could potentially be used to mitigate renal calculus formation, data on its efficacy in the specific setting of space-based hypercapnia are limited.[10] This topic continues to be an area of ongoing research, and additional studies are required to reach definitive conclusions.

#### Operational Implications and Cognitive Impact

Astronauts have reported malaise, sleep disruption, and cognitive sluggishness at $P_{CO_2}$ levels as low as 2.8 mmHg.[2,7] Performance decrements at these thresholds raise concerns for high-demand tasks, especially during extravehicular activity or emergency response. Furthermore, $CO_2$ hotspots, microenvironments with elevated local concentrations due to inadequate air mixing, are particularly worrisome in exercise areas, sleep stations, or confined work zones.[11]

In microgravity, the lack of convection means that exhaled $CO_2$ can linger near the astronaut's face, further increasing the inhaled $P_{CO_2}$.[12] Interestingly, some reports suggest that the heightened sensitivity to $CO_2$ observed during spaceflight may not only be due to the exposure itself, but also to individual predispositions to $CO_2$ retention, adaptation to microgravity, and fluctuations in local $CO_2$ levels that are not detected by fixed sensors.[7] This adds another layer of complexity when assessing astronaut health, as individual factors such as metabolic rate, hydration status, and adaptation to space can influence the body's response to environmental $CO_2$.

#### Mitigation Strategies

Mitigating $CO_2$ exposure requires integrated solutions across hardware, environmental monitoring, and individualized crew countermeasures. Engineering should prioritize improved air mixing via fans, redesigned ducts, and adaptive airflow technologies. Optimizing corridors and storage areas can reduce obstructions from clutter and equipment. Retractable racks may improve accessibility and airflow and help avoid dust accumulation.

Real-time $CO_2$ sensors with high spatial resolution are critical for detecting localized hotspots and tracking trends. This enables timely activation of scrubbers or ventilation before harmful levels are reached. Personalized ventilation or localized scrubbers can further protect vulnerable areas such as sleeping quarters, exercise zones, and dining spaces.

Artificial intelligence can enhance $CO_2$ management by analyzing continuous sensor data to detect trends and predict spikes, prompting timely life support adjustments. Integrating artificial intelligence into the Environmental Control and Life Support System can dynamically optimize strategies based on astronaut profiles such as metabolic rate, activity level, or $CO_2$ sensitivity and evolving environmental conditions, especially during long duration missions where resupply is not feasible.

Individualized $CO_2$ susceptibility profiles, based on ventilatory thresholds, genetic markers, or neurovascular imaging, may help identify vulnerable crewmembers. Pharmacological agents that modulate cerebral blood flow or promote renal calcium excretion may play a future role, although their safety and efficacy require rigorous space-specific validation.

Mission planning should incorporate $CO_2$ risk modeling. Factoring $CO_2$ effects into neurocognitive performance algorithms and integrated workload tools will be essential for preserving astronaut functionality, mental health, and operational capacity. Additionally, special consideration should be given to $CO_2$ exposure during extravehicular activity due to unique environmental challenges.

#### Conclusions

As space agencies move toward long-duration missions to the Moon and Mars, $CO_2$ should be addressed not as a passive variable, but as an active contributor to physiological strain. A comprehensive approach that integrates adaptive engineering, predictive physiology, and real-time environmental monitoring will be essential to ensure astronauts not only survive, but thrive as humanity explores deeper into space.

## ACKNOWLEDGMENTS

*Financial Disclosure Statement:* The author has no competing interests to declare.

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# Letter to the Editor re: Safety Pressure Effects in a Mechanical Demand Regulator

**DEAR EDITOR:**

I commend Shykoff et al.[1] for undertaking a technically complex study examining whether safety pressure (SP) in the CRU-103 oxygen regulator, when combined with a pressure-compensated expiratory valve, could contribute to unexplained physiological events in aviation.[2] This is an important operational and physiological question, addressed with careful laboratory work.

I read the article[1] with particular interest as a biomedical engineer developing an electronic breathing device for physiological event training in a flight simulator. My work requires replicating the breathing sensations produced by the oxygen regulator described, while delivering a freely variable oxygen fraction to the pilot mask and simulating various oxygen-equipment failure modes. Through this work, we have become very familiar with the intricate interplay between the SP oxygen regulator and the pressure-compensated expiratory valve of the MBU-series mask.

SP in the mask effectively "preloads" inhalation, making it feel assisted, while the pressure-compensated valve essential for SP operation adds to expiratory effort. As the authors note, SP assists inhalation but increases expiratory effort, while disabled SP has the opposite effect. In either case, the CRU-103 and MBU-23/P mask combination adds to a pilot's work of breathing (WOB), whether SP is engaged or not.

A purely mechanical design has inherent limits and cannot meet all operational requirements for all pilots in all situations. SP is, in principle, an effective countermeasure against inhalation of cockpit contaminants[3] and offers physiological benefits by maintaining positive airway pressure, helping to prevent alveolar collapse, and promoting alveolar recruitment,[4] particularly under high-G conditions where acceleration atelectasis is a concern.[5]

The WOB cost arises when expiratory resistance is present constantly, even when not physiologically or operationally required. From an engineering perspective, mechanical-only control is limiting. Our next-generation breathing-system prototypes show that modern respiratory science and electronics can provide adaptive control, maintaining contamination protection and positive end-expiratory pressure when indicated, while minimizing unnecessary expiratory load and supporting ventilation when WOB rises.

If the objective remains to preserve the current mechanical mask and oxygen regulators with spring-regulated valves, added resistance, whether inspiratory, expiratory, or both, will persist and manifest during different flight phases. This is because their rigid, fixed design lacks adaptability for all operational scenarios.

Harding's[6] observation remains relevant: the ideal breathing device imposes no restriction. The aviation life-support industry has yet to demonstrate, as medical ventilators in the clinical arena have, that such an advanced device can be developed and delivered to enhance pilot performance across all flight profiles while reducing WOB burden.

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## IN RESPONSE:

We thank the correspondent for his interest in our work. We agree that safety pressure (SP) provides benefits to aviators. We also recognize the limitations of mechanical systems. We are not convinced, though, that adaptive control can correct for them; gas flow through tubes has its own mechanical limitations. Further, individual differences in breathing pattern coupled with physiological reflex responses risk having human- and machine-control systems “chasing” each other.

The writer’s description of the effects of SP and the pressure-compensated expiratory valve, although intuitively reasonable, misses some nuances. SP does not, in principle, assist inspiration; both mask and alveolar gas should be at SP just before inspiration begins. In practice, mechanical delay in the expiratory valve compensation system assists inspiration with SP. Because the expiratory valve cannot close instantly, mask and alveolar pressure drop slightly below regulator outlet pressure before the end of expiration. That lowered pressure slightly assists flow at the start of inspiration. Similarly, the action of the expiratory valve compensation system, not SP per se, increases the pressure needed to start expiratory flow. Without SP there are no delays in expiratory valve cycling and also neither drops in mask pressure to assist the start of inspiratory flow nor extra valve cracking pressure to start expiration.

An adaptive control breathing system, like a mechanical regulator, can affect expiration only through action on the expiratory valve. The compensation system of the MBU-23/P expiratory valve is extremely adaptable. The pressure supplied to the mask controls the pressure to open the expiratory valve with or without SP for variable positive pressure breathing for altitude or for variable positive pressure for acceleration tolerance. The downside of the design is that valve operation cannot be instantaneous except when the supply pressure equals ambient pressure, because the compensation system relies on gas flow in narrow tubes.

A breathing system that maintained inspiratory mask pressure constant at the regulator setpoint would eliminate external inspiratory work of breathing. One that perfectly coupled expiratory valve resistance to expiratory driving pressure could match external expiratory work of breathing at any regulator output pressure to that at ambient pressure. The reality of control system limitations during rapid changes and the unpredictability of spontaneous human breathing with varied respiratory demand make those very difficult goals.

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*Reston, VA, United States*

## NOVEMBER 2000

Personality and aircrew stress *(NASA-Ames Research Center, Moffett Field, CA; U.S. Army Recruiting Command, Command Psychological Operation, Fort Jackson, SC; University of Bergen, Bergen, Norway; University of California-Davis, Davis, CA):* "This study was conducted … assessing the impact of captain's personality on crew performance and perceived stress in 24 air transport crews … Three different personality types for captains were classified based on a previous cluster analysis … Crews were comprised of three crewmembers: captain, first officer, and second officer/flight engineer. A total of 72 pilots completed a 1.5-d full-mission simulation of airline operations including emergency situations … Crewmembers were tested for perceived stress… High performance crews (who committed the least errors in flight) reported experiencing less stress in simulated flight than either low or medium crews. When comparing crew positions for perceived stress over all the simulated flights no significant differences were found. However, the crews led by the 'Right Stuff' (e.g., active, warm, confident, competitive, and preferring excellence and challenges) personality type captains typically reported less stress than crewmembers led by other personality types."[1]

*Maintainer human factors (Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD):* "Aeromedical studies of human factors have focused on the pilot and pilot error rather than on aircraft maintenance workers and maintenance error. This is a report of a survey on medication use in a group of U.S. Air Force aircraft mechanics. … A questionnaire was used to retrospectively examine aircraft mechanic medication use, side effects experienced, and return to work. … Of those surveyed, 67% (26/39) returned to work while taking medication that could potentially impair job performance. … For flying safety reasons, occupational medicine education for aircraft mechanics and their supervisors should address on-the-job use of prescribed medication and self-medication."[2]

## NOVEMBER 1975

*Predicting motion sickness (Pacific Missile Test Center, Point Mugu, CA):* "[A] motion sickness questionnaire can be used to predict susceptibility to motion sickness or flight training success … There is a discussion of the theory that motion sickness results from conflicting perceptual inputs. This theory is related to aircraft operating conditions. Scores on a personality test which appear to be related to similar perceptual phenomena are related to aviation success. One phenotype, field independence, seems to be promising in this regard. In addition to use of this finding in aviator selection, it is felt that studies of this trait, as it relates to an ability to reconcile conflict and to motion sickness insusceptibility, should be conducted."[3]

*How eyeballs work (San Jose State University, San Jose, and NASA-Ames Research Center, Moffett Field, CA):* "Stimulation of the vestibular system by angular acceleration produces widespread sensory and motor effects. The present study was designed to study a motor effect which has not been reported in the literature, i.e., the influence of rotary acceleration of the body on ocular accommodation. The accommodation of 10 young men was recorded before and after a high-level deceleration to zero velocity following 30 s of rotation. Accommodation was recorded continuously on an infrared optometer for 110 s under two conditions: while the subjects observed a target set at the far point, and while they viewed the same target through a 0.3-mm pinhole. Stimulation by high-level rotary deceleration produced positive accommodation or a pseudomyopia under both conditions, but the positive accommodation was substantially greater and lasted much longer during fixation through the pinhole. It is hypothesized that this increase in accommodation is a result of a vestibular-ocular accommodation reflex."[4]

## NOVEMBER 1950

*Coronary disease and flying (Northwestern University Medical School, Chicago, IL):* "Since we are here concerned with flying, we must have some ideas of the hazards involved for a group of patients who should be at rest and avoid anoxia. During the war we were forced to move many patients with myocardial infarctions at all stages of the disease. With proper sedation, insured rest in a bed or cot en route and adequate oxygen we had no trouble. We did not feel in any instance that the patients were harmed by being moved even though there was no alternative.

"Flying personnel (operators) who have any symptoms or signs of coronary disease should be advised not to fly because we have no objective means of estimating coronary reserve. We cannot prognosticate what an emergency might do to the heart in which the demand gets ahead of the blood supply.

> "Personally I have been very liberal with patients who have entirely recovered from myocardial infarction and have allowed them to fly commercially providing they were having no symptoms of coronary insufficiency. Since the pressurized cabins are in general use, I feel that the hazard of flying has been considerably diminished for the patient with a cardiac problem. Even those who have histories of mild insufficiency symptoms have been allowed to fly but warned to limit their activity while they are at high altitudes. Perhaps I have been over liberal or lucky in granting these privileges to some patients, but I have a deep conviction that the speed of air travel more than compensates for the fatigue encountered in long, tedious boat or train journeys."[5]

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This column is prepared each month by Walter Dalitsch III, M.D., M.P.H. Most of the articles mentioned here were printed over the years in the official journal of the Aerospace Medical Association. These are available for download at https://asma.kglmeridian.com/.



DOI: https://doi.org/10.3357/AMHP.6801.2025

## Important Announcements

### Print-on-Demand System Launched

*Aerospace Medicine and Human Performance* is pleased to announce that, in conjunction with the journal going online only, we launched a print-on-demand (PoD) service on October 1, 2025 (www.asma.directfrompublisher.com). This service will allow subscribers, members, and others who wish a print copy of the journal to order one each month. The storefront includes all issues from Vol. 78 to current. For those who have print or print & online subscriptions that run through July 31, 2026, we will continue to honor those through the PoD site. Affected subscribers should have received an email with instructions on how to order their copies. If you have are a print or print/online subscriber and have not received the email with instructions for ordering the print copy, please contact the Journal Department (rtrigg@asma.org and ssanchez@asma.org).

### Reminder: Journal Going Online Only

The Blue Journal will be going online only in January 2026. Therefore, we are no longer accepting or renewing print or print & online subscriptions. Current subscriptions with print will be fulfilled through the PoD service, as stated above, through July 2026.

### New Website Launched

In addition to the above, AsMA has been redesigning our website (www.asma.org). It launched on Sept. 29. The new website is more modern and easier to navigate. There are fresh visuals, easier access to the President's Page, and a full events calendar. We hope you enjoy the new look and take advantage of the extensive resources available for aerospace and space medicine professionals.

### Abstract Submission Now Open

The abstract submission site opened on October 1, 2025 (https://asma-abstracts.secure-platform.com/a). Important dates to remember are as follows. The deadline this year is January 4, 2026, no exceptions. Abstracts will be reviewed in mid-January and submitters will be notified by January 31, 2026. No updates to abstracts will be accepted after February 29, 2026. Interactive presentations (formerly posters) must be submitted to UHMS by February 23, 2026; no updates will be accepted after that date, even on site. For panels, like last year, Chairs are responsible for entering all abstracts associated with their panels. However, they can add collaborators to assist with this. Only the panel Chair can finalize the session. As a reminder, AsMA has a YouTube channel with "how to" videos which are also embedded in the Open Water site. Contact the Journal Department (rtrigg@asma.org or ssanchez@asma.org) with any questions. For more information about the 2026 AsMA-UHMS Annual Scientific Meeting in Denver, CO, visit https://asma-uhms-asm.org/.

## News of Members

**Dwight Holland, M.D., Ph.D., FAsMA, FRAeS, FRAI,** has been elected as the Secretary of the fairly new AsMA Constituent Space Surgery Association (SSA). He also won the Flying Physicians Association 2025 Tabari Award for the "best scientific/medical presentation at the Annual Meeting". He continues to serve as the Member-at-Large for the Aerospace Physiology Society, is the continuing Treasurer of the Air and Space Forces Association for Virginia, and is also the Historian/Social Chair for the Life Sciences and Biomedical Engineering Branch of AsMA.

Additionally, the band Dr. Holland leads, The Galactics and Friends Band, played for the LSBEB/UMHS-led Social Event at the Hyatt-Regency June 3rd, 2025. Some version of this band has now appeared at AsMA and in other places for 11 years since its first appearance in Orlando in May 2015. Over the years Dr. Holland has made the song selections, arrangements, sponsorships, and the like, with core members like **Dr. Michael Schmidt** contributing musically, and often to sound engineering, while original band member **Dr. Felix Porras** continues to provide expert overall support and musicianship. A new band member and keyboardist is Dr. David Wexler, who drove his keyboard all the way from Massachusetts to Atlanta to play his role! **Dr. George Pantalos** is the amazing percussion section Chief (and President of the Space Surgery Association), while past-President of the UHMS Dr. Marc Robins stepped up this year to play a key role as a new lead guitarist, and singer. The band thanks past AsMA President **Dr. Joe Devay** for once again coming and singing and appreciate original Galactics member **Dr. David Powell** coming back to play the sax, and new friend of the band Tom Hoffman for stepping up to play some trumpet this year for us!

LSBEB President **Dr. Carol Ramsey** continues to provide well-crafted harmonies, along with LSBEB friend and logistics support staff Sally Sappenfield (a recent Executive Director of an international research organization in her own right). New female singers **Niki Nair** and **Dr. Mical Kupke** had songs to shine on, with Debbie Garland-Holland taking on the lead vocals role overall for the band. **Drs Jeff Jones** and **Smith Johnston** provided some male vocals in special songs with flavor, with Smith playing the harp on multiple songs. He is also a very capable guitarist. **Dr. Diego Garcia** played some great jazz percussion and bass guitar on a song, while **Dr. Ari Epstein** laid down the drum beat with the full kit on multiple songs. Julian and **Caleb Schmidt** came from CO, and NC, respectively, to help with logistics and setup and take-down of the band.

Onward to the Mid-Year Meeting in Whitefish, MT, and then to Denver, CO, in May 2026.

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November 2025

# *Aerospace Medicine and Human Performance*
# INFORMATION FOR AUTHORS
# http: //editorialmanager.com/AMHP

These notes are provided for the convenience of authors considering preparation of a manuscript. Definitive information appears in the **Instructions For Authors** as published on the journal's website. Submissions that do not substantially conform to those instructions will be returned without review. We conform to the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

## JOURNAL MISSION AND SCOPE

*Aerospace Medicine and Human Performance* is published monthly by the Aerospace Medical Association. The journal publishes original articles that are subject to formal peer review as well as teaching materials for health care professionals. The editor will not ordinarily review for publication work that is under consideration or has been accepted or published by another journal except as an abstract or a brief preprint.

## TYPES OF PAPERS

The five types of articles specified below should be submitted through the web site and will undergo peer review. Other articles, including **Letters to the Editor**, **Book Reviews**, and teaching materials, should be submitted by e-mail to the Editorial Office. Letters to the Editor are limited to 500 words of discussion and/or criticism of scientific papers that have appeared in the journal within the past year. *If your manuscript does not fit the parameters laid out below, an exception may be granted. Please contact the Editorial Office to discuss your submission.*

***Research Articles*** present the results of experimental or descriptive studies with suitable statistical analysis of results. They should contain an Introduction, Methods, Results and Discussion with a statement of conclusions. Such manuscripts should not exceed 6000 words with approximately 25 references.

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***Case Reports*** and ***Case Series*** describe interesting or unusual clinical cases or aeromedical events. They should include a short Background to provide perspective, the Presentation of the Case, and Discussion that includes reference to pertinent literature and/or review of similar cases. Such manuscripts should not exceed 3000 words with approximately 12 references.

***Short Communications*** and ***Technical Notes*** describe new techniques or devices or interesting findings that are not suitable for statistical analysis. They should contain the same sections as a Research Article but should not exceed 3000 words with approximately 12 references.

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We also accept ***Historical Notes*** and ***Aerospace Medicine Clinic*** (formerly **You're the Flight Surgeon**) articles.

## RULES FOR DETERMINING AUTHORSHIP

Each person designated as an author should have made substantial intellectual contributions as specified in the Instructions for Authors.

## AI POLICY

The journal's AI policy can be found at https://www2.cloud.editorialmanager.com/amhp/account/Instructions_for_Authors_2025_July.pdf on p. 3, section 5.

## ETHICAL USE OF HUMAN SUBJECTS AND ANIMALS

The Aerospace Medical Association requires that authors adhere to specific standards for protection of human subjects and humane care and use of animals. The methods section of a manuscript must explicitly state how these standards were implemented. Details appear as specified in the Instructions for Authors.

## LANGUAGE, MEASUREMENTS AND ABBREVIATIONS

The language of the journal is standard American English. Authors who are not perfectly fluent in the language should have the manuscript edited by a native speaker of English before submission. Measurements of length, weight, volume and pressure should be reported in metric units and temperatures in degrees Celsius. Abbreviations and acronyms should be used only if they improve the clarity of the document.

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Tables and figures should be used strictly to advance the argument of the paper and to assess its support. Authors should plan their tables and figures to fit either one journal column (8.5 cm), 1.5 columns (12.5 cm), or the full width of the printed page (18 cm). Tables should be assigned consecutive Roman numerals in the order of their first citation in the text. Tables should not ordinarily occupy more than 20% of the space in a journal article. Figures (graphs, photographs and drawings) should be assigned consecutive Arabic numerals in the order of their first citation in the text. Line drawings of equipment are preferable to photographs. All graphics should be black & white: 1200 dpi for line art; 300 dpi for photos; 600 dpi for combination art. They must be sent electronically, preferably as high resolution TIFF or EPS files. See Documents to Download online for further instructions.

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When the paper is ready for publication, the printer places on its web site a PDF file depicting the typeset manuscript. The Corresponding Author will be notified by e-mail and is responsible for correcting any errors and for responding to any "Author Queries" (AQs).

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