SEPTEMBER 2023 • VOLUME 94 • NUMBER 9

Aerospace Medicine and Human Performance

THE OFFICIAL JOURNAL OF THE AEROSPACE MEDICAL ASSOCIATION

Aerospace Medicine and Human Performance

September 2023 VOLUME 94 NUMBER 9 [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.

AEROSPACE MEDICINE AND HUMAN PERFORMANCE, formerly *Aviation, Space, and Environmental Medicine,* is published monthly by the Aerospace Medical Association, a non-profit charitable, educational, and scientific organization of physicians, physiologists, psychologists, nurses, human factors and human performance specialists, engineers, and others working to solve the problems of human existence in threatening environments on or beneath the Earth or the sea, in the air, or in outer space. The original scientific articles in this journal provide the latest available information on investigations into such areas as changes in ambient pressure, motion sickness, increased or decreased gravitational forces, thermal stresses, vision, fatigue, circadian rhythms, psychological stress, artificial environments, predictors of success, health maintenance, human factors engineering, clinical care, and others. This journal also publishes notes on scientific news and technical items of interest to the general reader, and provides teaching material and reviews for health care professionals.

MEMBERSHIP—The Aerospace Medical Association welcomes members interested in aerospace medicine and human performance. Membership applications may be obtained online at www.asma.org or from the Aerospace Medical Association's headquarters at 320 S. Henry Street, Alexandria, VA 22314, or phone the Membership Department at (703) 739-2240; skildall@asma.org.

SUBSCRIPTIONS—*Aerospace Medicine and Human Performance* is provided to all members of the Aerospace Medical Association (in print, online, or both). Subscriptions and changes of address should be sent to the Subscription Department, *Aerospace Medicine and Human Performance*, 320 S. Henry Street, Alexandria, VA 22314, at least 90 days in advance of change. Institutional Subscription Rates (including online version; other options available): U.S.-$330, Canada-$345, Other countries-$380 (includes air delivery); Agent Disc. $20. Individual Subscription Rates (Print and Online): U.S.-$270, Canada-$300, Other countries-$320 (includes air delivery). Single copies and back issues: $30+P/H ($7.50 U.S./ $25 International Air). NOTE TO INTERNATIONAL SUBSCRIBERS: Please add $50 for bank handling charges on checks not drawn on U.S. banks.

Aerospace Medicine and Human Performance [ISSN 2375-6314 (print); ISSN 2375-6322 (online)], is published monthly by the Aerospace Medical Association, 320 S. Henry St., Alexandria, VA 22314-3579. Periodicals postage paid at Alexandria, VA, and at additional mailing offices. POST-MASTER: Send address changes to *Aerospace Medicine and Human Performance* 320 S Henry St., Alexandria, VA 22314-3579. Phone (703) 739-2240. Printed in U.S.A. CPC Int'l Pub Mail #0551775.

Aerospace Medicine and Human Performance

SEPTEMBER 2023 VOLUME 94 NUMBER 9

94th AsMA Annual Scientific Meeting: "Honoring the Past…Preparing for the Future"

Hyatt Regency Hotel, Chicago, IL, USA
May 5 – 9, 2024

Call for Abstracts

Deadline: November 1, 2023
No Exceptions!

The Aerospace Medical Association's 2024 Annual Scientific Meeting will be held in Chicago, IL, USA. The year's theme is **"Honoring the Past ... Preparing for the Future."** Since announcement of the Artemis program, efforts are underway to return humans to the Moon after more than 50 years. Throughout the Apollo, Skylab, ISS, and now Commercial Crew program, substantial advances in technology have arisen, and a greater understanding of human physiology and performance have progressed through longer duration spaceflight. Lunar missions will entail combined governmental, commercial, and International Partner collaboration. Extravehicular activity, environmental, and habitation challenges will be substantial. General, civil, and military aviation have also seen significant advances over past decades. Human factors, safety, mental health, and environmental aspects merit continued vigilance. Expansion of unpiloted aerial vehicles and eventual transorbital flight provide unique challenges. Advanced telescopes are re-writing the Astronomy textbooks with the search for planetary locales potentially harboring the building blocks of life. Developing the next generation of scientists, engineers, researchers, and clinicians for the exciting years ahead requires our collective energies.

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 94th 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 linked on the association's web site: *https://www.asma.org.*

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

ABSTRACT TYPES AND CATEGORIES

The Annual Scientific Meeting highlights several types of presentation formats. Posters are on display for two full conference days, each in its assigned space. Authors will be asked to present their poster for a single designated 120-min period on one of these days. PowerPoint presentations will be organized by topic area and presented during 90-minute blocks of time, 6 periods of 15 minutes each. **Individual PowerPoint presentations are limited to 15 minutes,** including 3 to 5 minutes for questions and discussion. Panels also have 90 minutes: ideally 5 presentations of 15 minutes each, followed by a 15-minute discussion period.

There are four **TYPES** of submissions:

1. Poster: Standalone Digital Poster presentation that will be integrated into a session, grouped by topic. The presntation must be submitted as a PowerPoint with up to 10 slides. Video and audio clips can be embedded. They will be displayed digially.

2. PowerPoint: Standalone 15-minute slide presentation with questions/discussion that will be integrated into a session, grouped by topic.

3. Individual Invited 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.

4. Individual Invited Workshop: Invited Presentation that will link to and support a Workshop Overview.

CATEGORIES

There are two categories based on the topic to be presented. Templates and examples (examples available on the submission site) are provided for each type and will be available at 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 4-5 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 Chairs to ensure that the abstract authors describe in each abstract how it relates to the Panel theme. If the Panel theme is not clearly identified and/or the abstracts do not support a central theme, the Scientific Programming Committee may unbundle individual abstracts and evaluate them as separate slide or poster abstracts. 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.

WORKSHOPS

Rules for workshops and the review process are similar to those for Panels (above). Overview abstracts should reflect the material to be presented in this long format for up to 8 hours of CME credit. 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 conflict of interest statements. Course materials should be made available for registrants. A separate fee is charged for Workshops registration. For additional information contact Jeff Sventek, Executive Director, at jsventek@asma.org.

AsMA ABSTRACT SUBMISSION PROCESS

All abstracts must be submitted via the electronic submission system linked to the association's web site: https://www.asma.org. Click on the link to the abstract submission site--available on the AsMA home page and Meetings page on or about September 1, 2023. Authors with questions regarding the abstract submission process should contact AsMA directly at (703) 739-2240, x 101 (Ms. Rachel Trigg); or e-mail rtrigg@asma.org.

The following information is required during the submission process: Abstract title, presenting author information (including complete mailing and e-mail addresses and telephone numbers), topic area (from list provided on back of form), contributing authors and their e-mails and institutions, abstract **(LIMIT: 350 words/2500 characters including spaces)**, **at least 2 Learning Objectives** (the Accreditation Council for Continuing Medical Education-ACCME requires brief statements on the speaker's learning objectives for the audience). In addition, three (3) multiple choice questions and answers will be required for each Slide and Panel presentation for Enduring Materials for CME credit. Read instructions online for further details. Poster presenters are required to upload their poster as a PowerPoint in advance of the meeting.

PLEASE NOTE: Presenters (including panelists) are required to register for the meeting. There is a discounted fee for nonmember presenters. *Registration limited to the day of presentation will be available onsite.*

Financial Disclosure/Conflict of Interest/Ethics

Abstracts will not be accepted without a financial disclosure/conflict of interest form. The form is included in the website 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, AV, or handout materials.*

Presentation Retention Policy

AsMA will use live capture to make presentations from the Meeting available to members / attendees after the meeting. Authors are required to provide permission for live capture and a nonexclusive license to repurpose the content. An electronic copy of the presentation suitable for release at the time of the presentation must be provided. Electronic copies of Poster presentations must be uploaded to a submission site when directed.

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** senior-authored presentation, unless given specific prior permission by the Scientific Program Committee Chair, Dr. Eilis Boudreau, at: sciprog@asma.org. Following review by the Scientific Program Committee in November, all contributors will receive a notification of acceptance or non-acceptance by e-mail. 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 Chair.

Abstract Withdrawal

Withdrawing abstracts is strongly discouraged. However, if necessary, a request to withdraw an abstract should be sent to Dr. Eilis Boudreau, 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. Due to publishing deadlines, withdrawal notification should be received by January 15, 2023. As abstracts are published in *Aerospace Medicine and Human Performance* prior to the scientific meeting, a list of abstracts withdrawn or not presented will be printed in the journal following the annual meeting.

MENTORSHIP

Optional review / feedback for student and resident presenters at AsMA 2024

AsMA is continuing its mentorship initiative for student and resident authors for the 2024 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 1 October 2023. The Program Mentor Group will review provide feedback via e-mail by 20 October 2023. 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 to the abstract submission site on our home page: **https://*www.asma.org***

Deadline is November 1, 2023 (NO EXCEPTIONS!!!!!!!)

"Honoring the Past - Preparing for the Future"

Joseph Dervay, M.D., M.P.H., MMS, FACEP, FAsMA, FUHM

The Aerospace Medical Association's 2024 Annual Scientific Meeting will be held in Chicago, IL, USA. The year's theme is "Honoring the Past - Preparing for the Future." While this theme was created to reflect historic and future aspects of aviation, aerospace medicine, and human performance, it is especially poignant regarding what we are witnessing in the arena of spaceflight.

With the inception of the Artemis program, efforts have been underway to return humans to the Moon after more than 50 years. Throughout the Apollo, Skylab, Space Shuttle, International Space Station (ISS), and more recent commercial crew and private astronaut missions, substantial advances in technology have emerged, and a greater understanding of human physiology and performance has progressed through longer duration spaceflight. Lunar missions will inevitably entail combined governmental, commercial, and International Partner collaboration. Substantial challenges lie ahead in areas such as: extravehicular activity (EVA), radiation, environmental, habitation, and clinical and behavioral health.

In many ways it is almost unfathomable that humans have not set foot on the Moon since the end of the Apollo program in 1972. The world population when Neil Armstrong stepped on the Moon in 1969 was 3.6 billion and now it is over 8 billion. It is estimated that less than 20% of everyone on Earth today was alive when humans first reached the Moon 50 years ago. Some of our AsMA members will recall being in elementary and high school when classes would stop during an Apollo mission. Teachers would wheel a black and white television into classrooms and students were riveted watching the scenes unfolding of launches, lunar landings, spacewalks, and subsequent splashdowns. At a young age, many of us were very intrigued and captivated by science and space exploration. We all seemed to know a great deal about the individual astronauts flying those historic missions. Currently, few people truly know much about the seven crewmembers on the ISS now. Perhaps this a result of the remarkable achievement of nearly 23 years of continuous human presence on ISS, whereby regular launches into space have progressed to become more commonplace.

As suborbital and commercial spaceflight launch frequency and capabilities accelerate, the years ahead will truly open the aperture of opportunities for science and exploration, as well as allowing more individuals to experience spaceflight. The Artemis initiative will hopefully re-ignite the magic of the Apollo years, reinforce the value of STEM to our youth, and highlight *the uniqueness of this overall epoch in history* marked by the first time a human stepped onto another celestial body in 1969. We can only imagine the incredible high-definition television and imagery we will witness forthcoming from the surface of the Moon compared to the Apollo era.

General, civil, and military aviation have also experienced significant advances over past decades. Human factors, safety, mental health, and environmental aspects merit continued vigilance. Expansion of unpiloted aerial vehicles and eventual transorbital flight provide unique challenges. Advanced telescopes are rewriting the Astronomy textbooks with the search for planetary locales potentially harboring the building blocks of life. Additionally, based on survey results of the recent Annual Scientific Meeting, the upcoming 94th meeting program will address categories of interest in aviation and aerospace medicine, human performance, aerospace physiology, aerospace nursing and transport medicine, AI, and human systems integration.

The six Apollo missions landing on the Moon were bookended with two famous quotes: Neil Armstrong, as the first person to set foot on the Moon on July 20, 1969, stating, "That's one small step for man, one giant leap for mankind", and CAPT Gene Cernan, as the last human on the Moon, stating on December 14, 1972, "As we leave the Moon at Taurus-Littrow, we leave as we came and, God willing, we shall return, with peace and hope for all mankind." *Unquestionably, future words expressed by astronauts from the Moon will leave us inspired and grateful for what we as humans can achieve.*

Developing the next generation of scientists, engineers, researchers, explorers, and clinicians for the exciting years ahead requires our collective energies. Let us embrace the challenge of creating a wonderful 2024 Scientific Meeting.

All the best.

Keep 'em flying…and Full Steam Ahead!

DOI: https://doi.org/10.3357/AMHP.949PP.2023

CONTACT DETAILS:
Email: President@asma.org • **Web site:** www.asma.org • **Facebook:** Aerospace Medical Association • **Twitter:** @Aero_Med

Decompression Sickness Risk in Parachutist Dispatchers Exposed Repeatedly to High Altitude

Desmond M. Connolly; Timothy J. D'Oyly; Stephen D. R. Harridge; Thomas G. Smith; Vivienne M. Lee

INTRODUCTION: Occurrences of severe decompression sickness (DCS) in military parachutist dispatchers at 25,000 ft (7620 m) prompted revision of exposure guidelines for high altitude parachuting. This study investigated residual risks to dispatchers and explored the potential for safely conducting repeat exposures in a single duty period.

METHODS: In this study, 15 healthy men, ages 20–50 yr, undertook 2 profiles of repeated hypobaric chamber decompression conducting activities representative of dispatcher duties. Phase 1 comprised two ascents to 25,000 ft (7620 m) for 60 and then 90 min. Phase 2 included three ascents first to 25,000 ft for 60 min, followed by two ascents to 22,000 ft (6706 m) for 90 min. Denitrogenation was undertaken at 15,000 ft (4572 m) with successive ascents separated by 1-h air breaks at ground level.

RESULTS: At 25,000 ft (7620 m), five cases of limb (knee) pain DCS developed, the earliest at 29 min. Additionally, multiple minor knee "niggles" occurred with activity but disappeared when seated at rest. No DCS and few niggles occurred at 22,000 ft (6706 m). Early, heavy, and sustained bubble loads were common at 25,000 ft, particularly in older subjects, but lighter and later loads followed repeat exposure, especially at 22,000 ft.

DISCUSSION: Parachutist dispatchers are at high risk of DCS at 25,000 ft (7620 m) commensurate with their heavy level of exertion. However, the potential exists for repeated safe ascents to 22,000 ft (6706 m), in the same duty period, if turn-around times breathing air at ground level are brief. Older dispatchers (>40 yr) with functional right-to-left (intracardiac or pulmonary) vascular shunts will be at risk of arterialization of microbubbles.

KEYWORDS: decompression sickness (DCS), high-altitude parachuting, parachutist dispatcher, venous gas emboli (VGE).

Connolly DM, D'Oyly TJ, Harridge SDR, Smith TG, Lee VM. *Decompression sickness risk in parachutist dispatchers exposed repeatedly to high altitude*. Aerosp Med Hum Perform. 2023; 94(9):666–677.

In 2017, two Royal Air Force parachutist dispatchers on the same sortie, at 25,000 ft (7620 m), developed symptoms of severe decompression sickness (DCS). This prompted a safety investigation and subsequent evidence-based review of procedures, resulting in revised guidance on altitude exposure limitations and denitrogenation requirements for high altitude parachuting.[17] The core features of these more conservative procedures are summarized in **Table I**. Of note, exposure to a jump altitude of 25,000 ft was limited to a single daily decompression lasting no longer than 60 min, following an obligatory 60-min denitrogenation period. This was required to be the final event of the day. Requirements were less restrictive for altitudes up to 22,000 ft (6706 m). The guidance was informed by risk estimation using the U.S. Air Force Research Laboratory (AFRL) Altitude DCS Risk Assessment Computer (ADRAC) model.[26] A "mild" level of physical activity was assumed, while recognizing that the predicted risk of DCS, based on laboratory studies, would likely over-estimate the operational risk. The guidance was introduced in November 2018, highlighting that risk of DCS at provocative altitudes remained nonzero and emphasizing the importance of minimizing physical work and exposure duration.

The current research study was required to validate the effectiveness of the revised guidance, in terms of satisfactorily

From QinetiQ PLC, Farnborough, Hampshire, UK.

This manuscript was received for review in January 2023. It was accepted for publication in June 2023.

Address correspondence to: Dr. Desmond M. Connolly, QinetiQ, Cody Technology Park, Ively Road, Farnborough, Hampshire, GU14 0LX, UK; dmconnolly@qinetiq.com.

DOI: https://doi.org/10.3357/AMHP.6231.2023

Table I. Royal Air Force Revised 2019 Guidance on Altitude Exposure Limits and Denitrogenation Requirements for High-Altitude Parachuting.

ALTITUDE (ft PA*)	DENITROGENATION TIME (min)	SINGLE EXPOSURE LIMIT (min)	CUMULATIVE EXPOSURE LIMIT (min)	PREDICTED DCS RISK (%)
>12,000 to 18,000	None	90	200	Up to 1–2%
>18,000 to 22,000	30	90	120	Up to 2%
>22,000 to 25,000	60	60	Single exposure only	Up to 7%

*PA = pressure altitude.

mitigating the residual risk of DCS in parachutist dispatchers, by conducting representative hypobaric chamber exposures. It was also considered that the more conservative approach might enable repeated exposures in the same duty period and that this should be explored at 25,000 ft and 22,000 ft.

Traditionally, repeated decompression to provocative altitudes has been regarded to increase risk of DCS. However, available recent data on risk with repeat exposure are limited and historical reports are contradictory.[14] On the one hand, a second ascent to an altitude over 18,000 ft (5486 m) within 3 h has been stated to "greatly increase the chance of decompression sickness occurring, even if the first exposure was asymptomatic."[16] On the other hand, repeated brief exposures, interleaved with intermittent recompression for 1 h at ground level, clearly exhibit decreased risk compared with sustained dwell at altitude for an equivalent cumulative duration.[24] The current work adds to the existing body of knowledge on repeat exposure, evaluating longer dwells at altitude interleaved with similar recompression periods at ground level.

Thus, the aims of this study were to:

a. Evaluate the risk of DCS specific to parachutist dispatchers (thereby requiring inclusion of representative levels of physical activity at altitude);
b. Evaluate current UK exposure limitations for high-altitude parachuting;
c. And assess the potential to conduct safely repeated high altitude ascents in a single duty period.

METHOD

Subjects

The study adhered to the principles of the Declaration of Helsinki. The research was funded by the UK Ministry of Defence (MOD) and the experimental protocol was approved in advance by the MOD Research Ethics Committee, an independent body constituted and operated in accordance with national and international guidelines.

Volunteers were briefed individually and provided written informed consent prior to medical screening. This encompassed all of the following: fitness for hypobaric decompression and hypoxia familiarization; factors predisposing to DCS; conditions that could be confused with DCS at altitude; suitability for magnetic resonance imaging (MRI); and conditions associated with white matter hyperintensities (WMH), including past history of concussive head injury with disturbance or loss of consciousness. A detailed physical examination was followed by an electrocardiogram, urinalysis, and hemoglobin estimation. Smokers were excluded, as smoking is linked with increased severity of DCS symptoms,[2] besides influencing vascular endothelial function.[3] Volunteers with a body mass index (BMI) greater than 30 were excluded, as excess weight and BMI may be associated with increased risk of DCS, particularly in men.[1,32] A history of neurological or respiratory DCS was also exclusive, but past limb pain DCS was not.

Volunteers underwent outpatient contrast transthoracic echocardiography (CTTE) screening at the Royal Brompton Hospital, London, UK, to exclude right-to-left intracardiac (patent foramen ovale, PFO) or pulmonary vascular shunt. A trivial PFO observed only upon Valsalva maneuver was considered acceptable. A total of 28 volunteers were screened, with 9 (32%) showing evidence of a right-to-left shunt, comprising 6 with low grade PFOs at rest, 2 with a pulmonary shunt, and 1 with both. Thus, seven volunteers (25%) had a right-to-left intracardiac shunt at rest and three had a pulmonary shunt (11%). Thereafter, volunteers underwent Fluid Attenuated Inversion Recovery (FLAIR) MRI screening to exclude excess pre-existing subcortical WMH, using a 3.0 Tesla Philips Achieva MRI scanner (Koninklijke Philips N.V., Amsterdam, Netherlands) at the Sir Peter Mansfield Imaging Centre, University of Nottingham, UK. The threshold for study entry was defined as no more than five punctate subcortical lesions, in accordance with recent UK altitude studies.[9,10] Thus, 2 volunteers, exhibiting 8 and 53 subcortical WMH, were excluded.

The resulting study cohort comprised 15 healthy civilian men, ages 18–50 yr, recruited by advertisement. This reflected the 95% male population of UK military parachutist dispatchers at the time of protocol submission. The single-sex cohort avoided possible confounds related to hormonal changes influencing DCS risk during the ovarian cycle,[7,20,31] as well as sex differences in vascular endothelial function influencing biomarker responses (reported separately).[15] The mean (± SD) age of participating subjects was 38 ± 11 yr. However, this misrepresents the age distribution of the cohort. By chance, the cohort comprised 5 young men in their third decade of life (mean 24 yr, range 20–28 yr) and 10 older men in their fifth decade (mean 46 yr, range 41–50 yr), enabling consideration of the influence of age between these subcohorts. Additional biometric data for the entire cohort (mean ± SD) were: height = 1.82 ± 0.07 m; weight = 82.2 ± 8.4 kg; and body mass index = $24.9 \pm 2.4\,\text{kg} \cdot \text{m}^{-2}$.

Equipment

Decompressions were conducted in the high-performance hypobaric chamber of QinetiQ's Altitude Research Facility at

MOD Boscombe Down, Wiltshire, UK, at an elevation of 406 ft (124 m) above mean sea level. Chamber occupants' 100% oxygen was supplied via Mk 17F pressure-demand breathing gas regulators (Honeywell Normalair-Garrett Ltd, Yeovil, UK). An Affinity 70C Ultrasound System (Koninklijke Philips N.V.) was used for 2D + Doppler echocardiography. Physiological monitoring employed noninvasive finger photoplethysmography (Finometer, Finapres Medical Systems, Amsterdam, Netherlands) for blood pressure, heart rate, and derived cardiovascular indices, and digital pulse oximetry (Kontron 7840, Kontron Instruments Ltd, Watford, UK) for peripheral oxygen saturation (S_pO_2). Breath-by-breath respired breathing gas composition was analyzed with an LR12000 mass spectrometer (Logan Research UK Ltd, Rochester, UK), calibrated repeatedly at ground level and altitude using various dry gas mixtures of known composition (BOC Gases Ltd, Guildford, UK). Data were recorded continuously using PC-based digital data acquisition systems (PowerLab with LabChart software, ADInstruments, Castle Hill, Australia). All pressure transducers, pneumotachographs, syringe volumes, flow meters, strain gauges, and temperature sensors employed were calibrated for each experiment.

Design

The study was conducted in two phases. Phase 1 (P1) experiments comprised two consecutive hypobaric chamber ascents to 25,000 ft (7620 m; P1A1 and P1A2), the first for 60 min and the second for 90 min, each preceded by 60 min of denitrogenation breathing 100% oxygen at 15,000 ft (4572 m). Phase 2 (P2) experiments comprised three consecutive ascents (P2A1, P2A2, and P2A3), the first of which was identical to P1A1. The subsequent two ascents were both to 22,000 ft (6706 m) for 90 min, each preceded by 30 min of denitrogenation at 15,000 ft. Pre-exposure denitrogenation is generally regarded as effective at altitudes up to 16,000 ft (4877 m),[27] and staged denitrogenation enables conservation of oxygen relative to denitrogenation at lower altitudes. The phase order was governed by the anticipation that the DCS risk associated with three ascents in Phase 2 would be greater than the two-ascent profile in Phase 1. Successive ascents were separated by breaks lasting 60–75 min breathing air at ground level. The altitude profiles for each Phase are shown in **Fig. 1**.

DCS endpoint criteria were managed conventionally,[25] except that it soon became clear that subjects could experience minor knee discomfort during activity that quickly settled once seated at rest. Such mild and transient symptoms ("niggles"), when present only during activity, were recorded but were not regarded as study endpoints, even if they recurred during subsequent bouts of activity. However, symptoms consistent with DCS immediately curtailed the experiment, including those that originated during activity and either persisted or progressed at rest, or any discomfort rated subjectively with a score greater than 4 out of 10. Intermittent symptoms recurring at rest over a 30-min period would also have prompted curtailment but did not occur. Symptoms that improved at rest but did not resolve entirely, prior to the next scheduled activity, curtailed the experiment at that point. Thus, no subjects commenced a later spell of activity with residual discomfort from the previous one. The same medical officer, an experienced aerospace medicine practitioner, supervised all exposures to ensure consistency in diagnosis.

The response to decompression stress was evaluated using precordial 2D + Doppler echocardiography ("echo") conducted every 15 min at altitude. Apical four-chamber views were obtained to enable grading of venous gas emboli (VGE) bubble loads passing through the right side of the heart. Any left-sided bubbles would immediately curtail an experiment. A single experienced investigator graded all echos to avoid interrater inconsistency. Audible Doppler grades 1–4 were treated conventionally in accordance with the Spencer scale.[29] These were augmented by additional visual grades 4+, 4++, and 4+++ according to the subjective appearance of heavy VGE loads passing through the right heart, where 4+++ equates to visual obscuration of intracardiac anatomy (modified Spencer grade 5). Overall, this approach mirrored use of the Expanded Eftedal-Brubakk scale.[22]

Subjects conducted activities throughout that were intended to represent the physical workload of a busy parachutist dispatcher. Activity at ground level reflected unloading and subsequent aircraft embarkation of 20 parachutes, each weighing 25 kg. During the hour of denitrogenation at 15,000 ft, six brief sets of activity were conducted, each representing movement along a "stick" of seated parachutists to monitor their prebreathe status. Finally, at the dispatch altitude, activities simulated assisting heavily laden parachutists to stand before doing right- and left-sided, top-to-toe equipment checks on each in turn, followed by overarm movements to represent retrieval of static lines post-dispatch. Precise actions and repetitions are detailed in **Table II**. Limb movements were balanced to load both sides equally.

Procedure

Subjects underwent instruction on hazards associated with altitude exposure, were familiarized with the altitude chamber, breathing gas regulator, and oxygen mask, and experienced hypobaric hypoxia familiarization at 25,000 ft (7620 m). They were required not to have been exposed to hypobaric or hyperbaric environments (e.g., flying, diving, parachuting, mountaineering) in the 72 h prior to decompression, nor for 24 h afterwards. They were asked to avoid alcohol and unusually strenuous physical exertion for 48 h prior to decompression and 24 h afterwards. They were also asked to declare any illnesses and injuries that occurred during the research program. All subjects completed Phase 1 before undertaking Phase 2 some months later.

Subjects arrived at the chamber at 0800 h for brief medical confirmation of fitness to proceed (ability to clear ears and review of fitness since medical screening). They were reminded about DCS symptoms and to report any symptom at altitude as soon as it occurred. They were encouraged to maintain normal hydration and nutrition by drinking and eating freely whenever at ground level during the day.

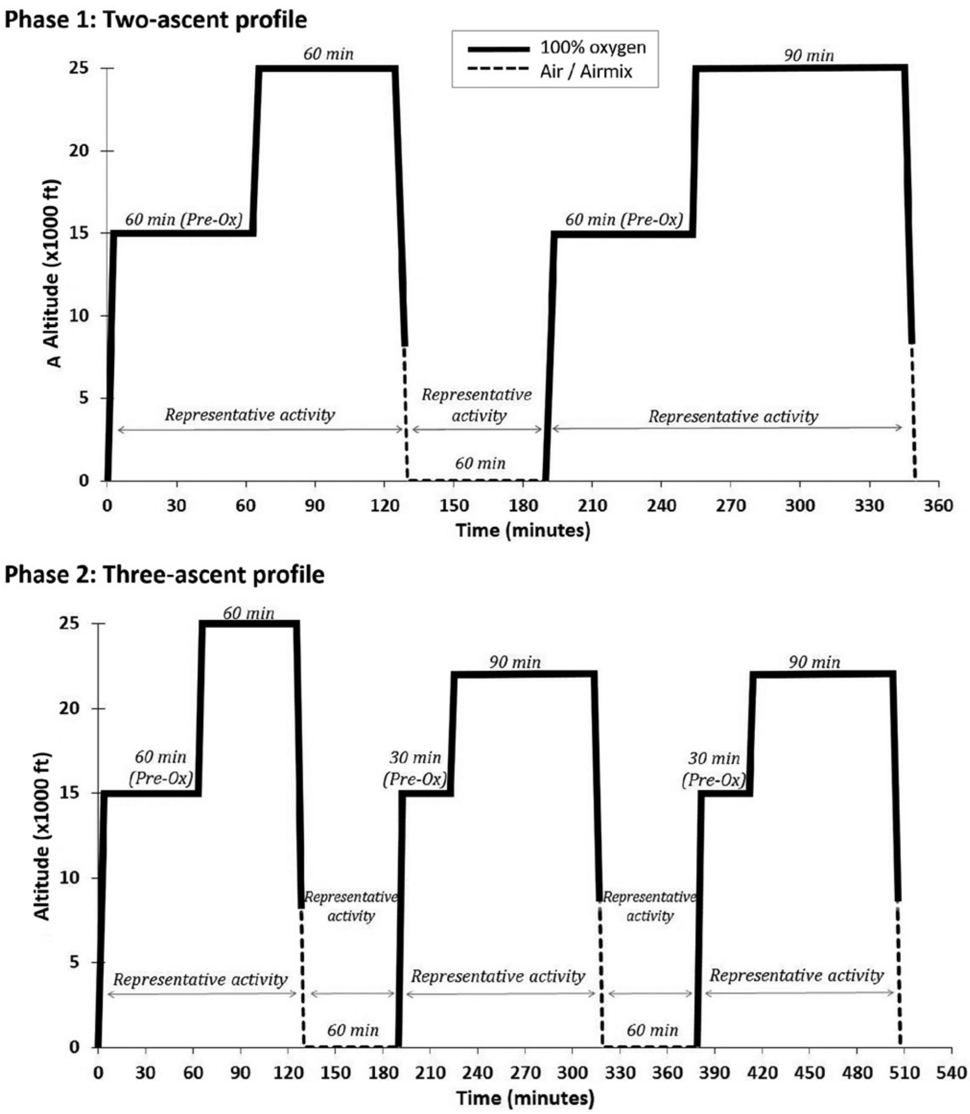

Fig. 1. Ascent profiles for Phase 1 (two ascents) and Phase 2 (three ascents). All ascent and descent rates were 5000 ft · min^{-1}. Oxygen breathing commenced at the start of each ascent. Subjects were switched from breathing 100% oxygen to breathing air at 8000 ft in the descent. Air breaks at ground level lasted a minimum of 60 min (as shown) and maximum 75 min, typically 65–70 min.

Subjects wore RAF-type aircrew t-shirts, flying coveralls, cloth type G hat and a P/Q oxygen mask, modified with a port to allow sampling of breathing gas composition by respiratory mass spectrometry. The aircrew t-shirt and coveralls were intentionally loose to facilitate echocardiography. Activity conducted 25 min prior to ascent, and again 10 min prior, represented prepositioning and embarkation of parachutist equipment (Table II). The subject then sat in the altitude chamber, donned the hat and mask, and was instrumented with physiological monitoring equipment and the mass spectrometer

Table II. Representative Parachutist Dispatcher Activities Conducted at Different Stages of Simulated Flight.

TIMING	ACTIVITY / REPETITIONS	DURATION	FREQUENCY
At ground level prior to each ascent.	Lift 25 kg load from ground level to chest for 10 s, move it 5 m, then lower. Complete 20 repetitions.	5 min	Two bouts starting at 25 min and 10 min prior to ascent.
During denitrogenation at 15,000 ft.	Stand, squat with 'thumbs up', stand. Side step and repeat. Complete four repetitions, alternating sides.	1 min	At rate of six bouts per hour of denitrogenation.
At maximum altitude, every 15 min starting upon arrival at plateau.	Stand, strop 'pull up' x2 (right and left). Squat, stand, 1/4 turn, squat, stand. Repeat eight times. Followed by:	4 min	Repeated every 15 min following echocardiography (four bouts per hour).
	Overarm "line retrieval" movements, moving carabiners along a rail. Eight repetitions (four right, four left).	1 min	

sampling line. The expiratory port of the mask was fitted with an expiratory hose and antiviral filter. This arrangement imposed no meaningful additional breathing resistance over use of the mask alone.

Accompanying investigators viewed a “slave” monitor displaying the subject’s echo image. Echos were conducted with the subject sitting still at rest but leaning slightly to the left, such that the left lateral chest wall was supported against a cushioned rail, to facilitate image acquisition. A practice echo at ground level allowed identification of optimal transducer placement. Each echo lasted about 5 min, with grading conducted first with the subject sitting quietly at rest, and then while gently moving all major articulations of each limb in turn to dislodge any gas emboli.

Initial ascents were identical in both Phases (P1A1 and P2A1) and generally commenced before 1000 h, with accompanying investigators completing an additional 30 min of denitrogenation beforehand. As ascent commenced, the subject’s inspiratory hose was connected to the breathing gas supply, delivering 100% oxygen with safety pressure. All ascents and descents were conducted at 5000 ft · min^{-1}. Safety pressure was de-selected at 12,000 ft (3658 m) in the ascent, when the regulator applies safety pressure automatically. The subject could stand to conduct activity representing checks of parachutist pre-breathe (Table II), undertaking six such episodes before completion of 1 h at 15,000 ft (4572 m). Also, four echos were completed at 15,000 ft, occupying the last 5 min of each 15 min at that altitude.

After 60 min at 15,000 ft, the chamber ascended to 25,000 ft where it remained for 1 h, managed as four 15-min test epochs. Each epoch comprised 5 min of simulated dispatcher activity, representative of preparation and dispatch of eight parachutists (Table II), followed by 5 min of rest (minimizing limb movements), and a final 5 min echo. Thus, each echo completed one 15-min cycle of activity-rest-echo before beginning the next 15-min test epoch. After precisely 60 min at 25,000 ft, the chamber was recompressed to ground level, with 100% oxygen de-selected at 8000 ft (2438 m).

The subject spent the next hour breathing air at ground level. Echos were repeated upon arrival at ground level and at 15-min intervals until VGE were no longer seen. At 25 min prior to the next ascent, and again 10 min prior, further representative parachute preparation and embarkation activities were repeated (Table II).

In Phase 1, the second ascent (P1A2) mirrored the first, except that dwell time at 25,000 ft was extended to 90 min, divided into six 15-min test epochs. A second in-chamber investigator accompanied the subject for this ascent, and was replaced by a third part-way through the exposure, to ensure that no investigator remained at 25,000 ft for longer than 60 min. In Phase 2, denitrogenation at 15,000 ft in the second ascent (P2A2) was limited to 30-min duration with representative activity, followed by 90-min dwell at 22,000 ft (6706 m), again with six 15-min test epochs. Upon completion of the second ascent and second ground-level interval as before, a third ascent (P2A3) was conducted that was identical to the second. A different in-chamber investigator accompanied the subject for each ascent to 22,000 ft in P2A2 and P2A3.

Ground-level dwell times between ascents never exceeded 75 min, and usually occupied 65–70 min. Following completion of the final ascent in each phase, subjects were monitored with 15-min echos until all VGE had disappeared, then remained under medical supervision for 1 h before being released from the facility. When an experiment was curtailed due to DCS, the chamber was recompressed immediately to ground level at 5000 ft · min^{-1} and the subject continued to breathe 100% oxygen at ground level for 1 h, having confirmed well-being and symptom resolution following recompression.[23] Thereafter, the ambulatory subject was monitored at the facility for a further hour. A subject experiencing DCS in Phase 1 remained eligible to return for Phase 2. No subjects or investigators experienced post-descent symptoms.

Apart from transient fluctuations with ascent and descent, ambient temperature in the chamber generally remained between 20–24 °C, minimizing any influence of temperature on either risk of DCS or vascular endothelial function.[11]

Analysis

The statistical analysis of data from small-scale DCS studies is challenging and the utility of inferential analysis is limited. DCS symptom occurrences are reported descriptively. VGE loads are ranked according to a nonlinear ordinal scale that limits the utility of statistical analysis. Hence, VGE scores for each test epoch in consecutive ascents are presented graphically as “heat maps”, ranked by subject age, first as the maximum VGE grade from any single limb, and second as the total VGE score from all four limbs (maximum contribution score of 4 from any one limb). To evaluate the influence of age, mean maximum VGE scores and mean combined scores, were calculated for the entire cohort and for the younger and older subcohorts, employing a score of 5 for obscuration of cardiac anatomy. Survival plots were derived for the two phases, where survival was defined as continued absence of DCS plus absence of grade 4 VGE. A 2×2 contingency matrix was used to assess the relationship between grade 4 VGE and DCS occurrences using accumulated data from the three ascents to 25,000 ft (7620 m), evaluated statistically using Fisher’s Exact Test.

RESULTS

All 15 subjects completed Phase 1. Due to an unrelated injury while exercising, 1 later withdrew, leaving 14 subjects for Phase 2. One of these was withdrawn following his first ascent in Phase 2 after experiencing brief, self-limiting palpitations at ground level. He remained well but did not participate further.

There were 5 diagnoses of DCS at 25,000 ft (7620 m), all lower limb (knee) pain bends affecting older subjects, comprising 2 (of 15) in P1A1 (incidence 13%), at 29 and 37 min of exposure; 1 (of 13) in P1A2 (8%), at 60 min; and 2 (of 14) in P2A1 (14%), at 44 and 60 min. All involved knee pain/discomfort that began during activity and persisted (static limb pain DCS) or worsened (progressive limb pain DCS) once seated at rest (**Table III**, serials 1–5). All cases improved with descent and had resolved upon arrival at ground level. All were managed breathing 100% oxygen for 1 h at ground level with no sequelae. One experienced DCS twice, i.e., in both P1A1 and P2A1, affecting different knees on each occasion (Table III, serials 2 and 4). There were no cases of DCS at 22,000 ft (6706 m) in Phase 2.

Additionally, six other subjects in Phase 1 experienced either mild knee pain/discomfort only during activity, being absent at rest, or trivial knee discomfort toward the end of an ascent (Table III, serials 6–11). These knee niggles varied in character but were either transient or trivial, and hence were not considered sufficient to allow diagnosis of DCS. Thus, 9 of 15 subjects in Phase 1 (60%) experienced a degree of knee discomfort at some point during the experiment, with 3 diagnosed as DCS and 6 with niggles. Similarly, 5 of 14 (36%) in Phase 2 experienced knee discomfort, 2 diagnosed with DCS and 3 with niggles.

No arterialized gas emboli were observed in the left cardiac chambers at any time. Individual VGE data for Phase 1 are shown in **Fig. 2**, ranked in order of increasing subject age, as the maximum VGE grade observed in any limb, and as the cumulative VGE score from all four limbs (where each limb has a maximum permissible score of 4). Corresponding data for Phase 2 are shown in **Fig. 3**.

VGE loads generally preceded and became heaviest in limbs that developed knee pain or niggles, with rapid, early progression to very heavy loads, from multiple limbs, preceding all DCS occurrences during initial ascents to 25,000 ft in both phases. However, there were also heavy VGE loads in both phases that were never associated with symptoms ("silent bubbles"). Grade 4 VGE preceded all 5 occurrences of DCS; of the remaining 37 exposures, 18 generated grade 4 VGE and 19 did not (Fisher exact test value = 0.0532). While not quite achieving statistical significance, the data suggest that DCS was unlikely in the absence of substantial VGE loads. The positive predictive value of grade 4 VGE for subsequent DCS was poor, at only 0.217. This is low but would probably have increased with further DCS diagnoses had exposure duration extended beyond 60 min, since VGE were detected early and their intensity increased rapidly and remained high.[4] On the other hand, the negative predictive value of absence of grade 4 VGE was 1.0 (100%), indicating ongoing absence of risk of DCS and consistent with expectation.[5]

Table III. Details of Limb Pain DCS Diagnoses and Minor Knee Symptoms ("Niggles") Reported Only During Activity (Absent at Rest) or Regarded as Trivial.

SERIAL	PHASE	ASCENT	AGE	DCS OCCURRENCES
1	1	1	43	Discomfort right knee above/behind patella, grade 2-3/10, when seated after second session of activity. Persisted as dull ache during second echo. Static limb pain DCS diagnosed at 29 min. Discomfort eased below 15,000 ft in descent, absent at 13,500 ft.
2	1	1	48	Worsening left peripatellar knee pain, maximum grade 3/10 during third bout of activity. Eased to popliteal fossa discomfort 1/10 when at rest then progressed and worsened over next 2-3 min. Progressive limb pain DCS diagnosed at 37 min. Discomfort eased at 20,000 ft in descent, absent at 17,000 ft. (See also P2A1, serial 4)
3	1	2	48	Third activity, discomfort left tibial tuberosity. Absent at rest but recurred and worse with next activity, grade 4/10. Eased once sitting but persisted, grade 2-3/10, as band across insertion of patellar tendon. Diagnosed static limb pain DCS at 60 min that resolved with descent below 12,000 ft.
4	2	1	48	Mild, bilateral, activity-related ache in knees, R = L, during second and third activity sessions. At 37 min mild right knee discomfort, grade 2/10, then worsening right knee and hamstring pain, 4/10. Progressive limb pain DCS diagnosed at 44 min. Improved with descent from 18,000 ft through 16,500 ft, 'hardly anything' at 15,000 ft and absent at 11,000 ft. Note opposite side to knee bend in P1A1 (Serial 2).
5	2	1	50	Vague discomfort anterior right knee and near quadriceps insertion after fourth activity, with minimal discomfort once at rest, grade 1/10. Static by start of descent at 60 min. Diagnosed static right limb pain DCS. Improving by 15,000 ft in descent and resolved at 5000 ft.
SERIAL	**PHASE**	**ASCENT**	**AGE**	**MINOR KNEE "NIGGLES"**
6	1	1 & 2	26	P1A1, third activity, mild left knee pain at end of squats, nil at rest. Bilateral on final activity, fading over 1-2 min at rest. Recurred with activity in P1A2, medial aspect both patellae over joint line, but progressively easier with each activity session. Only during squats, nil at rest, absent at ground level.
7	1	1	28	Single 'twinge' right quadriceps insertion on final squat of last activity.
8	1	1	41	Vague sense of pressure, anterior left knee, last 3-4 min of P1A1; 0.5/10.
9	1	1	42	Progressive bilateral knee pain during last few squats of final activity. Around patellar tendon bilaterally plus left-sided mild anterior knee pain. Eased at rest. Did not recur on second ascent.
10	1	2	43	Mild left anterior knee pain, either side of patella, when standing from squat during last two periods of activity. Nil at rest
11	1	2	45	Sense of knee "fullness" bilaterally, only during squats for last two activity sessions. Nil at rest.
12	2	1	41	Right thigh/calf ache and pressure over patellar tendon, last two sessions of activity, grade 1/10. Eased at rest and no recurrence
13	2	1 & 3	43	Slight altered sensation left knee during final activity of P2A1, grade 1/10. Nil at rest. P2A3 final echo, mild aches both knees. Absent at GL.
14	2	2 & 3	48	Bilateral trivial ache over tibial tuberosities for last 30 min of P2A2 and P2A3. Eased with mobilization at ground level.

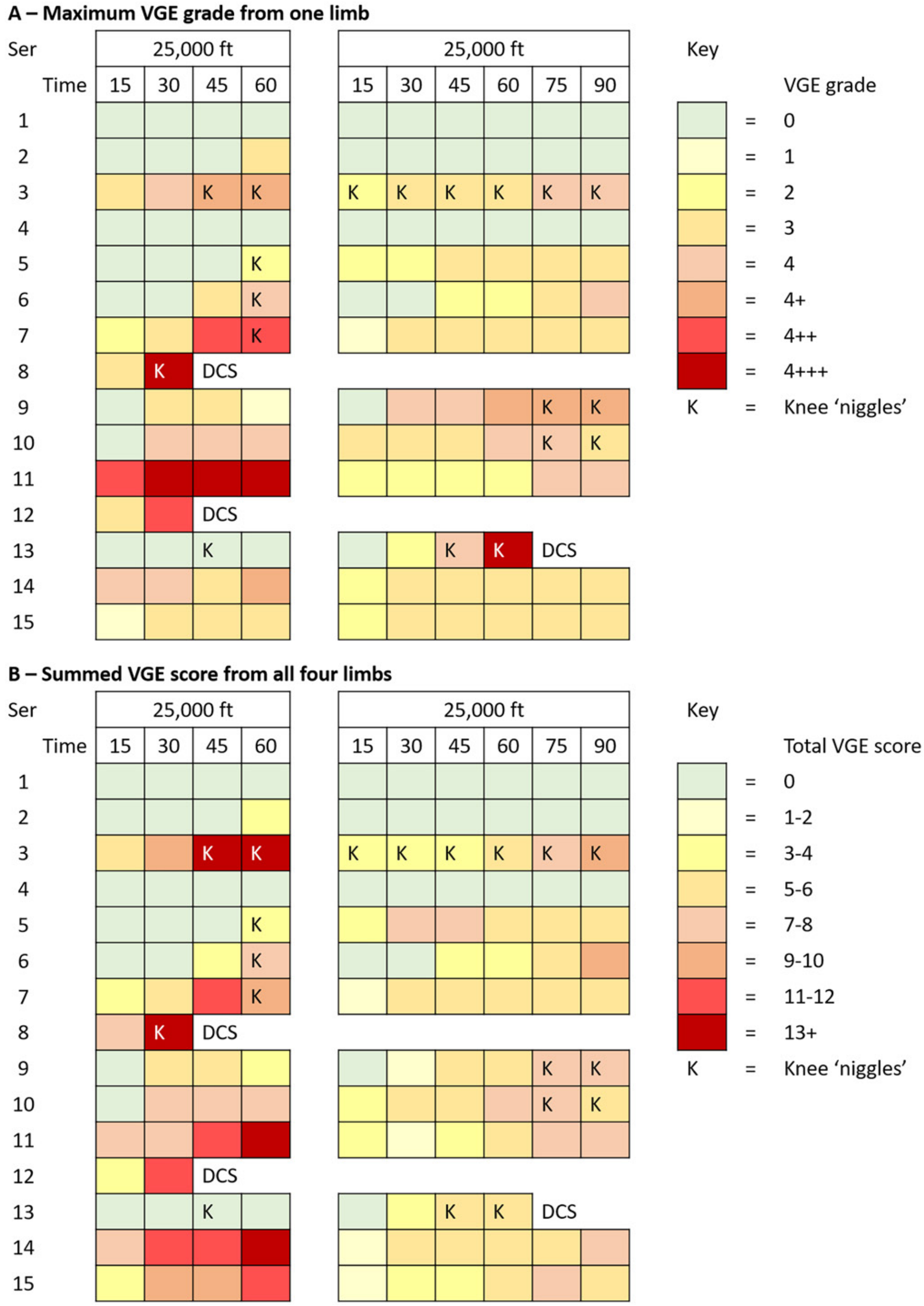

Fig. 2. VGE data from Phase 1, ranked by age for 5 subjects in their 20s (serials 1–5) and 10 > 40 yr of age (serials 6–15): A. Maximum VGE grade from a single limb; B. Summed VGE score of all four limbs (each limb contributing a maximum score of 4).

Considering the influence of repeat exposure, contrary to expectation, individuals' VGE loads appeared slightly lighter and later in P1A2 compared to P1A1, except for 3 subjects who generated more VGE on the second ascent (Fig. 2, serials 5, 9, and 13). In Phase 2 (Fig. 3), far lighter and later VGE loads were evident at 22,000 ft in P2A2 relative to 25,000 ft in P2A1, with the clear exception of subject serial 13, a fit long-distance runner who was apparently reluctant to give up his nitrogen during the initial ascents in either phase. This is misleading. He may have denitrogenated very effectively, without generating VGE, during his first ascent, but developed greater propensity toward bubble formation on the second ascent, following 1 h breathing air at ground level. Still fewer VGE were seen during P2A3 relative to P2A2. The overall impression from Figs. 2 and 3 is of a beneficial influence of prior altitude exposure to mitigate VGE loads during subsequent ascents.

Considering the influence of altitude, unsurprisingly, exposure to 22,000 ft in P2A2 was associated with lower maximum

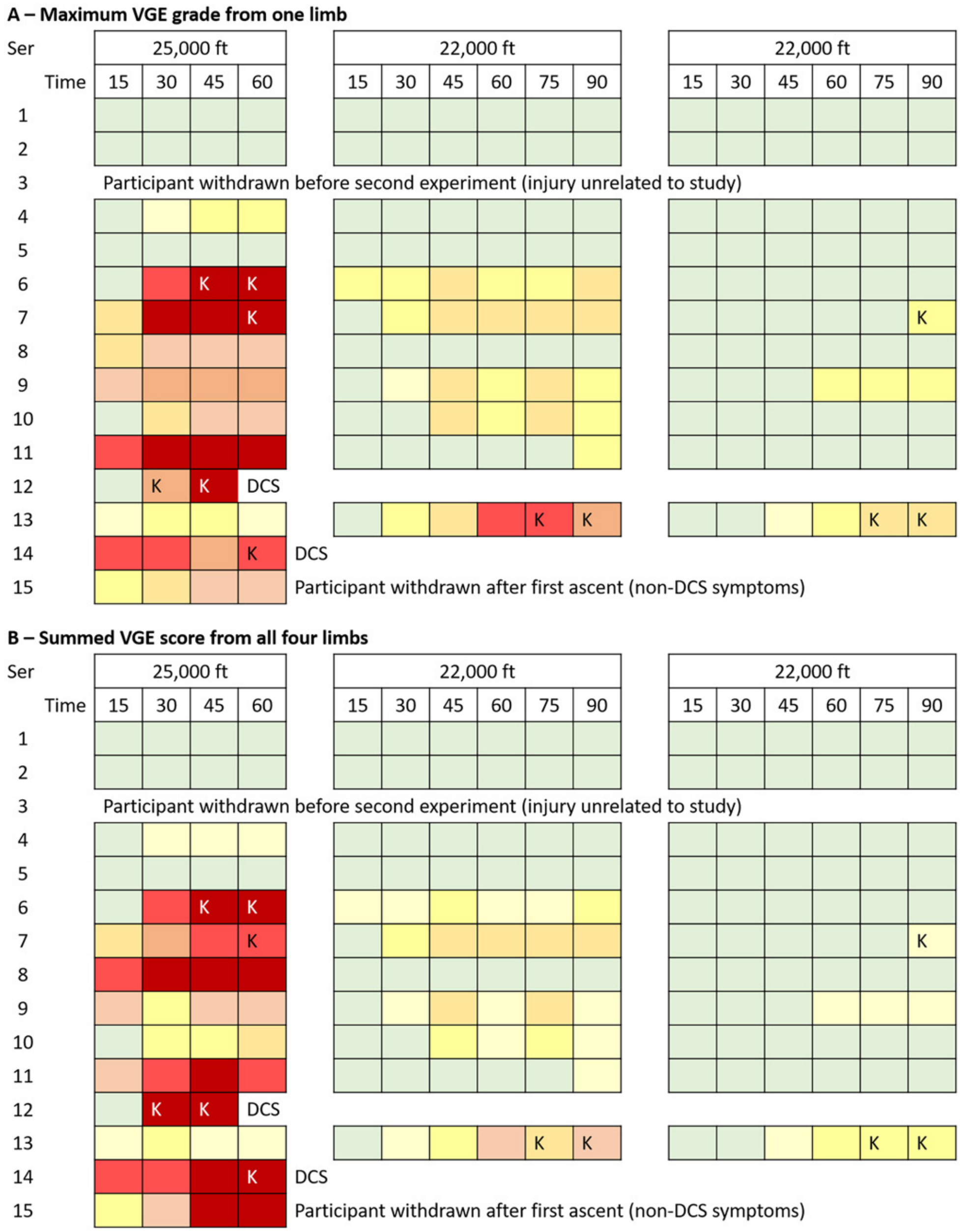

Fig. 3. VGE data from Phase 2, ranked by subject age: A. Maximum VGE grade from a single limb; B. Summed VGE score of all four limbs. For keys, see Fig 2.

grades of VGE from any single limb, and substantially lighter total VGE scores from all four limbs, than the second ascent to 25,000 ft in P1A2. For all ascents to 25,000 ft, in both phases, VGE loads tended to become heavier with longer duration exposure. This was far less evident during repeat ascents to 22,000 ft in Phase 2; the trend was still there, but bubble loads remained light. Survival curves were derived to enable further comparison of the response to decompression stress between phases and ascents, where "survival" was defined as continuing absence of both DCS and grade 4 VGE (**Fig. 4**). These illustrate well the relatively benign nature of repeat exposures to 22,000 ft in Phase 2 compared with the exposures to 25,000 ft. In contrast, survival during repeat exposure to 25,000 ft in Phase 1 (P1A2) appears little better than the initial exposures to 25,000 ft in either phase, with the slope of the survival curve only slightly shallower in P1A2.

Regarding age, younger volunteers (<30 yr) produced fewer and later VGE, and often none at all, whereas older subjects (>40 yr) produced early, heavy, and persistent bubble loads, from multiple limbs, notably during initial exposures in both phases. While such data are generally unsuitable for parametric analysis, in this instance average VGE scores very effectively highlight the gross disparity with age. **Fig. 5** shows mean maximum VGE grades and cumulative scores segregated into disparate younger (<30 yr) and older (>40 yr) subcohorts, the former exhibiting very few bubbles while the latter generate many.

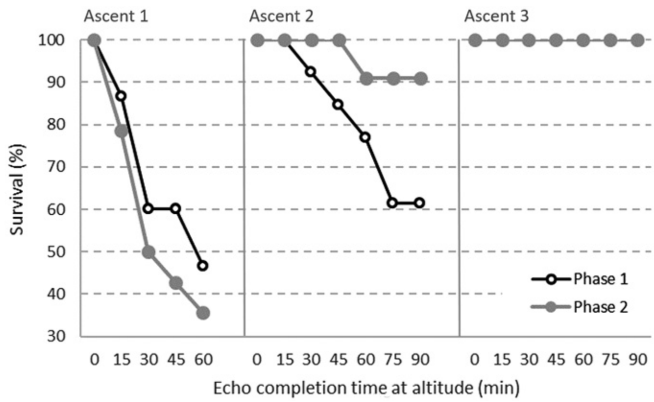

Fig. 4. Proportion of subjects commencing an ascent who "survive," where survival is defined as continued absence of decompression sickness together with absence of grade 4 venous gas emboli.

DISCUSSION

In this study, the consistent 13–14% incidence of DCS within 1 h of initial exposure to 25,000 ft, following denitrogenation for 60 min, exceeds the 5% laboratory threshold suggested as a surrogate for acceptable operational risk.[33] Cumulative DCS incidence data from Phase 1 and Phase 2 are shown in **Fig. 6** relative to ADRAC predictions for various levels of exertion. The plots indicate an incidence of DCS associated with heavy exertion at altitude and suggest further cases should be expected if exposure is extended beyond 60 min. Levels of activity in this study are considered representative of military parachutist dispatchers, and the greater risk associated with heavy exertion would readily explain sporadic occurrences of severe DCS at high altitude. Any future use of the ADRAC model to predict DCS risk

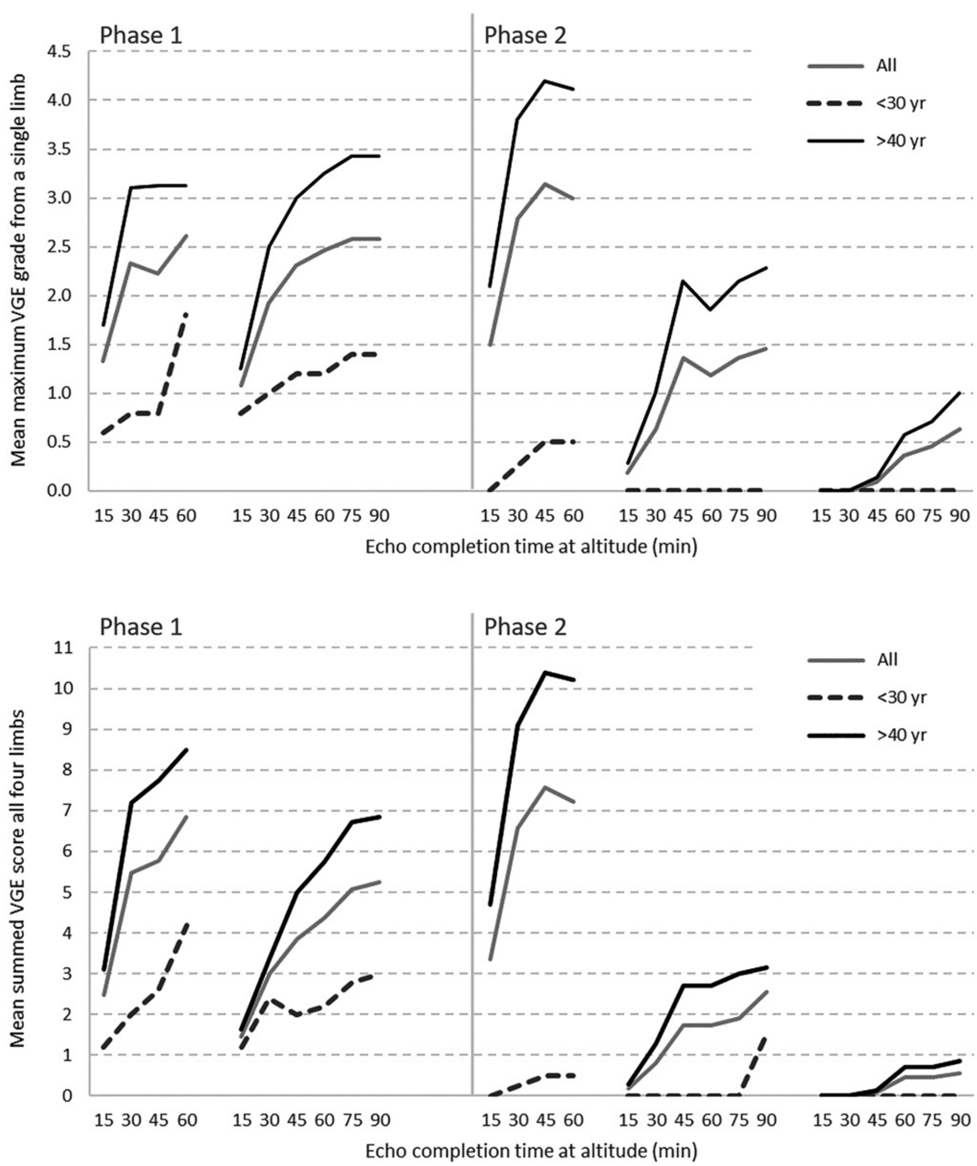

Fig. 5. Average VGE grades emphasize the disparity between younger (very few bubbles) and older (masses of bubbles) subcohorts. Upper graph: mean maximum VGE grade from a single limb (allowing maximum VGE score of 5 for obscuration of right heart anatomy). Lower graph: mean summed VGE scores from all four limbs. Data for both phases, for all subjects, and segregated into younger (<30 yr, $N = 5$) and older (>40 yr, $N = 10$) subcohorts.

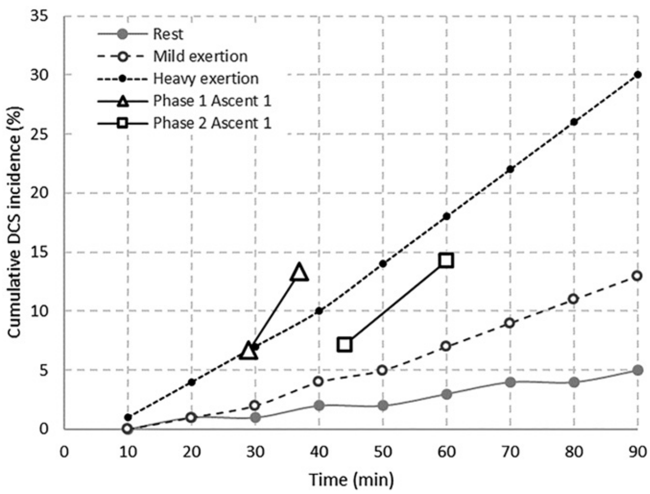

Fig. 6. Cumulative DCS incidence data for initial exposures to 25,000 ft in Phase 1 (triangles, $N = 15$) and Phase 2 (squares, $N = 14$), shown relative to predicted incidence at rest and with mild and heavy exertion, following denitrogenation for 60 min, using the US Air Force Altitude DCS Risk Assessment Computer (ADRAC) model. Phase 1 diagnoses at 29 and 37 min; Phase 2 diagnoses at 44 and 60 min. The data indicate that parachutist dispatcher activity is best represented to ADRAC as "heavy" exertion.

in dispatchers should represent their activities as "heavy" exertion, rather than "mild".

While occurrences of knee niggles were mostly trivial, with some representing minor musculoskeletal symptoms, others were undoubtedly decompression-related. Some squats associated consistently with mild discomfort at altitude were symptom-free when repeated at ground level following planned recompression. This was most evident in the individual described at Table III, serial 6, who experienced repeated episodes of discomfort for the last two sessions of activity in P1A1 and all six bouts of activity in P1A2. In retrospect, this individual might reasonably have been diagnosed with limb bend DCS. In the event, diagnostic consistency was maintained throughout the study, whereby DCS was not diagnosed in the absence of symptoms at rest. In this context, reports of knee niggles reflect low-grade symptoms that were not at all troublesome and would probably go unreported or unnoticed if they occurred during flight, particularly during busy periods of activity.

Early, heavy VGE loads were generated from multiple limbs at 25,000 ft (7620 m), particularly in those over 40 yr of age (Figs. 2 and 3), suggesting a strong propensity toward development of DCS.[19] While onset and progression of VGE were a little slower with repeat exposure in P1A2 (Figs. 3 and 4), some (older) individuals still produced heavy VGE loads on their second ascents, in one case preceding DCS (Fig. 2). Thus, the repeat exposure to 25,000 ft was not benign. However, the general appearances of Figs. 2 and 3 indicate decreasing VGE loads in response to repeated decompression stress, implying carry-over of protection from oxygen breathing during earlier ascents, as long as intervening air breaks on the ground are sufficiently brief. Depletion of bubble micronuclei may contribute in some subjects, but clearly not those who produce more VGE the second time around. VGE loads during repeat ascents to 22,000 ft (6706 m) in Phase 2 were particularly light, suggesting that repeat ascents to 22,000 ft may be achievable with minimal additional risk providing turn-around times on the ground are brief (Figs. 3 and 4). It is therefore possible that prior exposure to 22,000 ft could mitigate the risk of DCS during subsequent ascent to 25,000 ft, with relevant independent variables likely to include the total time spent breathing 100% oxygen on earlier ascent and the duration of the air break between ascents, such that replenishment of nitrogen in the tissues remains incomplete. As in diving, the order of exposures would be important but, unlike repeated dives, to minimize the risk of altitude DCS, the ascent imposing greatest decompression stress should be conducted last while the gap between ascents should be minimized.

While denitrogenation at altitudes up to 16,000 ft (4877 m) may be effective, one individual in this study produced low grade VGE toward the end of the initial pre-breathes at 15,000 ft (4572 m), consistent with previous reports.[33] Any tissue bubbles present at 15,000 ft should be expected to enlarge upon further ascent to 25,000 ft, and, consistent with expectation, this subject progressed rapidly to grade 4 VGE soon after arrival at 25,000 ft. Staged denitrogenation for high altitude parachuting should be conducted at altitudes that avoid bubble generation.

Exercise promotes bubble formation, with subsequent bubble growth depending on the levels of exertion and decompression stress.[13] In the current study, periods of physical exertion at the simulated jump altitude were relatively brief and of modest intensity but involved repetitive squats with knee flexion beyond 90° followed by full extension, generating the associated mechanical stresses around knee joints. This activity clearly predisposed to knee pain DCS and niggles, particularly affecting the soft tissues around the patella and patellar tendon. Susceptibility to knee bend DCS may be modifiable by adjusting the nature of the activities undertaken at the jump altitude to reduce the stress on knees especially. Nonetheless, other risk factors being equal, maintaining a similar general level of exertion is likely to retain a comparable residual risk of more severe (neurological or respiratory) DCS, even if sparing the knees. In contrast, none of the investigators accompanying subjects to 25,000 ft experienced either DCS or niggles, despite moving about the chamber, bending, kneeling, sitting, and standing at different times, and adopting a variety of postures to accomplish the echos. Their activities were less intensive and less repetitive, and their risk of DCS mitigated by the extra 30 min of denitrogenation.

Individuals >42 yr of age are at increased risk of DCS,[30] while age also influences propensity to generate heavy loads of VGE.[6] Data from the current study are consistent with these findings. Older dispatchers undertaking physical work at altitude, including assisting parachutists to stand and adjusting their equipment, are likely to perform brief strains that transiently promote a right-to-left shunt across a PFO, if one is present. In older dispatchers particularly, the early appearance, and persistence at altitude, of heavy VGE loads must then incur some risk of arterialization of gas. While PFOs have attracted considerable attention over the last three decades with regard to risk of right-to-left shunt and arterial embolization, pulmonary vascular shunts have been largely ignored but may be quite common. For both this study and a previous UK study of DCS,[8] approximately 10% of volunteers screened by CTTE had evidence of an extra-alveolar pulmonary shunt allowing microbubbles to bypass the pulmonary filter. Transpulmonary arterio-venous passage of gas may also be promoted by exertion,[12] and arterialization of VGE may also occur through normal lungs at rest.[21] Dispatchers are often experienced (older) parachute jump instructors who may be at increasing risk of arterialization over time, as their propensity to develop VGE increases with age.

With early recompression to ground level, minor symptoms of DCS may be expected to resolve completely during the descent. Traditionally, these cases have been managed breathing 100% oxygen at ground level for 2 h with a very low risk of symptom recurrence,[18,28] although the evidence underpinning this regime is unclear.[23] In this laboratory, providing symptoms at altitude have resolved fully following descent, such cases have been managed by breathing oxygen for 1 h at ground level, followed by observation for another hour. No symptom recurrences or adverse sequelae have been observed.

The main limitation of the current work, common to all human studies of DCS risk, is the small subject sample, offset to some degree by the repeated measures approach. Other limitations are the absence of female subjects, which we intend to address specifically in a follow-on study, and a lack of diversity in this predominantly Caucasian sample. The subjects' health status is broadly representative of military parachutist dispatchers, except that volunteers are prescreened for right-to-left vascular shunts and pre-existing WMH. The unusual age distribution of volunteers was entirely fortuitous but enabled some consideration of the influence of age, directly relevant to the population of military dispatchers, which includes more experienced parachute jump instructors. On the other hand, unfortunately, data were unavailable for any individuals in their fourth decade (30–39 yr). Another limitation is loss of subjects due to withdrawal during and between experiments. Other constraints common to DCS studies include the challenges of consistently high-quality echocardiography, within and between both subjects and imagers, and associated difficulty with consistent bubble grading. Nonetheless, highly reproducible environmental exposures were achieved, minimizing sources of bias.

In summary, parachutist dispatchers are at considerable risk of DCS following aircraft depressurization owing to their high levels of physical activity. Prediction of dispatchers' risk of DCS using the USAF ADRAC model should assume that their level of exertion is "heavy" and interpret the associated risk accordingly. At 25,000 ft, older dispatchers (>40 yr) are liable to generate early, heavy, and sustained VGE loads, with attendant risk of arterialization of bubbles through any functional intracardiac or pulmonary right-to-left shunt. On the other hand, repeated high-altitude parachuting sorties at slightly more modest altitudes (22,000 ft) in the same duty period may be safe, with carryover benefit of oxygen breathing to successive sorties, providing turn-around times breathing air at ground level are brief. Staged denitrogenation should be avoided at altitudes that risk bubble generation prior to final depressurization of the aircraft cabin.

ACKNOWLEDGMENTS

This work was funded by the UK Ministry of Defence under the Aircrew Systems Research Project. The authors would like to thank the many volunteers, subjects, investigators, colleagues, collaborators and advisers, too numerous to mention individually, who have helped make these demanding experiments not just possible, but even enjoyable and rewarding, at a particularly challenging time due to the pandemic. Besides the risk of DCS, in many cases their support has incurred considerable personal inconvenience, but has been freely and enthusiastically offered and has proven invaluable.

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

Authors and Affiliations: Desmond M. Connolly, PhD., MBBS, Timothy J. D'Oyly, MSc., BSc., and Vivienne M. Lee PhD., BSc., QinetiQ PLC, Cody Technology Park, Ively Road, Farnborough, Hampshire, GU14 0LX, UK; and Desmond M. Connolly, PhD., MBBS, Stephen D. R. Harridge, PhD., BSc., and Thomas G. Smith, DPhil, FRCA, Centre for Human and Applied Physiological Sciences, King's College London, UK.

REFERENCES

1. Allen TH, Maio DA, Bancroft RW. Body fat, denitrogenation and decompression sickness in men exercising after abrupt exposure to altitude. Aerosp Med. 1971; 42(5):518–524.
2. Buch DA, El Moalem H, Dovenbarger JA,Uguccioni DM, Moon RE. Cigarette smoking and decompression illness severity: a retrospective study in recreational divers. Aviat Space Environ Med. 2003; 74:1271–1274.
3. Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. Circulation. 1993; 88(5):2149–2155.
4. Conkin J, Foster PP, Powell MR, Waligora JM. Relationship of the time course of venous gas bubbles to altitude decompression illness. Undersea Hyperb Med. 1996; 23:141–149.
5. Conkin J, Powell MR, Foster PP, Waligora JM. Information about venous gas emboli improves prediction of hypobaric decompression sickness. Aviat Space Environ Med. 1998; 69:8–16.
6. Conkin J, Powell MR, Gernhardt ML. Age affects severity of venous gas emboli on decompression from 14.7 to 4.3 psia. Aviat Space Environ Med. 2003; 74:1142–1150.
7. Conkin J. Gender and decompression sickness: a critical review and analysis. Houston (TX): NASA Johnson Space Center; November 2004. NASA Technical Report, NASA/TP-2004-213148.
8. Connolly DM, Lee VM, D'Oyly TJ. Decompression sickness risk at 6553 m breathing two gas mixtures. Aviat Space Environ Med. 2010; 81(12): 1069–1077.
9. Connolly DM, Lee VM, Hodkinson PD. White matter status of participants in altitude chamber research and training. Aerosp Med Hum Perform. 2018; 89(9):777–786.
10. Connolly DM, Lupa HT. Prospective study of white matter health for an altitude chamber research program. Aerosp Med Hum Perform. 2021; 92(4):215–222.
11. Donald AE, Charakida M, Falaschetti E, Lawlor DA, Halcox JP, et al. Determinants of vascular phenotype in a large childhood population: the Avon Longitudinal Study of Parents and Children (ALSPAC). Eur Heart J. 2010; 31(12):1502–1510.

12. Eldridge MW, Dempsey JA, Haverkamp HC, Lovering AT, Hokanson JS. Exercise-induced intrapulmonary arteriovenous shunting in healthy humans. J Appl Physiol. 2004; 97(3):797–805.
13. Foster PP, Feiveson AH, Boriek AM. Predicting time to decompression illness during exercise at altitude, based on formation and growth of bubbles. Am J Physiol Regul Integr Comp Physiol. 2000; 279(6): R2317–R2328.
14. Furr PA, Sears WJ. Physiological effects of repeated decompression and recent advances in decompression sickness research: a review. Warrendale (PA): Society of Automotive Engineers 1988. Technical Paper Series # 881702.
15. Hashimoto M, Akishita M, Eto M, Ishikawa M, Kozaki K, et al. Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. Circulation. 1995; 92(12):3431–3435.
16. Heimbach RD, Sheffield PJ. Decompression sickness and pulmonary overpressure accidents. In: DeHart RL, editor. Fundamentals of Aerospace Medicine, Chapter 7. Philadelphia (PA): Lea and Febiger; 1985:139.
17. Hodkinson PD, Green NDC. Evidence based revision of pre-oxygenation and altitude exposure guidelines for high altitude parachuting. Aerosp Med Hum Perform. 2019; 90(3):189.
18. Krause KM, Pilmanis AA. The effectiveness of ground level oxygen treatment for altitude decompression sickness in human research subjects. Aviat Space Environ Med. 2000; 71:115–118.
19. Kumar KV, Calkins DS, Waligora JM, Gilbert JH III, Powell MR. Time to detection of circulating microbubbles as a risk factor for symptoms of altitude decompression sickness. Aviat Space Environ Med. 1992; 63:961–964.
20. Lee V, St Leger Dowse M, Edge C, Gunby A, Bryson P. Decompression sickness in women: a possible relationship with the menstrual cycle. Aviat Space Environ Med. 2003; 74:1177–1182.
21. Ljubkovic M, Marinovic J, Obad A, Breskovic T, Gaustad SE, Dujic Z. High incidence of venous and arterial gas emboli at rest after trimix diving without protocol violations. J Appl Physiol. 2010; 109(6): 1670–1674.
22. Møllerløkken A, Blogg SL, Doolette DJ, Nishi RY, Pollock NW. Consensus guidelines for the use of ultrasound for diving research. Diving Hyperb Med. 2016; 46(1):26–32.
23. Muehlberger PM, Pilmanis AA, Webb JT, Olson JE. Altitude decompression sickness symptom resolution during descent to ground level. Aviat Space Environ Med. 2004; 75:496–499.
24. Pilmanis AA, Webb JT, Kannan N, Balldin U. The effect of repeated altitude exposures on the incidence of decompression sickness. Aviat Space Environ Med. 2002; 73:525–531.
25. Pilmanis AA, Webb JT, Kamian N, Balldin UI. The risk of altitude decompression sickness at 12,000 m and the effect of ascent rate. Aviat Space Environ Med. 2003; 74:1052–1057.
26. Pilmanis AA, Petropoulos LJ, Kannan N, Webb JT. Decompression sickness risk model: development and validation by 150 prospective hypobaric exposures. Aviat Space Environ Med. 2004; 75:749–759.
27. Pilmanis AA, Webb JT, Balldin U. The impact of high levels of nitrogen in the breathing gas and in-flight denitrogenation on the risk of decompression sickness (DCS) during simulated altitude exposure. Wright-Patterson AFB (OH): U.S. Air Force Research Laboratory Report; April 2005. Report No.: AFRL-HE-BR-TR-2005-0036.
28. Rudge FW. The role of ground level oxygen in the treatment of altitude chamber decompression sickness. Aviat Space Environ Med. 1992; 63: 1102–1105.
29. Spencer MP. Decompression limits for compressed air determined by ultrasonically detected blood bubbles. J Appl Physiol. 1976; 40(2):229–235.
30. Sulaiman ZM, Pilmanis AA, O'Connor RB. Relationship between age and susceptibility to altitude decompression sickness. Aviat Space Environ Med. 1997; 68:695–698.
31. Webb JT, Kannan N, Pilmanis AA. Gender not a factor for altitude decompression sickness risk. Aviat Space Environ Med. 2003; 74:2–10.
32. Webb JT, Pilmanis AA, Balldin UI, Fischer JR. Altitude decompression sickness susceptibility: influence of anthropometric and physiologic variables. Aviat Space Environ Med. 2005; 76:547–551.
33. Webb JT, Pilmanis AA, O'Connor RB. An abrupt zero-preoxygenation altitude threshold for decompression sickness symptoms. Aviat Space Environ Med. 1998; 69:335–340.

Brain Microstructure and Brain Function Changes in Space Headache by Head-Down-Tilted Bed Rest

Masayuki Goto; Yasushi Shibata; Sumire Ishiyama; Yuji Matsumaru; Eiichi Ishikawa

INTRODUCTION: Several astronauts have experienced severe headaches during spaceflight, but no studies have examined the associated brain microstructure and functional changes. Head-down-tilted bed rest (HDBR) is a well-established method for studying the physical effects of microgravity on the ground. In this study, we analyzed the changes in brain microstructure and function during headache caused by HDBR using diffusion tensor imaging (DTI) and resting state functional magnetic resonance imaging (R-fMRI).

METHODS: We imaged 28 healthy subjects with DTI and R-fMRI in the horizontal supine position and HDBR. Using Tract-Based Spatial Statistics, fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity were compared between the headache and non-headache groups. Additionally, an analysis of functional connectivity (FC) was performed, followed by a correlation analysis between FC and numerical rating scale.

RESULTS: HDBR caused headaches in 21 of 28 subjects. DTI analysis showed no significant change in fractional anisotropy after HDBR, whereas axial diffusivity, radial diffusivity, and mean diffusivity increased significantly. R-fMRI analysis showed a significant decrease in FC in several areas after HDBR. The headache group showed significantly higher FC before HDBR, and both groups showed higher FC after HDBR. Correlation analysis showed a positive correlation between FC and numerical rating scale before HDBR but negative after HDBR.

DISCUSSION: We demonstrated the image change in the acute phase of space headache by HDBR using DTI and R-fMRI. Changes in brain microstructure and function specific to patients developing headaches may be evaluated by imaging.

KEYWORDS: space headache, head-down-tilted bed rest, diffusion tensor imaging, resting state functional MRI.

Goto M, Shibata Y, Ishiyama S, Matsumaru Y, Ishikawa E. *Brain microstructure and brain function changes in space headache by head-down-tilted bed rest*. Aerosp Med Hum Perform. 2023; 94(9):678–685.

Many astronauts develop severe headaches during spaceflight. It has been suggested that these headaches are caused by increased intracranial pressure as a result of fluid shift to the head in microgravity, abnormal sensory integration due to changes in the vestibular system and deep senses, and high carbon dioxide (CO_2) concentration in the International Space Station (ISS).[23]

This space headache is newly listed as "spaceflight headache" in Appendix A.10.8 Headache Due to Other Homeostasis Disorders in the International Classification of Headache, Third Edition (ICDH-3).[8] Human space exploration will soon accelerate human expansion into space, and space headaches that degrade astronaut performance and affect mission success will become an important issue.[17] Therefore, further research on the pathogenesis of such headaches is required.

In the first report in 2009, 12 of 17 astronauts (71%) (1 woman and 16 men, aged 28–58 yr) experienced headaches during spaceflight.[24] A total of 21 headaches occurred in 12 astronauts, 2 (9.5%) of which met the diagnostic criteria for migraine based on the International Classification of Headache, Second Edition (ICDH-2); the remaining were tension-type or nonspecific pain. The majority of the pain (71%) was moderate-to-severe, and headaches (76%) occurred independently of space motion sickness symptoms. Moreover, there was no relationship between headache onset and duration of stay in space.

From the Department of Neurosurgery, Headache Clinic, Mito Medical Center, Mito Kyodo General Hospital, Mito, Japan.

This manuscript was received for review in September 2022. It was accepted for publication in June 2023.

Address correspondence to: Yasushi Shibata, M.D., Ph.D., Department of Neurosurgery, Headache Clinic, Mito Medical Center, Mito Kyodo General Hospital, 3-2-7 Miyamachi, Mito-shi, Ibaraki-ken 310-0015 Japan; yshibata@md.tsukuba.ac.jp.

DOI: https://doi.org/10.3357/AMHP.6177.2023

In a ground-based replication study of space headaches caused by head-down-tilted bed rest (HDBR), 14 of 22 subjects (63.6%) developed headaches, and centrifugal accelerator and aerobic exercise coping strategies during HDBR did not eliminate the headache but decreased its severity, and the headache occurred most frequently on the first day of the experiment.[23]

Moreover, in a study of 12 healthy subjects who also underwent a 5-d −6° HDBR, 7 (58.3%) developed headaches.[5] The results showed that the levels of epinephrine, hematocrit, hemoglobin, and other blood cell components increased, but the levels of salivary cortisol decreased in headache-prone subjects. The levels of zonulin, a tight junction marker, also increased. The study suggests that hemoconcentration occurs in all subjects and that fluid redistribution due to intravascular-to-extravascular water transfer, as well as fluid shift, is the cause of headaches.

HDBR is a well-established method for studying the physical effects of microgravity in space on the ground.[18] In recent headache research, magnetic resonance imaging (MRI) has been used to clarify the pathophysiology of some headaches, and diffusion tensor imaging (DTI) and resting state functional MRI (R-fMRI) can noninvasively evaluate dynamic changes in brain microstructure and functions in real time.[22] Although many findings have been reported on the pathophysiology of primary headaches, such as migraine and cluster headaches, by using these MRI methods,[3,18] there are no reports of such imaging analysis on space headaches.

We hypothesized that patients with space headache would have some alterations in brain microstructure and that there would be differences in brain function between the patients with and without space headache. These differences might be useful in predicting the onset of space headache. Therefore, to clarify these hypotheses, we performed HDBR on healthy subjects and analyzed how their brain microstructure and function differed according to headache occurrence.

METHODS

Subjects

There were 28 healthy adult volunteers, 11 men and 17 women, with a mean age of 47.7 ± 11.7 yr, participating in this study from March 2021 to December 2021. The inclusion criteria were as follows: 1) had no primary headache and 2) had no organic intracranial lesions. Participants' medical history included overactive bladder, hyperuricemia, anemia, sinusitis, duodenal ulcer, dermatomyositis, spinal canal stenosis, and diabetes. The exclusion criteria were as follows: 1) pregnancy; 2) had been enrolled to participate in other clinical trials; and 3) had claustrophobia, a pacemaker, and/or other medical issues causing them to be inappropriate for MRI imaging. Written informed consent was obtained from all subjects.

The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association, the Ethical Guidelines for Clinical Research, and related laws and guidelines such as the Pharmaceutical Affairs Law. The study protocol was approved by the Ethics Committee of Mito Kyodo General Hospital (No. 20-52) and was registered in the University hospital Medical Information Network trial registry (ID: UMIN000043583).

Procedure

This was a single-arm study. All subjects were first imaged in the horizontal supine position with R-fMRI and DTI. Then, HDBR was performed in the supine position by lowering the head 10° from the horizontal position, and the subjects were observed for 10 min. Next, the same MRI imaging was performed again in HDBR. Before the start of imaging, the patient's physical condition was thoroughly confirmed by interview.

Headache was assessed 10 min after starting HDBR and again after the second MRI, which was performed under HDBR conditions. Headache symptoms and headache intensity were evaluated. Headache symptoms were classified into "congestion," "heavy feeling," and "pressing" based on the subject's representation. Subjects were also asked about the presence or absence of accompanying symptoms such as nausea. Headache intensity was evaluated objectively using the numerical rating scale (NRS), which is a well-established method for the quantitative assessment of pain in headache research,[1,4] and was also assessed on a three-point scale of "mild," "moderate," and "severe" in accordance with prior reports of space headaches (**Fig. 1**).[5,23,24]

Image Acquisition

Data were acquired with a 3.0-Tesla MRI scanner (Siemens, Erlangen, Germany) using a 3-channel head coil. Our routine protocols included: T1-weighted volume with the magnetization-prepared rapid acquisition with gradient echo (sagittal), R-fMRI and DTI. T1-weighted imaging parameters were as follows: repletion time (TR)/echo time (TE) = 2300/2.32 msec, FOV = 240 mm, 192 sagittal slices, slice thickness = 0.9 mm, and base resolution = 256 × 256. Diffusion-weighted acquisition using spin-echo planar imaging parameters were as follows: TR/TE = 7500/95 ms, matrix size = 128 × 128, 65 axial slices, and b values of 0, 1000, and 2000 s · mm^{-2}. R-fMRI parameters were as follows: TR/TE = 2500/35 ms, FOV = 192, slice thickness = 4 mm, slice axial = 40, matrix = 64 × 64, and voxel size = 3.0 × 3.0 × 4.0.

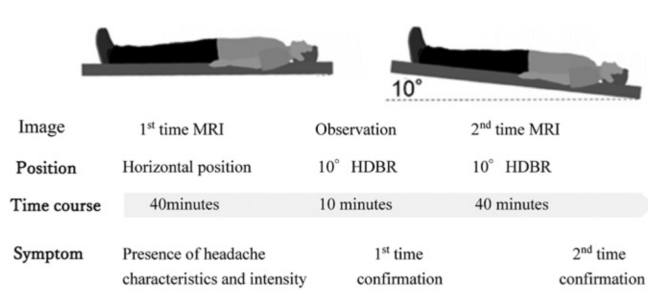

Fig. 1. All subjects underwent R-fMRI and DTI on a 3.0-T MRI scanner in the horizontal supine position and HDBR for 40 min each. First, imaging was performed in the horizontal position, followed by 10 min of observation as HDBR, and if there were no problems, a second imaging was performed as is. Headache symptoms and intensity were evaluated 10 min after the start of HDBR and after the second MRI under HDBR.

Image Analysis

DTI is a method to analyze the amount and direction of diffusion of water molecules by applying a tilted magnetic field in six directions. The amount of diffusion in the direction of the long axis of the molecule is known as axial diffusivity (AD), the amount of diffusion perpendicular to AD is known as radial diffusivity (RD), and the average of the three directions is known as mean diffusivity (MD). Fractional anisotropy (FA) is an indicator of the directionality of diffusion, and its value is 0 for all isotropic directions in free water and 1 when restricted to only one direction.[22] In this study, Tract-Based Spatial Statistics (TBSS) was performed by aggregating the voxel unit values of the whole brain into a mean white matter skeleton, with standardized brain morphology, and comparing them in the horizontal supine position and HDBR to perform whole-brain analysis. The FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl) was used to create FA, AD, RD, and MD skeletons for each subject. From these white matter skeletons, we extracted regions of interest (ROIs) in the knee and body and the splenium of corpus callosum, where several significant differences between subjects with migraine and healthy subjects have been reported in previous studies[25–27] using the ICBM-DTI-81 white-matter labels atlas.[15]

Functional MRI (fMRI) is an imaging method that captures changes in the amount of oxidized hemoglobin associated with increased brain activity as blood-oxygenation-level-dependent.[6] Although fMRI is usually performed with some tasks, R-fMRI which explores brain activity at rest without a task, is highly reproducible and reliable and is suitable for observing network changes during headaches. In the present study, we used R-fMRI and the subjects were asked to keep their eyes closed and not to think during the 7-min imaging period. We selected 30 ROIs, including the frontal cortex, cingulate cortex, insular cortex, bridges, and cerebellum, which have been reported to change functional connectivity (FC) in many studies of headache.[21]

Statistical Methods

All analyses were performed using SPSS version 28.00 (IBM, Armonk, NY), with Fisher's exact test for gender and a two-sample unpaired *t*-test for age between the two groups of headache and non-headache subjects. Mean FA, MD, AD, and RD in the ROIs of the corpus callosum of all 28 subjects were calculated using the paired *t*-test program, MATLAB (R2017a). Non-parametric tests (permutation test; 5000 times) and family-wise error correction were performed for each voxel using the randomized program, with a significance level of < 5%. CONN was used in the R-fMRI analysis, and a paired *t*-test was conducted before and after HDBR in all 28 cases for each of the mean FC values in 30 ROIs, viz., the above-described pain-related regions. Next, FC comparisons were performed between the headache and non-headache groups using *t*-tests in the same 30 ROIs. In both analyses, $P < 0.05$ was considered significant using multiple comparison corrections for the false discovery rate (FDR). Correlation analyses were performed between NRS and all FCs obtained from the 30 ROIs before and after HDBR. The Pearson correlation coefficient was determined. The significance level was set at $P < 0.05$.

RESULTS

Of the 28 subjects in this study, 21 developed headaches and 7 did not. The mean age was 44.3 ± 11.6 yr in the headache group and 54.7 ± 10.9 yr in the non-headache group ($P = 0.05$). Headache intensity was mild in 13 patients, moderate in 7 patients, and severe in 1 patient, with a median NRS of 1.5 at 10 min after the start of HDBR and 1.5 at the end of the second MRI. Headache symptoms included a sense of heavy feeling in 12 patients, congestion in 7 patients, and pressing in 2 patients. None of the subjects complained of nausea or other associated symptoms (**Table I**). After the second MRI with HDBR, the condition of the patients in the headache group immediately recovered, and no patient had a prolonged headache.

DTI analysis showed no significant difference in FA values between before and after HDBR. On the other hand, AD, RD, and MD significantly increased in the genu of the corpus callosum after HDBR. AD and MD also increased significantly in the body and splenium of the corpus callosum after HDBR (**Fig. 2**, **Table II**).

R-fMRI analysis showed a significant decrease in FC after HDBR between the left cerebellum and bilateral inferior frontal gyrus (pars opercularis and triangularis) as well as

Table I. Characteristics of All Subjects Included in the Study.

CHARACTERISTIC	HEADACHE GROUP (*N* = 21)	NON-HEADACHE GROUP (*N* = 7)	*P*-VALUE
Mean of age, yr ± SD.	44.3 ± 11.6	54.7 ± 10.9	0.05*
Gender, women/men	14/7	3/4	0.381**
Basic disease (%)			
Overactive bladder	0	1	NA
Hyperuricemia	1	0	NA
Anemia	2	0	NA
Sinusitis	1	0	NA
Duodenal ulcer	0	1	NA
Dermatomyositis	0	1	NA
Spinal canal stenosis	1	1	NA
Diabetes	0	1	NA
Median NRS (percentile)			
10 min after starting HDBR	1.5 (0.00-3.00)	—	NA
After HDBR imaging	1.5 (0.25-4.00)	—	NA
Severity			
Mild	13	—	NA
Moderate	7	—	NA
Severe	1	—	NA
Character			
Heavy feeling	12	—	NA
Congestion	7	—	NA
Pressing	2	—	NA

SD = standard deviation; NA = not applicable.

*Two-sample unpaired t-test.

**Fisher's exact test.

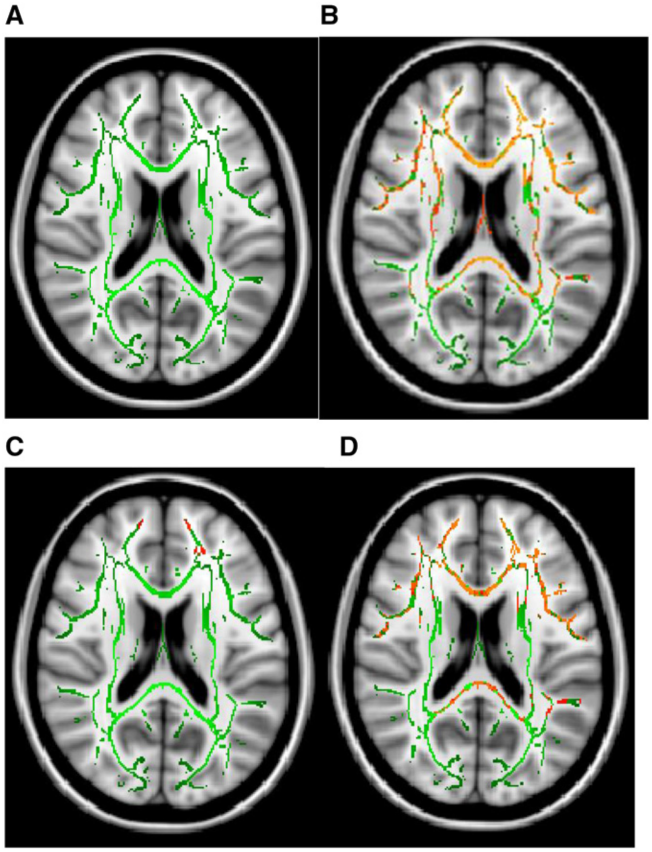

Fig. 2. TBSS shows changes in FA, AD, RD, and MD before and after HDBR. The orange part shows a significant increase in AD, RD, and MD after HDBR. AD and MD also increased significantly in the body and splenium of the corpus callosum after HDBR.

bilateral frontal orbital cortex (family-wise error corrected, $P < 0.05$). FC also significantly decreased between the right cerebellum and right inferior frontal gyrus (pars triangularis), as well as right frontal orbital cortex and between the frontal medial cortex and cingulate gyrus (posterior division). There was no increase in FC after HDBR in all regions (**Fig. 3A**). In comparison between the headache and nonheadache groups,

Table II. DTI Values Before and After HDBR.

DIRECTION OF DTI IN AREA OF CORPUS CALLOSUM	PRE-HDBR ($mm^2/s \times 10^{-3}$)	POST-HDBR ($mm^2/s \times 10^{-3}$)	*P*-VALUE
AD			
Genu	0.974 ± 0.058	1.012 ± 0.087	0.0227*
Body	1.005 ± 0.053	1.049 ± 0.086	0.00915*
Splenium	0.999 ± 0.055	1.031 ± 0.092	0.0467*
RD			
Genu	0.238 ± 0.049	0.246 ± 0.051	0.0273*
Body	0.279 ± 0.047	0.287 ± 0.054	0.169*
Splenium	0.190 ± 0.029	0.195 ± 0.033	0.214*
MD			
Genu	0.483 ± 0.045	0.501 ± 0.054	0.0206*
Body	0.521 ± 0.039	0.541 ± 0.055	0.0266*
Splenium	0.460 ± 0.028	0.473 ± 0.046	0.0735*

*Two-sample paired t-test.

FC was significantly higher between the right inferior frontal gyrus and left cerebellum in the headache group before HDBR, i.e., before headache onset (Family Wise Error corrected, $P < 0.05$, **Fig. 3B**). After HDBR, FC was significantly higher between the brainstem and left inferior frontal gyrus (pars opercularis, triangularis), left hypothalamus, and left cerebellum in the headache group. FC was significantly higher between right frontal eye field and right cerebellum in the nonheadache group (uncorrected, $P < 0.01$, **Fig. 3C**). Correlation analysis of NRS and all FCs obtained from the 30 ROIs revealed a positive correlation between NRS and FC related to the "hypothalamus" before head down (Pearson correlation coefficient 0.448, $P = 0.017$). In other words, the higher the FC associated with the hypothalamus at rest, the stronger the headache at head down (**Fig. 4A**).

After head-down, we detected a negative correlation between NRS and FC related to the thalamus and cerebellum (Pearson correlation coefficient −0.541, $P = 0.003$). In other words, the higher the headache intensity, the lower the functional coupling related to the thalamus and cerebellum (**Fig. 4B**).

DISCUSSION

We were able to capture the acute change in brain microstructure due to headache that occurs during a short HDBR. A study reported that increases in FA, MD, RD, and AD were observed in the optic nerve sheaths of 5 head-down tilt conditions in 9 subjects: (−6°, −12°, −18°, −12°, and 1% CO_2, and −12° + lower body negative pressure) after 4.5 h, which were reported to be due to increased perioptic cerebral spinal fluid hydrodynamics during head-down tilt.[8] Another report indicated that at −6° HDBR for 30 d, FA increased in some areas and decreased in others, and it was concluded that increased FA might reflect the strengthened connectivity in microgravity conditions, and that decreased FA was linked to an increase in the extracellular space (dysmyelination, axonal degeneration, and release of white matter fibers) and a decrease of the intracellular space (edema) in the white matter.[11]

Other headache pathophysiology studies have also reported fluctuations in these diffusions, with reports of decreased AD, RD, and MD in the corpus callosum in idiopathic intracranial hypertension.[19] Idiopathic intracranial hypertension is a disease of unknown pathogenesis characterized by headache, nausea, and optic papillary edema, which is thought to be caused by excessive cerebrospinal fluid production and absorption and venous return disorders.[13]

In idiopathic intracranial hypertension, axonal degeneration due to long-term intracranial hypertension and ventricular size enlargement may have resulted in decreased water molecule diffusion, whereas in the present study, acute white matter compression due to head-down tilt may have resulted in increased diffusion per unit volume. Thus, microstructural changes can be detected even in acute headaches due to HDBR and may represent anatomical changes similar to those in space headaches.

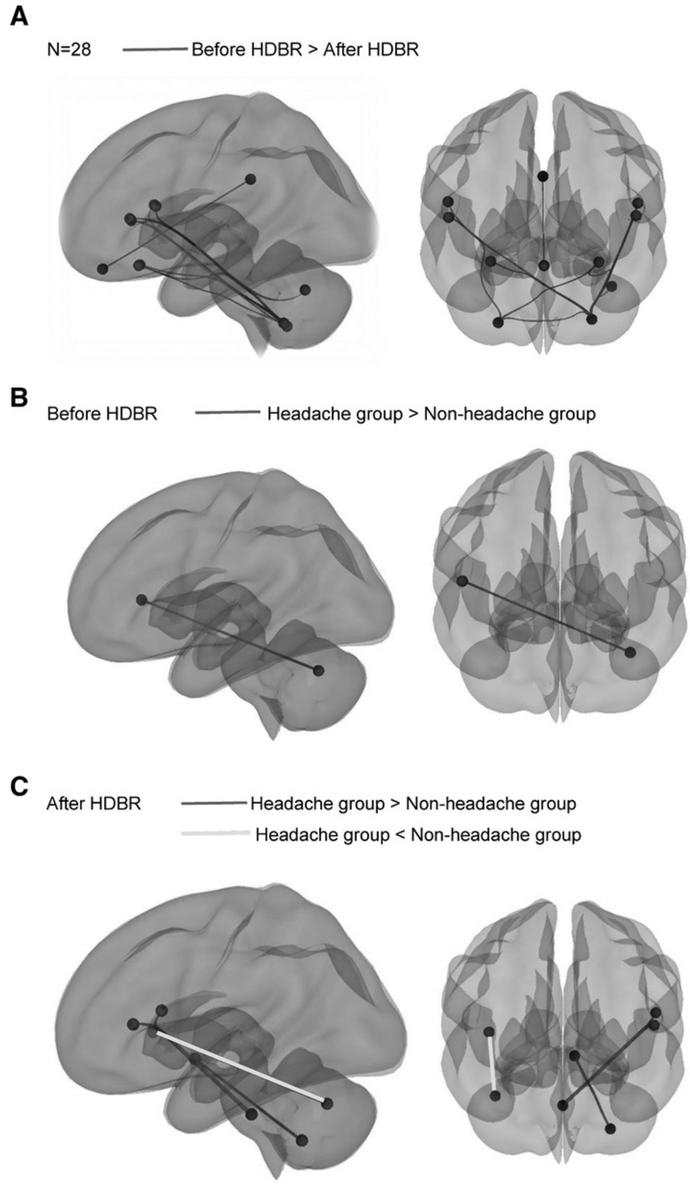

Fig. 3. Comparison of FC in 28 subjects before and after HDBR and comparison of FC between the headache and non-headache groups. A) The gray lines show that FC decreased significantly after HDBR in comparison to before HDBR. B) The gray line shows that FC significantly increased before HDBR between the right inferior frontal gyrus and left cerebellum in the headache group, in comparison between the headache and non-headache groups. C) The gray lines show that FC significantly increased after HDBR between the brainstem and left inferior frontal gyrus valgus and triangle, and between the left hypothalamus and left cerebellum in the headache group, in comparison between the headache and non-headache groups. The white line shows that FC significantly increased after HDBR between the right frontal eye field and right cerebellum in the non-headache group, in comparison between the headache and non-headache groups.

Regarding the relationship between headache and FC, it has been reported that FC in the brainstem and hypothalamus increases during migraine attacks.[15] But in the present study, the R-fMRI analysis revealed a significant decrease in FC after HDBR, and there was no increase in FC after HDBR. These results indicate that headache due to HDBR is associated with reduced brain function. In other words, the ability to control pain may be transiently reduced. Comparing the headache and non-headache groups, FC was significantly higher in the headache group before and after HDBR. In comparison with normal subjects, migraine patients in the interictal period showed higher connectivity between the periaqueductal white matter of the midbrain and right dorsolateral prefrontal cortex, right superior border gyrus, right anterior insular cortex, bilateral precentral gyrus, right postcentral gyrus, right thalamus, left angular gyrus, left supramarginal gyrus, and parietal opercular part.[12] The periaqueductal gray matter of the midbrain is known as a descending pain suppression pathway in the central nervous system, which descends from the insula and hypothalamus to the trigeminospinal tract nucleus.[16] It is possible that the brain activity in these regions is higher in the headache group than in the normal group from normal times. In a comparative study of migraine patients during the paroxysmal phase with healthy controls, migraine patients showed increased

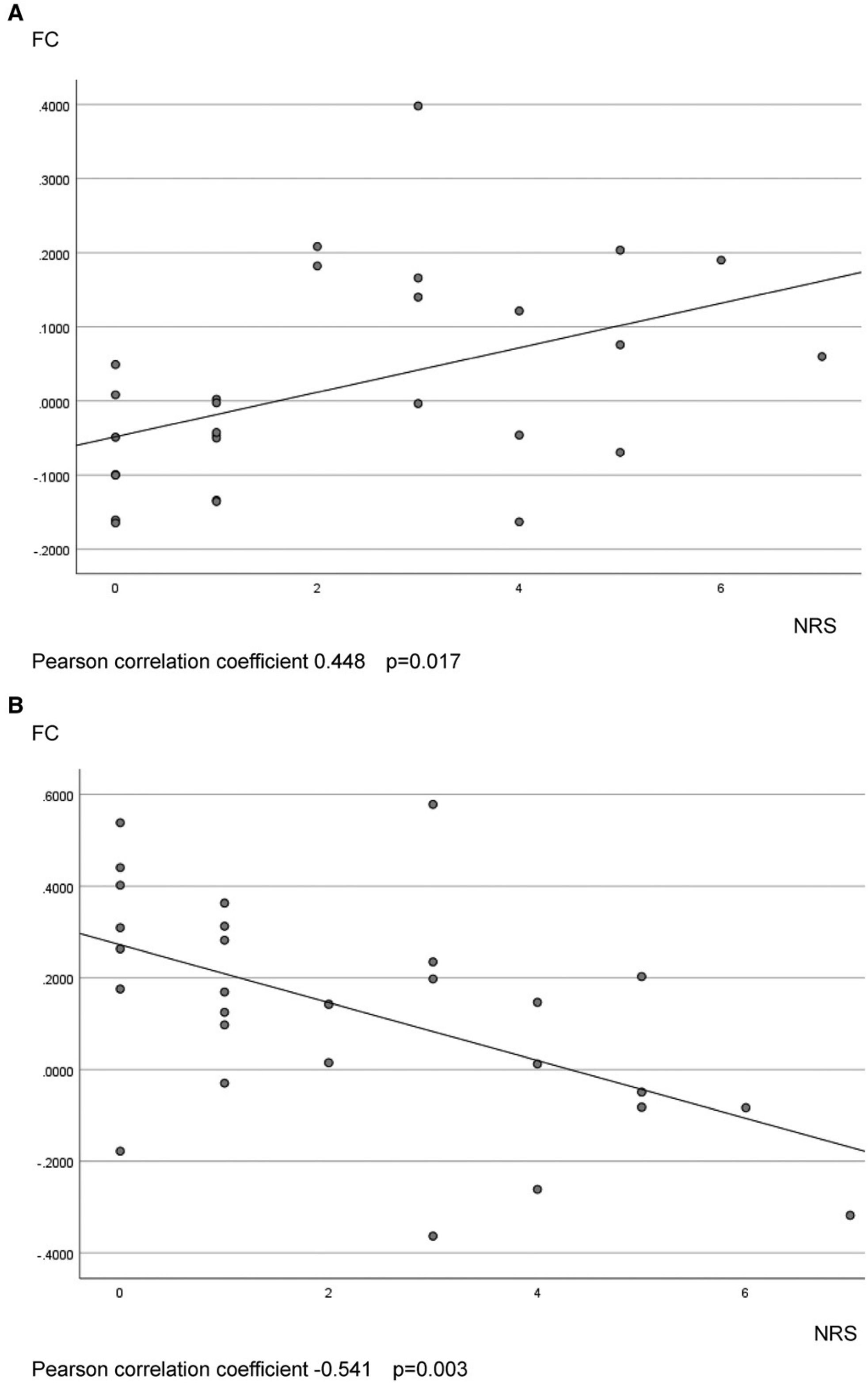

Fig. 4. Correlation analysis of NRS and all FCs obtained from the 30 ROIs. A) Positive correlation between NRS and FC related to the "hypothalamus" before head-down. B) Negative correlation between NRS and FC related to the "thalamus and cerebellum" after head-down.

connectivity between the medial prefrontal cortex (MPFC) and the insula and posterior cingulate gyrus.[2] The brainstem, cerebellum, and hypothalamus, which had significantly higher FC in the headache group after HDBR, have been recognized as pain-related regions in known headache studies, including migraine,[16] suggesting that these regions are also activated in this headache. Regarding the correlation analysis between FC and NRS, previous migraine studies have reported that the hypothalamic activity increases 48 h before an attack and that the hypothalamus and areas with high FC change from the aura period to the attack period.[20] The positive correlation between FC and NRS associated with the hypothalamus before head-down in the present study suggests that the hypothalamus is also more active than normal in the headache group.

Furthermore, the thalamus and cerebellum are pain-related regions in headache. The thalamus transmits pain signals from the trigeminal nerve to the cerebral cortex in migraine. The cerebellum is one of the ascending tracts where pain is transmitted from the trigeminal spinal nucleus to the hypothalamus and brainstem (parabarachial nucleus and solitarius of the midbrain and pons).[16] The negative correlation between FC and NRS associated with the thalamus and cerebellum after head-down in the present study suggests that the higher the headache intensity, the lower the function of the thalamus and cerebellum. However, it is unclear from the present study whether the functional decline was the cause of the headache or the result of the headache and requires further investigation.

There are several limitations to this study. First, it is a single-arm study with a small population of 28 participants. Second, the HDBR time is short, approximately 50 min. Several previous studies using HDBR, not only headache studies, have performed HDBR from a few hours to 30 d.[7,11] In this study, due to the limitation of the examination schedule, the imaging analysis captured only the acute changes immediately after HDBR. Analysis of the microstructure of headache produced by prolonged HDBR is a subject for future study. Third, ROIs were placed in 30 locations and we did not devise detailed segmentation, including a breakdown of the interior of the brainstem. Similar studies on headaches (such as migraine) have measured FC in detailed ROIs (such as the trigeminal nucleus),[20] but the CONN used in this study automatically obtains ROIs covering the entire brainstem, including the midbrain, pons, and medulla. Therefore, analysis including detailed brainstem segmentation is a topic for future research.

In this study, the most fundamental limitation is that HDBR does not reproduce the complete space environment. Although HDBR studies have been considered as established models to mimic the physiological effects of outer space microgravity on the human body,[5] in addition to fluid shifts due to microgravity, other effects of the space environment on the human body include galactic cosmic rays and localized high CO_2 effects in the ISS. It has been reported that CO_2 concentration is higher on the ISS than on the ground, and that the higher the concentration, the higher the frequency of headaches.[10] It has also been noted that high CO_2 concentrations in the ISS affect the ability to regulate cerebral blood flow.[28] Previously, HDBR has been mainly performed at −6°,[5,11,23] but a recent study reported that a combination of mild hypercapnia (exposure to 3% CO_2, which increases end-tidal CO_2 to 6 mmHg) and −10° HDBR affected dynamic cerebral autoregulation and cerebral blood flow.[9] In the present study, we employed −10° HDBR only to investigate the effect of fluid shift alone (excluding the CO_2 effect) on headache onset. Studying the effects of combined exposure to fluid upward shift and high CO_2 on space headache is a subject for future study.

Although there have been imaging studies using DTI and fMRI during HDBR,[11,14] there have been no previous studies using MRI to analyze microstructural and brain function changes during HDBR-induced headache, which we believe is highly novel.

In this study, we reproduced the pathophysiology of space headache by using HDBR to simulate the space environment and revealed acute changes in brain microstructure and function. The results suggest that changes in brain microstructure during headache onset and the strength of FC characteristic of patients who develop headaches may be evaluated by imaging. These results may be useful for predicting the onset of space headaches and for health management during human space exploration.

ACKNOWLEDGMENTS

The authors would like to thank Enago (www.enago.jp) for the English language review. This work was supported by JSPS (Japan Society for the Promotion of Science) KAKENHI Grant Numbers JP16K10306, JP16H06280, and JP20K08099.

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

Authors and Affiliations: Masayuki Goto, M.D., Ph.D., Department of Neurosurgery, Headache Clinic, Mito Medical Center, Mito Kyodo General Hospital, University of Tsukuba, Tsukuba, Japan, and Seirei Memorial Hospital, Hitachi, Japan; Yasushi Shibata, M.D., Ph.D., Department of Neurosurgery, Headache Clinic, Mito Medical Center, Mito Kyodo General Hospital, University of Tsukuba, Tsukuba, Japan; Sumire Ishiyama, Ph.D., Ibaraki Prefectural University of Health Sciences, Ami, Japan; Yuji Matsumaru, M.D., Ph.D., Department of Stroke and Cerebrovascular Diseases, University of Tsukuba, Tsukuba, Japan; and Eiichi Ishikawa, M.D., Ph.D., Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan.

REFERENCES

1. Barbanti P, Egeo G, Aurilia C, d'Onofrio F, Albanese M, Cetta I, Di Fiore P, Zucco M, Filippi M, Bono F, Altamura C, Proietti S, Bonassi S, Vernieri F; FRIEND-Study Group. Fremanezumab in the prevention of high-frequency episodic and chronic migraine: a 12-week, multicenter, real-life, cohort study (the FRIEND study). J Headache Pain. 2022; 23(1):46.
2. Coppola G, Di Renzo A, Tinelli E, Di Lorenzo C, Scapeccia M, et al. Resting state connectivity between default mode network and insula encodes acute migraine headache. Cephalalgia. 2018; 38(5):846–854.
3. Coppola G, Tinelli E, Lepre C, Iacovelli E, Di Lorenzo C et al. Dynamic changes in thalamic microstructure of migraine without aura patients: A diffusion tensor magnetic resonance imaging study. Eur J Neurol. 2014; 21(2):287–e13.
4. Dunning JR, Butts R, Mourad F, Young I, Fernandez-de-Las Peñas C, Hagins M, Stanislawski T, Donley J, Buck D, Hooks TR, Cleland JA. Upper cervical and upper thoracic manipulation versus mobilization and exercise in patients with cervicogenic headache: a multi-center randomized clinical trial. BMC Musculoskelet Disord. 2016; 17:64:26852024
5. Feuerecker M, van Oosterhout WPJ, Feuerecker B, Matzel S, Schelling G, et al. Headache under simulated microgravity is related to endocrine, fluid distribution, and tight junction changes. Pain. 2016; 157(5): 1072–1078.

6. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007; 8(9):700–711.
7. Gerlach DA, Marshall-Goebel K, Hasan KM, Kramer LA, Alperin N, Rittweger J. MRI-derived diffusion parameters in the human optic nerve and its surrounding sheath during head-down tilt. Microgravity. 2017; 3(18)
8. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd ed. (beta version). Cephalalgia. 2013; 33(9):629–808.
9. Kurazumi T, Ogawa Y, Yanagida R, Morisaki H, Iwasaki K. Non-invasive intracranial pressure estimation during combined exposure to CO_2 and head-down tilt. Aerosp Med Hum Perform. 2018; 89(4):365–370.
10. Law J, Van Baalen M, Foy M, Mason SS, Mendez C, et al. Relationship between carbon dioxide levels and reported headaches on the international space station. J Occup Environ Med. 2014; 56(5):477–483.
11. Li K, Guo X, Jin Z, Ouyang X, Zeng Y, et al. Effect of simulated microgravity on human brain gray matter and white matter – evidence from MRI. PLoS One. 2015; 10(8):e0135835.
12. Mainero C, Boshyan J, Hadjikhani N. Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray network in migraine. Ann Neurol. 2011; 70(5):838–845.
13. Markey KA, Mollan SP, Jensen RH, Sinclair AJ. Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions. Lancet Neurol. 2016; 15(1):78–91.
14. McGregor HR, Lee JK, Mulder ER, De Dios YE, Beltran NE, et al. Brain connectivity and behavioral changes in a spaceflight analog environment with elevated CO2. Neuroimage. 2021; 225:117450.
15. Mori S, Wakana S, van Zijl PCM, Nagae-Poetscher LM. MRI Atlas of human white matter. Amsterdam (Netherlands): Elsevier; 2005.
16. Ota T, Kawahara N, Nozaki K, Yoshizaki T, Wakabayashi T. Noshinkeigekagaku I. 12th ed. Kyoto (Japan): Kinpodo; 2016.
17. Parisa Gazerani. Space headache. Future Neurol. 2017; 12(2):61–64.
18. Planchuelo-Gómez Á, García-Azorín D, Guerrero ÁL, Aja-Fernández S, Rodríguez M, De Luis-García R. White matter changes in chronic and episodic migraine: a diffusion tensor imaging study. J Headache Pain. 2020; 21(1):1–15.
19. Sarica A, Curcio M, Rapisarda L, Cerasa A, Quattrone A, Bono F. Periventricular white matter changes in idiopathic intracranial hypertension. Ann Clin Transl Neurol. 2019; 6(2):233–242.
20. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. Brain. 2016; 139(7):1987–1993.
21. Schwedt TJ, Chiang CC, Chong CD, Dodick DW. Functional MRI on migraine. Lancet Neurol. 2015; 14(1):81–91.
22. Shibata Y, Goto M, Ishiyama S. The analysis of migraine pathophysiology using magnetic resonance imaging. OBM Neurobiol. 2022; 6(1):115.
23. van Oosterhout WP, Terwindt GM, Vein AA, Ferrari MD. Space headache on Earth: head-down-tilted bed rest studies simulating outer-space microgravity. Cephalalgia. 2015; 35(4):335–343.
24. Vein AA, Koppen H, Haan J, Terwindt GM, Ferrari MD. Space headache: a new secondary headache. Cephalalgia. 2009; 29(6):683–686.
25. Yu D, Yuan K, Qin W, Zhao L, Dong M, et al. Axonal loss of white matter in migraine without aura: a tract-based spatial statistics study. Cephalalgia. 2013; 33(1):34–42.
26. Yu D, Yuan K, Zhao L, Dong M, Liu P, et al. White matter integrity affected by depressive symptoms in migraine without aura: a tract-based spatial statistics study. NMR Biomed. 2013; 26(9):1103–1112.
27. Yuan K, Qin W, Liu P, Zhao L, Yu D, et al. Reduced fractional anisotropy of corpus callosum modulates inter-hemispheric resting state functional connectivity in migraine patients without aura. PLoS One. 2012; 7(9): e45476.
28. Zuj KA, Arbeille P, Shoemaker JK, Blaber AP, Greaves DK, et al. Impaired cerebrovascular autoregulation and reduced CO_2 reactivity after long duration spaceflight. Am J Physiol Heart Circ Physiol. 2012; 302(12): H2592–H2598.

Exercise Effect on Mental Health in Isolating or Quarantining Adults

Vichai Chu; David G. Newman

INTRODUCTION: In response to coronavirus disease 2019 (COVID-19), travelers are typically subject to quarantine, which is often associated with poorer mental health (MH). While the protective benefits of community-based exercise are widely recognized, the degree to which this extends to the confined setting is unknown. This systematic review aims to evaluate the effect of exercise on MH in isolating or quarantining adults.

METHODS: A literature search of Ovid MEDLINE, APA PsycInfo, and the Cochrane Database of Systematic Reviews limited to January 2019–September 2021 inclusive yielded five eligible studies.

RESULTS: Data comprised a total of 2755 college and university students, most of whom were confined. Depending on the scale used, 24.9–76.7% of respondents demonstrated impaired MH, which improved with physical activity (PA), especially when regular and moderate or vigorous. The frequency, duration, and participants of exercise increased as lockdown progressed. One study showed that while sleep, diet, and PA all have an impact on MH, PA was the factor most strongly correlated with MH.

DISCUSSION: Physical fitness should be optimized before and maintained during quarantine while exercise space and equipment should be accessible. Importantly, the sustainability of persistent quarantine must be considered given the pervasiveness of COVID-19.

KEYWORDS: air travel, COVID-19, lockdown, depression, anxiety, stress, mood, well-being, physical activity.

Chu V, Newman DG. *Exercise effect on mental health in isolating or quarantining adults*. Aerosp Med Hum Perform. 2023; 94(9):686–695.

In March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic.[24] Globally, 226.8 million cases, including 4.7 million deaths, were reported as of 17 September 2021,[89] the direct and indirect costs estimated at 16 trillion USD.[25] Balancing health costs against economic costs, government responses varied widely, fluctuating over the course of the outbreak. The Stringency Index records out of 100 the strictness of policies that primarily restrict people's behaviors. On 18 March 2020, this ranged from 0 in Dominica (no restrictions) to 100 in Jordan (nationwide curfew).[81] Absent definitive treatment, nonpharmaceutical interventions such as hand hygiene, personal protective equipment, and physical distancing became the mainstay.[49] COVID-19 cannot be differentiated from influenza based on symptomology alone. COVID-19's incubation period ranges from 2.33 to 17.60 d, with the average of 6.38 increasing 1 d per decade in the elderly.[30,66] Thus, travelers are subject to control measures such as travel restrictions, border screening, and quarantine,[13] typically 14 d, sometimes longer.[80]

Pursuant to the Australian Biosecurity Act,[9] leaving isolation or quarantine without permission except under exigent circumstances is a criminal offense liable to imprisonment and a fine. Food and medication must be delivered since visiting public places is prohibited,[7,8] effectively restricting Maslow's Hierarchy of Needs[60] to the bottom two tiers (**Fig. 1**).[68] Failing to fulfill the first three tiers may contribute to suicidal ideation when "psychache," a cognitive state of mental torment or "constriction," reaches a limit and no effective methods are

From the School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia.

This manuscript was received for review in February 2022. It was accepted for publication in June 2023.

Address correspondence to: Professor David G. Newman, MB, BS, DAvMed, MBA, PhD, Hon FRAeS, FAsMA, FACAsM, FAICD, FRSM, FGIA, Visiting Professor of Aerospace Medicine, Center for Human & Applied Physiological Sciences, King's College London, Shepherd's House, Guy's Campus, London SE1 1UL, United Kingdom; david.1.newman@kcl.ac.uk.

DOI: https://doi.org/10.3357/AMHP.6073.2023

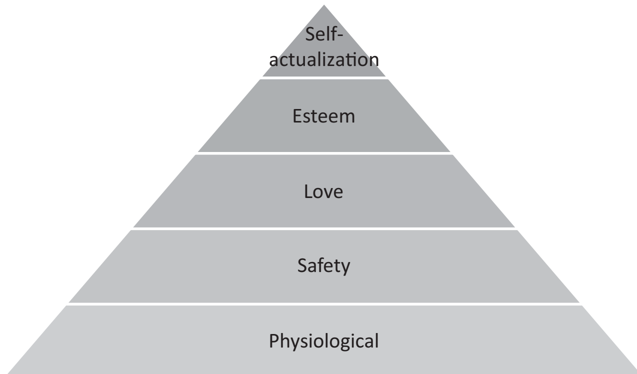

Fig. 1. Maslow's Hierarchy of Needs. Maslow theorized that basic human needs are prioritized in an ascending hierarchy, such that a "higher" need will not be pursued unless the "lower" need is met.[60]

identified to reduce it.[40] Indeed, being quarantined is associated with anxiety, depression, and suicidality,[35,50,90] the first two significantly worsening with stricter restrictions.[69] Poor mental health (MH) is a leading cause of disability globally and negatively impacts productivity[58] and gross domestic product[32,71] to the extent that workplace interventions like education programs, cognitive behavioral therapy, and physical exercise have been trialed extensively.[74]

While there are multiple factors that contribute to MH, sleep is an important one. Adequate hours of sleep and good quality of sleep are important in promoting general well-being and health, and insomnia and sleep disturbances have been linked to poor MH outcomes.[2,56,75] Inadequate sleep, insomnia, and changes in sleep onset times due to circadian dysrhythmia are frequent issues in those who travel,[14,15] especially aircrew crossing multiple time zones.[21,86] Several studies have shown that physical activity (PA) can improve sleep quality and therefore lead to improved MH.[37,78,79]

WHO ranks physical inactivity fourth in risk factors for mortality, after hypertension, smoking, and diabetes.[88] Exercise provides many biopsychosocial benefits, including improved functional capacity, mood states, improved sleep quality, and quality of life.[64] Up to recommended levels, exercise and mental well-being are positively correlated.[29] Rather than a neutral effect, sedentary behavior and mental illness are positively correlated.[92] While research consistently indicates a relationship between exercise and depression, the mechanism remains unclear.[23] Several, such as the thermogenic, endorphin, monoamine, distraction, and self-efficacy hypotheses, have been proposed, but not universally accepted.[23]

The American Heart Association recommends that adults undergo an equivalent of at least 150 min of moderate or 75 min of vigorous aerobic activity per week, with more benefits derived from at least 300 min of activity weekly. Further, muscle-strengthening activity of moderate-to-high intensity should be added at least 2 d/wk.[5] Meeting these targets under confinement may be impractical for most aircrew and passengers given the limited access to space and equipment. Indeed, significantly decreased levels of PA in the community and those under confinement have been reported in many nations since the pandemic. Internationally, mean step count decreased 27.3%,[76] vigorous PA decreased 42.2%,[85] and sedentary time increased 23.8%.[17] Nonetheless, the aforementioned consequences of nonadherence may outlast the quarantine period,[50] yet some populations such as aircrew are subject to repetitive cycles of quarantine.

The International Air Transport Association's (IATA) forecasted recovery of the aviation industry has been delayed to 2024,[45] complicated by mutating variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since 83% of passengers are reluctant to undergo 14 d of isolation,[46] air travel demand reduced 65.9%.[43] Because Available Seat-Kilometers and the associated passenger belly freight plummeted, Cargo Ton-Kilometers reached a record high,[42] led by freighter airlines such as Federal Express and United Parcel Service,[43] straining freighter pilots in particular.[38] Notably, some Cathay Pacific crew operate 21-d "closed-loop" patterns followed by 14 d of quarantine.[26] In 2015, an Airbus A320 carrying 150 persons was intentionally flown into the French Alps by the copilot of Germanwings flight 9525, who had a history of severe depression with possible psychosis.[33] This fatal accident reminded stakeholders that mental illness among flight crews, if undetected, can lead to catastrophic outcomes, prompting the European Aviation Safety Agency to recommend an Action Plan that includes improved psychological evaluations, psychoactive substances testing, and peer support programs.[31]

This systematic review aims to evaluate the effect of exercise on MH in isolating or quarantining adults. To the authors' knowledge, while some have studied the relationship between PA and mental well-being during the pandemic,[82,87] few have focused on individuals confined under isolation or quarantine. A recent review made recommendations on how to reduce the psychological impact of quarantine, but exercise was not mentioned.[12]

METHODS

Articles sought include primary experimental and observational studies examining associations between PA and MH in adults confined under isolation or quarantine. Randomized control trials were preferred, although other study designs such as cohort, case-control, and cross-sectional studies were considered. Literature reviews, systematic reviews, and communiques such as editorials, commentaries, and letters were excluded.

Subjects included adults up to 64 yr of age inclusive [within 1 SD or interquartile range (IQR) unless the range is explicitly reported] to better match both the traveling public and aircrew. The upper age limit for professional pilots in multicrew aircraft is 65.[47] Subjects were isolated or quarantined, regardless of location, without access to outdoor PA. While both are public health practices involving segregation, isolation is for confirmed cases of COVID-19 and quarantine is for potential cases.[18] For the purposes of this review, both terms can be used interchangeably. Unless confinement parameters are explicitly defined, the Oxford COVID-19 Government Response Tracker (OxCGRT) will be cross-referenced for Stay At Home Requirements,[62] where Total Confinement is coded as 3.[61] Studies focusing on the elderly, pregnant, or specific comorbidities were excluded to discourage the confounding effect of risk factors known to be occasionally associated with impaired MH.

PA is defined as any bodily movement generated by the musculoskeletal system requiring energy exertion that is purposeful, structured, and repetitious, with the primary objective of improving or maintaining physical fitness.[16] Aerobic exercise such as low-intensity steady-state or high-intensity interval training and resistance training with bands, body weight, or free weights are examples that satisfy this definition. Provided it can be performed during isolation or quarantine, it was considered regardless of type, intensity, duration, or frequency and whether dedicated equipment was required. For the purposes of this study, the presence or absence of exercise was more important than the specifics of exercise. The comparator was physical inactivity, which may include sedentary behaviors such as watching television. Ideally, only studies using standardized measurement scales such as the International Physical Activity Questionnaire (IPAQ) were included, but due to the paucity of data, nonstandardized responses were also considered.

Per evidence-based principles, MH should be measured by a published scale to minimize measurement bias, encourage standardization, and improve comparability. Across some 65 unique instruments largely suitable for the general, nonclinical adult population, the commonest endpoints are depression, anxiety, and distress,[11] which formed the foundation of the search strategy. Most of the 65 instruments are self-administered, which is conducive to minimizing unnecessary clinical contact in observance of physical distancing directives. Few of these 65 instruments require specific training prior to use, which will facilitate recruitment and response rates. An example of a practical instrument is the Patient Health Questionnaire-9 (PHQ-9), which exhibits generally good psychometric properties such as construct validity, criterion validity, internal consistency, and test-retest reliability.[11]

An advanced search was conducted on 12 September 2021 in Ovid MEDLINE (1946 to 10 September 2021), APA PsycInfo (1806 to September Week 1, 2021), and the Cochrane Database of Systematic Reviews (2005 to 9 September 2021) using the following medical subject heading terms and keywords:

- Quarantine/OR quarantin*.mp. OR (Patient Isolation/OR isolat*.mp.); AND
- Exercise/OR Exercise Therapy/OR exercis*.mp.; AND
- Mental Health/OR Psychological Distress/OR Stress, Psychological/OR Anxiety.mp. OR Depression/OR (Mood Disorders/OR mood.mp.).

Results were limited to human studies published in English from 2019 to 2021 inclusive to capture potential studies from the first COVID-19 case to the time of writing then deduplicated with the integrated function in descending preference of Ovid MEDLINE, APA PsycInfo, and then the Cochrane Database of Systematic Reviews. Results were exported as a text file.

Table I. Inclusion and Exclusion Criteria.

INCLUSION	EXCLUSION
Primary studies.	Secondary studies.
Published in English from 1 January 2019 to 12 September 2021 inclusive.	Irretrievable studies.
Subjects ages 18 to 64 inclusive (within one SD or IQR unless range explicitly reported).	Studies focusing on subjects who are pregnant or with specific comorbidities.
Addresses PA, MH with validated scales, and isolation or quarantine (± subgroup analysis).	

PA: physical activity; MH: mental health.

Per the inclusion and exclusion criteria presented in **Table I**, both authors independently screened the studies by title, abstract, and index terms. The remainder and any equivocal studies were fully examined for eligibility. Studies applying nonprobability sampling were included provided subgroup analysis was performed.

The Mixed Methods Appraisal Tool (MMAT)[39] was used as the critical appraisal tool because of its efficiency and reliability in assessing quality and bias in qualitative and quantitative evidence.[63] Meta-analysis was not performed due to the heterogeneity and restricted number of studies included in this preliminary review.

RESULTS

Identified were 241 potentially relevant studies; 27 duplicates were removed and 135 records were excluded at the screening stage. Of the 79 examined, 74 were excluded because of age (N = 33), confinement status (N = 22), study type (N = 13), disqualifying condition (N = 4), and other reasons (N = 2; absence of exercise intervention and subgroup analysis), leaving 5 studies that met the criteria (see **Table II**). A flowchart of the selection process is provided in **Fig. 2**.

The included studies were separately analyzed then summarized in Table II. Two are cohort studies[3,34] and three are cross-sectional studies[52,53,67]; experimental studies were lacking. Two were conducted in Spain,[34,67] one in Italy,[3] one in Bangladesh,[52] and one in the Middle East and North Africa region.[53] Two studies applied convenience sampling,[3,52] one snowball sampling,[53] and two expanded on prior studies.[34,67] Data were collected online in all studies, which comprised a total of 2755 college and university students, 1397 men and 1358 women, most of whom were confined in the context of COVID-19.

Two studies reported significantly increased frequency or duration of exercise as lockdown progressed,[34,67] one of which reported an increase in the number of exercisers.[34] The median hours of PA per week were two before lockdown, three after 10 d (P = 0.072), and four after 40 d (P < 0.001).[34] One study reported significantly increased PA and sitting time regardless of feelings of anxiety or depression.[67]

Table II. Summary of Included Studies.

REFERENCE	DESIGN	SUBJECTS	INTERVENTION	OUTCOME	FINDINGS
Amatori et al., Italy[3]	Cohort study	176 male (92) and female (84) college students ages 23 ± 4 yr under home isolation for entire 3 wk (except 7 subjects).	Exercise in the form of indoor walks, runs, rides, skipping, or free-weight exercises 4.6 ± 3.3 times/wk; mean duration 54 ± 41 min; RPE 6.6 ± 1.8 as measured by modified CR-10.	Respectively, men and women scored a median of 31 and 27 for PANAS+, 18 and 23 for PANAS–, 6 and 7 for PHQ-9, and 39 and 37 for SF-12; 76.7% reported mild-to-severe depression as measured by PHQ-9.	At 21 d, exercise partially mediated the relationship between PANAS, PHQ-9, SF-12, and fruit, vegetable, and fish consumption ($P < 0.05$), counterbalancing the impact of negative psychological states on dietary habits.
Gallego-Gómez et al., Spain[34]	Cohort study	138 male (30) and female (108) nursing students with a median age of 20 yr (IQR 19–23), home-bound.	Exercise duration and number of exercisers increased significantly as lockdown progressed (P < 0.001).	Median SSI-SM scores were 40 (IQR 30.8–48.3) before lockdown, 41 (IQR 33.0–51.0) at 10 d ($P = 0.001$), and 41 (IQR 34.8–49.0) at 40 d ($P = 0.004$).	At 40 d, students exercising regularly reported significantly lower stress levels (39, IQR 32.0–48.0) than their counterparts (45, IQR 38.0–56.0) ($P = 0.014$). Differences were not significant at 10 d or before lockdown.
Khan et al., Bangladesh[52]	Cross-sectional study over 15 d inclusive	505 male (317) and female (188) college and university students ages predominantly 20–24 yr under home quarantine.	26.73% reported exercising during quarantine.	46.92% reported depression, 33.28% anxiety, and 28.50% stress as measured by DASS-21; 69.31% reported ESD as measured by IES, worse in university students.	Exercise was significantly associated with lower scores of depression subscale (B = −2.10, 95% CI: −4.02 to −0.17)
Kilani et al., Middle East and North Africa[53]	Cross-sectional study over 55 d inclusive	1723 male (917) and female (806) university members ages 34.9 ± 12.8 yr under home confinement.	PA (MET-min/wk) stratified as low, moderate, or high as measured by IPAQ-SF.	32.6% reported poor mental well-being as measured by WHO-5.	Mental well-being showed a dose-response relationship with PA, especially when moderate or vigorous (P < 0.001). Between sleep, diet, and PA, the latter was by far the major determinant of MH.
Romero-Blanco et al., Spain[67]	Cross-sectional study over 63–92 d inclusive	213 male (41) and female (172) health sciences students ages 20.5 ± 4.56 yr under lockdown.	Especially for female and non-overweight students, duration and frequency of PA significantly increased during lockdown as measured by IPAQ-SF ($P < 0.001$). Sitting time increased significantly in most groups ($P < 0.001$).	24.9% reported feelings of anxiety/depression as measured by EQ-5D.	PA and sitting time increased regardless of feelings of anxiety/depression. Students reporting feelings of anxiety/depression exercised more than their counterparts. Students on a Mediterranean diet exercised more than their counterparts.

B: beta; CI: confidence interval; CR-10: Category-Ratio 10; ESD: event-specific distress; MET: metabolic equivalent of task; RPE: Borg Rating of Perceived Exertion; PANAS: Positive and Negative Affect Schedule; PHQ-9: Patient Health Questionnaire-9; SF-12: Short Form-12; IQR: interquartile range; SSI-SM: Student Stress Inventory-Stress Manifestations; DASS-21: Depression Anxiety Stress Scale-21; IES: Impact of Events Scale; PA: physical activity; IPAQ-SF: International Physical Activity Questionnaire-Short Form; EQ-5D: EuroQol 5-Dimension.

Impaired MH was reported by 24.9–76.7% of respondents depending on the study and the scale used: Positive and Negative Affect Schedule (PANAS), PHQ-9, Short Form-12 (SF-12), Student Stress Inventory-Stress Manifestations (SSI-SM), Depression Anxiety Stress Scale-21 (DASS-21), Impact of Events Scale (IES), WHO-5 Wellbeing Index (WHO-5), or EuroQol 5-Dimension (EQ-5D). The scales are summarized in **Table III**.

One study examined PA and MH separately and did not directly analyze the relationship between them.[3] Three studies showed that improved MH is significantly associated with PA,[34,52,53] especially when regular[34] and moderate or vigorous (**Fig. 3**).[53] One study showed that subjects reporting feelings of anxiety or depression exercised more than their counterparts; the authors attribute this to the subjects' health sciences

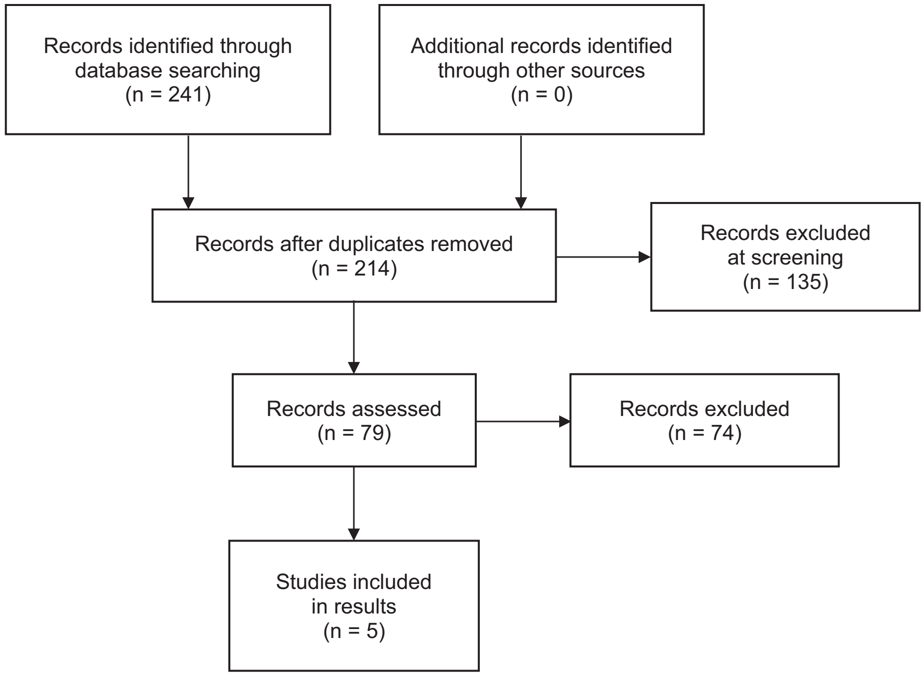

Fig. 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

background, although causation could not be established due to the study design.[67]

In a study by Kilani et al., MH was found to be affected by several factors (diet, sleep, and PA).[53] Sleep quality was strongly associated with MH and a balanced diet with good quality food was linked with enhanced MH. However, the study found that PA was the best predictor of MH, and that it had a much greater impact on MH than either sleep or diet (beta = 0.348, $P < 0.001$, r = 0.427). Other regression analyses indicate that a change in PA is the best single predictor of a change in MH.[54,77] Additionally, PA may act as a partial mediator between diet and mood, particularly via fruit, vegetable, and fish consumption.[3] Higher PANAS positive scores were associated with higher intake of cereals, legumes, and lean meats.[3] Students on a Mediterranean diet exercised more than their counterparts.[67] Thus, the relationship between mood, exercise, and diet may be illustrated by **Fig. 4**.

Table IV shows the criteria and summary of MMAT. All the studies are categorized as quantitative nonrandomized studies. Collected data appropriately addressed their clearly defined research questions. Tertiary students are not necessarily representative of the traveling public and aircrew. All studies measured MH with standardized scales; two studies did not measure PA with a standardized scale.[34,52] In Amatori et al.'s study,[3] all but seven subjects spent the entire lockdown in their residences.

DISCUSSION

Stress is a normal response to a stressor, whether actual or perceived.[70] While mental well-being is multifaceted, influenced by factors such as socioeconomic status, education level, and psychological support,[57] PA seems to play a major mitigating role.[53] While the anxiolytic and antidepressant effects of community-based exercise are widely recognized, this review shows that those benefits appear to extend to the confined setting. Incidentally, not only is exercise associated with improved mood, it is also associated with improved dietary habits. A recent systematic review concluded that certain diets could improve mood.[6] Thus, associations are observed between exercise, mood, and diet (Fig. 4).

The American College of Sports Medicine provided recommendations on how to remain active during COVID-19.[4] Yoga, calisthenics, and dancing are examples of suggested activities. However, given the dose-response relationship (Fig. 3),[53] moderate and vigorous PA may be difficult to achieve without dedicated space or equipment. Practical solutions include provision of rental exercise bikes in hotel rooms[28] or bringing a skipping rope[5] or resistance bands.[59] The routine should comprise aerobic, strengthening, and stretching components.[73] App- or web-based programs are useful adjuncts, subject to personal preference and technical proficiency.[4,27]

Some subjects may proactively buffer the anticipated impact of lockdowns by changing their lifestyle in the form of increased exercise and modified diets.[3] Indeed, this should occur long before confinement, as the positive effects of PA on MH continue beyond the cessation of exercise.[72] One study found that athletes scored better in DASS-21 and IES scales compared to nonathletes, despite at least a 2-mo break in training due to home isolation.[72] Likewise, individuals identifying as healthier had higher mental well-being scores, even under confinement.[53] It is worth emphasizing that, in Romero-Blanco et al.'s study, students on a Mediterranean diet and those not overweight exercised more than their counterparts, suggesting that individuals who lead a healthy lifestyle tend to persist with their

Table III. Summary of MH Scales.

SCALE	RANKING	SCORE
PANAS[3]		
Affect	Positive (+) Negative (–)	Range 10–50 Range 10–50
PHQ-9[3]		
Depression	None Mild Moderate Moderately severe Severe	0–4 5–9 10–14 15–19 ≥20
SF-12[3]		
Physical health	Physical component summary	Range 10–70
Mental health	Mental component summary	Range 6–72
SSI-SM[34]		
Stress		Total out of 95
DASS-21[52]		
Depression	Normal Mild Moderate Severe	0–9 10–13 14–20 21–21
Anxiety	Normal Mild Moderate Severe	0–7 8–9 10–14 15–19
Stress	Normal Mild Moderate Severe	0–14 15–18 19–25 26–33
IES[52]		
Event-specific distress	Subclinical Mild Moderate Severe	0–8 9–25 26–43 ≥44
WHO-5[53]		
Mental well-being	Poor Good	≤13 >13
EQ-5D[67]		
Quality of life		Response other than "I am not anxious or depressed" is positive for anxiety or depression symptoms

PANAS: Positive and Negative Affect Schedule; PHQ-9: Patient Health Questionnaire-9; SF-12: Short Form-12; SSI-SM: Student Stress Inventory-Stress Manifestations; DASS-21: Depression Anxiety Stress Scale-21; IES: Impact of Events Scale; WHO-5: WHO-5 Wellbeing Index; EQ-5D: EuroQol 5-Dimension.

habits regardless of their environment.[67] Gallego-Gómez et al. found that while exercise made no significant difference to stress levels before lockdown, significant improvements were observed as lockdown progressed.[34] Thus, physical fitness should be optimized before and maintained during quarantine. Because the primary outcomes of interest are PA and MH, cross-cultural differences were not considered. Likewise, data on cultural or religious adjustments of PA or MH scales are limited and were therefore not examined.[55]

Accordingly, exercise space and equipment should be accessible to isolating or quarantining individuals, not just for cardiovascular health, but for MH as well, since the presence of an exercise environment is a potential source of fitness

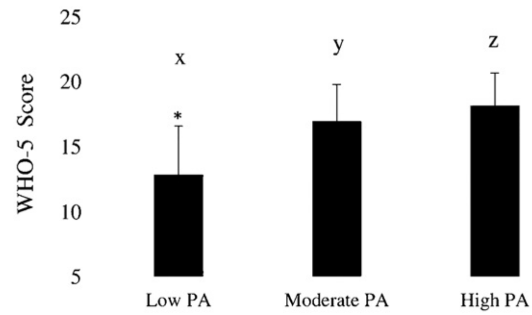

Fig. 3. Mental well-being stratified by PA levels. High PA (18.2 ± 2.5) showed a significantly higher overall WHO-5 score than moderate (17.0 ± 2.8; $P < 0.001$) and low PA (12.9 ± 3.7; $P < 0.001$).[53]

motivation.[51] As Gallego-Gómez and Romero-Blanco et al. found, the duration or frequency of exercise and the number of exercisers increased as lockdown progressed.[34,67] A 2020 study of 13,696 respondents modeled that those who rarely exercise before a lockdown tend to increase their exercise frequency, and those who are frequent exercisers before a lockdown tend to maintain it,[10] so lockdowns appear to create a demand for exercise. Optionally, individuals may bring their own portable equipment, since even light activity can offset some of the risks of sedentary behavior.[5] Just as importantly, healthy food options should also be available due to their mood-regulating effects.[6] These efforts may improve the perception of quarantine and, by extension, the number of passengers willing to undergo isolation, thereby helping to restart the aviation industry.

Effective as PA may be, the root cause that is quarantine ought to be addressed. The status quo may no longer be justifiable 2 yr on, as SARS-CoV-2 has become widespread. In a poll conducted by *Nature*, nearly 90% of international experts think that COVID-19 will eventually become endemic, not unlike influenza, likely requiring annual vaccination.[65] As progress is made on definitive treatment, antigen testing, and herd immunity, IATA proposed alternatives that rely less on quarantine yet still reduce the risk of imported cases via travelers and mitigate risk in cases where an infected person does travel.[44] Border restrictions and extended quarantine yield diminishing returns as the pandemic evolves, especially where epidemics are not controlled at its source.[19,36] Retrospective data from Bahrain shows that only 0.2–0.6% of air travelers tested positive during quarantine compared to 2.1–2.6% community transmission in the same period.[1] Depending on the setting, mass 14-d quarantine can be relaxed,[1,91] taking into account incidence gradients[83,91] as robust local control is at least as likely to reduce viral

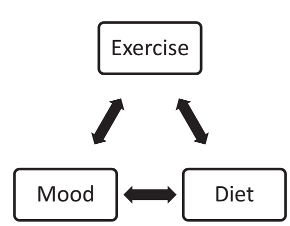

Fig. 4. Associations between exercise, mood, and diet. Exercise directly and indirectly improves mood.[3,67]

Table IV. Risk of Bias Assessment Using MMAT.[39]

QUESTION	AMATORI ET AL.[3]	GALLEGO-GÓMEZ ET AL.[34]	KHAN ET AL.[52]	KILANI ET AL.[53]	ROMERO-BLANCO ET AL.[67]
Are there clear research questions?	Yes	Yes	Yes	Yes	Yes
Do the collected data address the research questions?	Yes	Yes	Yes	Yes	Yes
Are the subjects representative of the target population?	No	No	No	No	No
Are measurements appropriate regarding both the outcome and intervention (or exposure)?	Yes	Yes	Yes	Yes	Yes
Are there complete outcome data?	Yes	Yes	Yes	Yes	Yes
Are the confounders accounted for in the design and analysis?	Yes	Yes	Yes	Yes	Yes
During the study period, is the intervention administered (or exposure occurred) as intended?	Yes	Yes	Yes	Yes	Yes

MMAT: Mixed Methods Appraisal Tool.

transmission.[20,22] Updated recommendations from the International Civil Aviation Organization include exempting immunized individuals, especially crew, from testing and quarantine, subject to risk assessment.[48]

This review has several limitations. Only five studies were included due to the novelty of COVID-19 and the paucity of literature relating PA and MH in quarantine, reflecting the limited data available at the time. More studies and larger samples would provide more statistical power. Because cross-sectional studies demonstrate association but not causation, experimental studies, particularly randomized control trials, would be beneficial. However, this may raise ethical concerns given the strong body of evidence linking PA and MH. In contrast, an advantage of cohort studies is that temporality of exposure and outcome can be established. Recall bias is possible, although this is likely minimized by daily diary entries as was the case in Amatori et al.'s study.[3] Online questionnaires require internet access, which may be available only to respondents from a higher socioeconomic background in some countries. This, together with nonprobability sampling, introduces selection bias.

Isolation, quarantine, and lockdowns are variably defined and enforced across different jurisdictions,[62] so heterogeneity of confinement status is possible, potentially confounding the findings. A study of around 42,000 Brazilians showed only 73.5–77.0% adhered to quarantine directives,[84] which is relevant as psychological distress is associated with reduced access to outside or green space.[41] Subnational data was not always available for cross-referencing in the OxCGRT where studies did not explicitly define confinement parameters, potentially affecting screening and eligibility.

Aircrew and passengers are groups frequently subject to isolation or quarantine. While the study was designed to match both, relevant studies focusing on the target populations were lacking. Though the studies demonstrated high internal validity, external validity may be improved by including studies focusing on aircrew and passengers. For instance, students are generally younger, may come from contrasting socioeconomic backgrounds, and experience different (e.g., academic) stressors, potentially skewing the results. There were 33 studies excluded because of invalid age, so a broader dataset may be available by relaxing age criteria.

In conclusion, PA appears to be a major, if not the strongest correlate, of MH for isolating or quarantining adults and, therefore, should be optimized before and maintained during confinement. Many cost-effective, practical solutions are available and should be accessible during isolation or quarantine. Other factors known to have an effect on MH, such as sufficient sleep and good nutrition, should not be neglected as part of a holistic approach. While effective, the sustainability of persistent quarantine must be considered. More experimental studies, especially those of aircrew and passengers, are encouraged.

ACKNOWLEDGMENTS

Dr. Vichai Chu would like to thank the teaching staff of The School of Public Health and Preventive Medicine at Monash University for their technical and supporting role in this systematic review.

Financial Disclosure Statement: Dr. Chu is a commercial pilot at an international airline. Dr. Newman has no competing interests to declare.

Authors and Affiliations: Vichai Pak To Chu, M.B.B.S., D.Av.Med., Aerospace Medicine Registrar, The Australasian College of Aerospace Medicine, Hawthorn, Victoria, Australia, and David G. Newman, MBA, Ph.D., Visiting Professor of Aerospace Medicine, Aerospace Medicine & Physiology Group, Centre for Human and Physiological Sciences, King's College London, London, United Kingdom.

REFERENCES

1. Abdulrahman A, AlSabbagh M, AlAwadhi A, Al-Tawfiq JA, Rabaan AA, et al. Quarantining arriving travelers in the era of COVID-19: balancing the risk and benefits: a learning experience from Bahrain. Trop Dis Travel Med Vaccines. 2021; 7(1):1.
2. Afonso P, Fonseca M, Pires J. Impact of working hours on sleep and mental health. Occup Med (Lond). 2017; 67(5):377–382.
3. Amatori S, Donati Zeppa S, Preti A, Gervasi M, Gobbi E, et al. Dietary habits and psychological states during COVID-19 home isolation in Italian college students: the role of physical exercise. Nutrients. 2020; 12(12):3660.
4. American College of Sports Medicine. Staying active during the coronavirus pandemic. Indianapolis: Exercise is Medicine; 2020 [updated

2020 Nov. 18]. [Accessed 2021 Oct. 2]. Available from https://www.exerciseismedicine.org/assets/page_documents/EIM_Rx%20for%20Health_%20Staying%20Active%20During%20Coronavirus%20Pandemic.pdf.
5. American Heart Association. American Heart Association recommendations for physical activity in adults and kids. Dallas: American Heart Association; 2018 [updated 2018 April 18]. [Accessed 2021 Sept. 16]. Available from https://www.heart.org/en/healthy-living/fitness/fitness-basics/aha-recs-for-physical-activity-in-adults.
6. Arab A, Mehrabani S, Moradi S, Amani R. The association between diet and mood: a systematic review of current literature. Psychiatry Res. 2019; 271:428–437.
7. Australian Department of Health. Isolation for coronavirus (COVID-19). Canberra: Australian Department of Health; 2020 [updated 2020 Oct. 13]. [Accessed 2021 Sept. 18]. Available from https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/how-to-protect-yourself-and-others-from-coronavirus-covid-19/isolation-for-coronavirus-covid-19#steps-you-need-to-take-while-in-isolation.
8. Australian Department of Health. Quarantine for coronavirus (COVID-19). Canberra: Australian Department of Health; 2021 [updated 2021 July 9]. [Accessed 2021 Sept. 18]. Available from https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/how-to-protect-yourself-and-others-from-coronavirus-covid-19/quarantine-for-coronavirus-covid-19.
9. Australian Federal Register of Legislation. Biosecurity Act 2015. Canberra: Australian Federal Register of Legislation; 2021 [updated 2021 June 30]. [Accessed 2021 Sept. 18]. Available from https://www.legislation.gov.au/Details/C2021C00265.
10. Brand R, Timme S, Nosrat S. When pandemic hits: exercise frequency and subjective well-being during COVID-19 pandemic. Front Psychol. 2020; 11:570567.
11. Breedvelt JJF, Zamperoni V, South E, Uphoff EP, Gilbody S, et al. A systematic review of mental health measurement scales for evaluating the effects of mental health prevention interventions. Eur J Public Health. 2020; 30(3):510–516.
12. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet. 2020; 395(10227):912–920.
13. Burns J, Movsisyan A, Stratil JM, Biallas RL, Coenen M, et al. International travel-related control measures to contain the COVID-19 pandemic: a rapid review. Cochrane Database Syst Rev. 2021; 3(3):CD013717.
14. Caldwell JA. Fatigue in aviation. Travel Med Infect Dis. 2005; 3(2):85–96.
15. Caldwell JA. Fatigue in the aviation environment: an overview of the causes and effects as well as recommended countermeasures. Aviat Space Environ Med. 1997; 68(10):932–938.
16. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985; 100(2):126–131.
17. Castañeda-Babarro A, Arbillaga-Etxarri A, Gutiérrez-Santamaría B, Coca A. Physical activity change during COVID-19 confinement. Int J Environ Res Public Health. 2020; 17(18):6878.
18. Centers for Disease Control and Prevention. Quarantine and isolation. Atlanta: Centers for Disease Control and Prevention; 2020 [updated 2020 Jan. 27]. [Accessed 2021 Sept. 17]. Available from https://www.cdc.gov/quarantine/quarantineisolation.html.
19. Chinazzi M, Davis JT, Ajelli M, Gioannini C, Litvinova M, et al. The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak. Science. 2020; 368(6489):395–400.
20. Chong KC, Ying Zee BC. Modeling the impact of air, sea, and land travel restrictions supplemented by other interventions on the emergence of a new influenza pandemic virus. BMC Infect Dis. 2012; 12(1):309.
21. Cingi C, Emre IE, Muluk NB. Jetlag related sleep problems and their management: a review. Travel Med Infect Dis. 2018; 24:59–64.
22. Cooper BS, Pitman RJ, Edmunds WJ, Gay NJ. Delaying the international spread of pandemic influenza. PLoS Med. 2006; 3(6):e212.
23. Craft LL, Perna FM. The benefits of exercise for the clinically depressed. Prim Care Companion J Clin Psychiatry. 2004; 6(3):104–111.
24. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020; 91(1):157–160.
25. Cutler DM, Summers LH. The COVID-19 pandemic and the $16 trillion virus. JAMA. 2020; 324(15):1495–1496.
26. Davies W, Park K. Cathay crew to work 21-day stints to avoid quarantine. New York: Bloomberg; 2021 [updated 2021 Feb. 19]. [Accessed 2021 Sept. 16]. Available from https://www.bloomberg.com/news/articles/2021-02-18/cathay-crew-face-49-day-work-cycle-on-new-quarantine-rules.
27. Deng CH, Wang JQ, Zhu LM, Liu HW, Guo Y, et al. Association of web-based physical education with mental health of college students in Wuhan during the COVID-19 outbreak: cross-sectional survey study. J Med Internet Res. 2020; 22(10):e21301.
28. D'Onise K, Meena S, Venugopal K, Currie M, Kirkpatrick E, et al. Holistic approach supporting mental wellbeing of people in enforced quarantine in South Australia during the COVID-19 pandemic. Aust N Z J Public Health. 2021; 45(4):325–329.
29. Dunn AL, Trivedi MH, Kampert JB, Clark CG, Chambliss HO. Exercise treatment for depression: efficacy and dose response. Am J Prev Med. 2005; 28(1):1–8.
30. Elias C, Sekri A, Leblanc P, Cucherat M, Vanhems P. The incubation period of COVID-19: a meta-analysis. Int J Infect Dis. 2021; 104:708–710.
31. European Aviation Safety Agency. Action plan for the implementation of the Germanwings Task Force recommendations. Cologne: European Aviation Safety Agency; 2015 [updated 2015 Oct. 7]. [Accessed 2021 Sept. 16]. Available from https://www.easa.europa.eu/download/various/GW_actionplan_final.pdf.
32. Evans-Lacko S, Knapp M. Global patterns of workplace productivity for people with depression: absenteeism and presenteeism costs across eight diverse countries. Soc Psychiatry Psychiatr Epidemiol. 2016; 51(11):1525–1537.
33. French Civil Aviation Safety Investigation Authority. Final report—Accident on 24 March 2015 at Prads-Haute-Bléone (Alpes-de-Haute-Provence, France) to the Airbus A320-211 registered D-AIPX operated by Germanwings. Le Bourget Airport (France): BEA; 2016.
34. Gallego-Gómez JI, Campillo-Cano M, Carrión-Martínez A, Balanza S, Rodríguez-González-Moro MT, et al. The COVID-19 pandemic and its impact on homebound nursing students. Int J Environ Res Public Health. 2020; 17(20):7383.
35. Ganesan B, Al-Jumaily A, Fong KNK, Prasad P, Meena SK, Tong RK. Impact of coronavirus disease 2019 (COVID-19) outbreak quarantine, isolation, and lockdown policies on mental health and suicide. Front Psychiatry. 2021; 12:565190.
36. Gwee SXW, Chua PEY, Wang MX, Pang J. Impact of travel ban implementation on COVID-19 spread in Singapore, Taiwan, Hong Kong and South Korea during the early phase of the pandemic: a comparative study. BMC Infect Dis. 2021; 21(1):799.
37. Heyman E, Gamelin FX, Goekint M, Piscitelli F, Roelands B, et al. Intense exercise increases circulating endocannabinoid and BDNF levels in humans—possible implications for reward and depression. Psychoneuroendocrinology. 2012; 37(6):844–851.
38. Hilditch CJ, Flynn-Evans EE. Fatigue, schedules, sleep, and sleepiness in U.S. commercial pilots during COVID-19. Aerosp Med Hum Perform. 2022; 93(5):433–441.
39. Hong QN, Fàbregues S, Bartlett G, Boardman F, Cargo M, et al. The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. Educ Inf. 2018; 34(4):285–291.
40. Howard MC, Follmer KB, Smith MB, Tucker RP, Van Zandt EC. Work and suicide: an interdisciplinary systematic literature review. J Organ Behav. 2022; 43(2):260–285.
41. Hubbard G, Daas CD, Johnston M, Murchie P, Thompson CW, Dixon D. Are rurality, area deprivation, access to outside space, and green space associated with mental health during the COVID-19 pandemic? A cross-sectional study (CHARIS-E). Int J Environ Res Public Health. 2021; 18(8):3869.
42. International Air Transport Association. Air cargo demand reaches all-time high in March, up 4.4% vs. pre-COVID levels. Montréal: International Air Transport Association; 2021 [updated 2021 May 4]. [Accessed

2021 Sept. 16]. Available from https://www.iata.org/en/pressroom/pr/2021-05-04-01/.

43. International Air Transport Association. Airline industry statistics confirm 2020 was worst year on record. Montréal: International Air Transport Association; 2021 [updated 2021 Aug. 3]. [Accessed 2021 Sept. 16]. Available from https://www.iata.org/en/pressroom/pr/2021-08-03-01/.
44. International Air Transport Association. IATA proposes alternatives to quarantine. Montréal: International Air Transport Association; 2020 [updated 2020 June 24]. [Accessed 2021 Oct. 6]. Available from https://www.iata.org/en/pressroom/pr/2020-06-24-02/.
45. International Air Transport Association. Recovery delayed as international travel remains locked down. Montréal: International Air Transport Association; 2020 [updated 2020 July 28]. [Accessed 2021 Sept. 16]. Available from https://www.iata.org/en/pressroom/pr/2020-07-28-02/.
46. International Air Transport Association. Traveler survey reveals COVID-19 concerns. Montréal: International Air Transport Association; 2020 [updated 2020 July 28]. [Accessed 2021 Sept. 16]. Available from https://www.iata.org/en/pressroom/pr/2020-07-28-02/.
47. International Civil Aviation Organization. Manual of civil aviation medicine. 3rd ed. Montréal: International Civil Aviation Organization; 2012:I-3–I-9.
48. International Civil Aviation Organization. Manual on COVID-19 cross-border risk management. Montréal: International Civil Aviation Organization; 2021. [Accessed 12 July 2023]. Available from https://www.icao.int/safety/CAPSCA/PublishingImages/Pages/ICAO-Manuals/10152_manual_3rd_edition.en.pdf.
49. Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. Cochrane Database Syst Rev. 2020; 11(11):CD006207.
50. Jurblum M, Ng CH, Castle DJ. Psychological consequences of social isolation and quarantine: issues related to COVID-19 restrictions. Aust J Gen Pract. 2020; 49(12):778–783.
51. Kaur H, Singh T, Arya YK, Mittal S. Physical fitness and exercise during the COVID-19 pandemic: a qualitative enquiry. Front Psychol. 2020; 11:590172.
52. Khan AH, Sultana MS, Hossain S, Hasan MT, Ahmed HU, Sikder MT. The impact of COVID-19 pandemic on mental health & wellbeing among home-quarantined Bangladeshi students: a cross-sectional pilot study. J Affect Disord. 2020; 277:121–128.
53. Kilani HA, Bataineh MF, Al-Nawayseh A, Atiyat K, Obeid O, et al. Healthy lifestyle behaviors are major predictors of mental wellbeing during COVID-19 pandemic confinement: a study on adult Arabs in higher educational institutions. PLoS One. 2020; 15(12):e0243524. Erratum in: PLoS One. 2022; 17(8):e0273276.
54. Kim ACH, Du J, Andrew DPS. Changes in physical activity and depressive symptoms during COVID-19 lockdown: United States adult age groups. Front Psychol. 2022; 13:769930.
55. Kriska A. Ethnic and cultural issues in assessing physical activity. Res Q Exerc Sport. 2000; 71(sup2):47–53.
56. Kyle SD, Morgan K, Espie CA. Insomnia and health-related quality of life. Sleep Med Rev. 2010; 14(1):69–82.
57. Lei L, Huang X, Zhang S, Yang J, Yang L, Xu M. Comparison of prevalence and associated factors of anxiety and depression among people affected by versus people unaffected by quarantine during the COVID-19 epidemic in Southwestern China. Med Sci Monit. 2020; 26:e924609.
58. Lim D, Sanderson K, Andrews G. Lost productivity among full-time workers with mental disorders. J Ment Health Policy Econ. 2000; 3(3): 139–146.
59. Marcos-Pardo PJ, Espeso-García A, López-Vivancos A, Abelleira Lamela T, Keogh JWL. COVID-19 and social isolation: a case for why home-based resistance training is needed to maintain musculoskeletal and psychosocial health for older adults. J Aging Phys Act. 2021; 29(2):353–359.
60. Maslow A. A theory of human motivation. Psychol Rev. 1943; 50(4): 370–396.
61. Oxford University. OxCGRT coding interpretation guide. Oxford: Oxford University; 2021 [updated 2021 Sept. 27]. [Accessed 2021 Oct. 1]. Available from https://github.com/OxCGRT/covid-policy-tracker/blob/master/documentation/interpretation_guide.md.
62. Oxford University. Stay-at-home requirements. Oxford: Oxford University; 2021 [updated 2021 Oct. 1]. [Accessed 2021 Oct. 1]. Available from https://github.com/OxCGRT/covid-policy-tracker/blob/master/data/timeseries/c6_stay_at_home_requirements.csv.
63. Pace R, Pluye P, Bartlett G, Macaulay AC, Salsberg J, et al. Testing the reliability and efficiency of the pilot Mixed Methods Appraisal Tool (MMAT) for systematic mixed studies review. Int J Nurs Stud. 2012; 49(1):47–53.
64. Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. Curr Opin Psychiatry. 2005; 18(2):189–193.
65. Phillips N. The coronavirus is here to stay - here's what that means. Nature. 2021; 590(7846):382–384.
66. Quesada JA, López-Pineda A, Gil-Guillén VF, Arriero-Marín JM, Gutiérrez F, Carratala-Munuera C. Incubation period of COVID-19: a systematic review and meta-analysis. Rev Clin Esp (Barc). 2021; 221(2):109–117.
67. Romero-Blanco C, Rodríguez-Almagro J, Onieva-Zafra MD, Parra-Fernández ML, Prado-Laguna MDC, Hernández-Martínez A. Physical activity and sedentary lifestyle in university students: changes during confinement due to the COVID-19 pandemic. Int J Environ Res Public Health. 2020; 17(18):6567.
68. Ryan BJ, Coppola D, Canyon DV, Brickhouse M, Swienton R. COVID-19 community stabilization and sustainability framework: an integration of the Maslow Hierarchy of Needs and social determinants of health. Disaster Med Public Health Prep. 2020; 14(5):623–629.
69. Salanti G, Peter N, Tonia T, Holloway A, White IR, et al. The impact of the COVID-19 pandemic and associated control measures on the mental health of the general population: a systematic review and dose-response meta-analysis. Ann Intern Med. 2022; 175(11):1560–1571.
70. Schneiderman N, Ironson G, Siegel SD. Stress and health: psychological, behavioral, and biological determinants. Annu Rev Clin Psychol. 2005; 1(1):607–628.
71. Schofield DJ, Shrestha RN, Percival R, Passey ME, Callander EJ, Kelly SJ. The personal and national costs of mental health conditions: impacts on income, taxes, government support payments due to lost labor force participation. BMC Psychiatry. 2011; 11(1):72.
72. Şenışık S, Denerel N, Köyağasıoğlu O, Tunç S. The effect of isolation on athletes' mental health during the COVID-19 pandemic. Phys Sportsmed. 2021; 49(2):187–193.
73. Shariat A, Ghannadi S, Anastasio AT, Rostad M, Cleland JA. Novel stretching and strength-building exercise recommendations for computer-based workers during the COVID-19 quarantine. Work. 2020; 66(4):739–749.
74. Tan L, Wang MJ, Modini M, Joyce S, Mykletun A, et al. Preventing the development of depression at work: a systematic review and meta-analysis of universal interventions in the workplace. BMC Med. 2014; 12(1):74. Erratum in: BMC Med. 2014; 12:212.
75. Taylor DJ, Lichstein KL, Heith Durrence H. Insomnia as a health risk factor. Behav Sleep Med. 2003; 1(4):227–247.
76. Tison GH, Avram R, Kuhar P, Abreau S, Marcus GM, et al. Worldwide effect of COVID-19 on physical activity: a descriptive study. Ann Intern Med. 2020; 173(9):767–770.
77. Trabelsi K, Ammar A, Masmoudi L, Boukhris O, Chtourou H, et al. Sleep quality and physical activity as predictors of mental wellbeing variance in older adults during COVID-19 lockdown: ECLB COVID-19 international online survey. Int J Environ Res Public Health. 2021; 18(8):4329.
78. Toups MS, Greer TL, Kurian BT, Grannemann BD, Carmody TJ, et al. Effects of serum brain derived neurotrophic factor on exercise augmentation treatment of depression. J Psychiatr Res. 2011; 45(10):1301–1306.
79. Uchida S, Shioda K, Morita Y, Kubota C, Ganeko M, Takeda N. Exercise effects on sleep physiology. Front Neurol. 2012; 3:48.
80. United States Consulate-General Hong Kong & Macau. COVID-19 information. Hong Kong: United States Consulate-General Hong Kong

& Macau; 2021 [updated 2021 Sept. 10]. [Accessed 2021 Sept. 16]. Available from https://hk.usconsulate.gov/covid-19-information/.
81. University of Oxford. COVID-19 government response tracker. 2021 [updated 2021 Sept. 17]. [Accessed 2021 Sept. 18]. Available from https://www.bsg.ox.ac.uk/research/research-projects/covid-19-government-response-tracker.
82. Violant-Holz V, Gallego-Jiménez MG, González-González CS, Muñoz-Violant S, Rodríguez MJ, et al. Psychological health and physical activity levels during the COVID-19 pandemic: a systematic review. Int J Environ Res Public Health. 2020; 17(24):9419.
83. Wells CR, Pandey A, Fitzpatrick MC, Crystal WS, Singer BH, et al. Quarantine and testing strategies to ameliorate transmission due to travel during the COVID-19 pandemic: a modelling study. Lancet Reg Health Eur. 2022; 14:100304.
84. Werneck AO, Silva DRD, Malta DC, Souza-Júnior PRB, Azevedo LO, et al. Lifestyle behaviors changes during the COVID-19 pandemic quarantine among 6,881 Brazilian adults with depression and 35,143 without depression. Cien Saude Colet. 2020; 25(suppl. 2):4151–4156.
85. Wilke J, Mohr L, Tenforde AS, Edouard P, Fossati C, et al. A pandemic within the pandemic? Physical activity levels substantially decreased in countries affected by COVID-19. Int J Environ Res Public Health. 2021; 18(5):2235.
86. Wingelaar-Jagt YQ, Wingelaar TT, Riedel WJ, Ramaekers JG. Fatigue in aviation: safety risks, preventive strategies and pharmacological interventions. Front Physiol. 2021; 12:712628.
87. Wolf S, Seiffer B, Zeibig JM, Welkerling J, Brokmeier L, et al. Is physical activity associated with less depression and anxiety during the COVID-19 pandemic? A rapid systematic review. Sports Med. 2021; 51(8):1771–1783.
88. World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization; 2009:10–11.
89. World Health Organization. WHO coronavirus (COVID-19) dashboard. Geneva: World Health Organization; 2021 [updated 2021 Sept. 18] [Accessed 2021 Sept. 18]. Available from https://covid19.who.int/.
90. Xin M, Luo S, She R, Yu Y, Li L, et al. Negative cognitive and psychological correlates of mandatory quarantine during the initial COVID-19 outbreak in China. Am Psychol. 2020; 75(5):607–617.
91. Yang B, Tsang TK, Wong JY, He Y, Gao H, et al. The differential importation risks of COVID-19 from inbound travelers and the feasibility of targeted travel controls: a case study in Hong Kong. Lancet Reg Health West Pac. 2021; 13:100184.
92. Zhai L, Zhang Y, Zhang D. Sedentary behavior and the risk of depression: a meta-analysis. Br J Sports Med. 2015; 49(11):705–709.

Categorization of Select Cockpit Performance Evaluation Techniques

Eric M. Brighton; David M. Klaus

INTRODUCTION: The modern aircraft cockpit has evolved into a complex system of systems. Numerous performance evaluation metrics and techniques exist that can measure the effectiveness of cockpit components in terms of how they influence the human operator's ability to perform tasks relevant to mission success. As no prior review of these metrics has been found in the literature, this effort attempts to do so, albeit without applying the metrics to a novel cockpit evaluation.

METHODS: These metrics and techniques are discussed and presented in five defined categories as they relate to evaluating cockpit subsystems: ergonomics and anthropometrics; human-computer interaction; data management and presentation; crew resource management and operations; and ingress and egress.

DISCUSSION: While this effort is significant and novel, it is not necessarily comprehensive. In conclusion, it is noted that no single holistic quantitative metric to evaluate cockpit design and performance yet exists. Utilizing some of the preexisting metrics presented to develop such a metric would be beneficial in efforts to evaluate aircraft cockpit designs and performance, as well as aiding future cockpit designs.

KEYWORDS: human factors, aircraft cockpit, aviation, aircrew performance, human engineering, anthropometrics, human computer interaction, crew resource management.

Brighton EM, Klaus DM. *Categorization of select cockpit performance evaluation techniques*. Aerosp Med Hum Perform. 2023; 94(9):696–704.

Aerospace cockpits and control systems are evolving in ever-more complex workspaces. Presently, the act of flying an aircraft is being supplemented with vast amounts of data management as well as the rise of automation. More often than not, the challenge of aerospace engineering lies in the design of a "system of systems," rather than a focus on traditional disciplinary topics such as aerodynamics and flying qualities calculations. Space exploration and commercial space tourism present other unique rubrics, where cockpits, depending on design and purpose, will be required to function in both horizontal and vertical layouts, ranging from 1-G level flight to high-G ascent and entry accelerations to weightlessness. NASA has identified inadequate crewmember human–computer interaction as a potential issue for future long-duration space missions.[26] Similarly, the U.S. Navy (USN) has sought additional support for human systems engineering and human performance assessment and modeling.[27]

When optimizing the design of a modern aircraft cockpit, whether for crewed or remotely piloted vehicles, for general aviation, commercial flight, or military applications, many factors can influence the effectiveness of the human operator. A USN study in the late 1980s identified 13 distinct technologies that are incorporated in a crewed cockpit, and this number has likely increased since then.[47] While many of these devices are normally running transparently in the background, others require ongoing direct interface or manual intervention in the event of an anomaly. In particular, for military operations on the modern battlefield, poorly designed and implemented cockpit ergonomics and interfaces can significantly, and adversely, impact the effectiveness of combat aircraft as an effective weapons system.[2] And in any flight environment, overreliance on automated systems has been shown to be a concern that can cause piloting skills to atrophy and impact performance in critical situations.[44] For these and other reasons, an

From the University of Colorado-Boulder, Boulder, CO, United States.

This manuscript was received for review in October 2022. It was accepted for publication in June 2023.

Address correspondence to: Mr. Eric Brighton, University of Colorado-Boulder, Aerospace Engineering Sciences Department, 3775 Discovery Dr., Boulder, CO 80303, United States; brighton@colorado.edu.

DOI: https://doi.org/10.3357/AMHP.6185.2023

effective means of assessing how well these integrated cockpit systems perform has become increasingly important for modern cockpit design.

Several individual evaluation metrics exist to assess how well the cockpit system accommodates the needs of the pilot. Various approaches are widely accepted as industry standards (e.g., NASA TLX, Cooper-Harper, etc.) and, although there are recognized shortcomings in some of these methods, they represent the current state-of-the-art for evaluating general, commercial, and military aircraft. Because of the demanding mission goals for military combat aircraft, optimizing the human–machine interface is especially critical. No standardized process, however, could be identified for conducting a systematic evaluation of cockpit system performance in military aircraft, nor could a published means of compiling a comprehensive outcome from the individual metric inputs be found. This gap extends to designing pilot interfaces for remotely piloted drones as well.

The design trade study process employs identification and weighing of individual parameters, as well as codependent factors, that collectively affect the optimal solution differently than their individual performance would suggest (e.g., an ergonomically designed, comfortable seat that is difficult to ingress/egress). Combinations of cockpit systems are not only codependent, but also mission dependent. Therefore, establishing a holistic metric that represents the overall integrated design performance would provide useful insight to cockpit design. This work provides a categorical summary of key existing cockpit performance evaluation techniques as a foundation for defining a comprehensive, integrated approach.

BACKGROUND

The USN desired to standardize a systems engineering approach to cockpit design with the Advanced Technology Crew Station (ATCS) program, with McDonnell Douglas and Boeing electing to participate.[23,30] This new codified approach to aircraft cockpit design sought to overcome the discrepancies where pilot–operator performance was the limiting factor to overall system effectiveness.[23] Ultimately, the results of the ATCS program were never formalized by the Department of Defense, but they influenced future carrier-borne fighter aircraft cockpit design and motivated smaller efforts to formalize approaches to cockpit and aircrew system design.[6] While ATCS produced multiple techniques and tools for development and validation of cockpit subsystem design, none of these deliverables yielded an overall holistic evaluation metric or tool for the entire cockpit.[14,23,30]

ATCS also attempted to firm up connections between research and application in the late 1980s by identifying 13 technologies utilized in cockpit system design, including seating and escape, controls and displays, man–machine functional requirements and interface, and computer/software.[47] From this starting point, one can assume that the number of technologies has only increased in modern cockpits.

The Department of Defense is presently looking toward sixth-generation fighters being fielded in the 2030s.[25] The USN first identified the F/A-XX in June 2008, with Analysis of Alternatives completed in June 2019.[18] A hypothetical next-generation cockpit design would include advanced technologies such as automation, artificial intelligence, augmented reality, embedded or conformal cockpit structures and aerodynamics, and possibly an opaque canopy. Ultimately, this work intends to contribute insight towards achieving that goal.

METHODS

Groupings of quantitative evaluation metrics have been proposed for crew utilization of space habitat systems.[11] Extending this approach to the modern cockpit environment, in both aircraft and piloted spacecraft, would provide an insightful tool for designers to evaluate cockpit and control layouts in the preliminary design phase of the acquisition lifecycle. Research is moving forward in numerous subareas that could ultimately be compiled into a holistic cockpit evaluation metric, which is the motivation of this current study. Approaching these needs from a categorical perspective, a suite of metrics can be grouped into those affecting the following: ergonomics and anthropometrics; human–computer interaction; data management and presentation; operations/crew resource management (CRM); and ingress and egress. The following sections provide a summary of existing cockpit and crew performance evaluation techniques grouped under these functional headings. Defining a standardized multi-metric-based approach merging select combinations of these current techniques would provide cockpit designers with insights from a systems engineering perspective while still in the preliminary design phase, where modifications and optimizations can readily be incorporated before designs are finalized. Additional references are presented in **Table I**, **Table II**, **Table III**, **Table IV**, and **Table V** for completeness but not necessarily thoroughly discussed in the text. While some metrics may offer beneficial evaluation techniques across multiple categories, for the purpose of cataloging, each metric is assigned to its "best fit" category as assessed by the authors.

RESULTS

Ergonomics and Anthropometrics

"Ergonomics" and "anthropometrics" are two terms with unique definitions used when discussing cockpit layouts, the former addressing fit of a workspace and the latter characterizing dimensional reach envelope of the human operator. "Ergonomics" implies designing equipment to maximize how efficiently people are working in an environment. "Anthropometrics" refers to measuring size and proportions of the human body. "Poor ergonomics" is cited as a significant enabling factor of perception errors leading to RAF aviation accidents, including visual illusion, disorientation, and misinterpreted displays.[4]

Table I. Table of Anthropometrics & Ergonomics Evaluation Metrics.

METRIC	DESCRIPTION
Card-Sorting[38]	Contrasts with MCDM as it factors in end user/ pilot's desires in location placement for cockpit items. Pilots place indicators (cards) around the cockpit display panel. Comments and reasoning behind placement are also noted. Preference means and frequency after all (eight) pilots complete the card-sorting are then analyzed to reach a preferred design location.
Hess Force/Feel Metrics[17]	Set of five metrics (that must be all used in conjunction with one another) based on pilot Cooper-Harper ratings and measurement of "stick and rudder" control force inputs. Designed for use in aircraft/cockpit certification.
Different Types of Uncertain Linguistic Multiple Attribute Combination Decision-Making (DTULDM)[5]	Cockpit ergonomics evaluation. Approaches cockpit layout as multiple attribute decision-making (MADM) problem. Very rigorous mathematical background to deal with "fuzziness" of ergonomics evaluation.
Anthropometric Measurements[37]	Helicopter aircrew focus.

In practical application, the U.S. Air Force (USAF) and USN use very similar processes for anthropometric accommodation evaluations of aircraft cockpits. These evaluations are conducted when the introduction of new aircraft or aircraft modifications impact cockpit accommodation. These evaluations identify anthropometric restrictions for a particular aircraft and determine maximum and minimum values for areas such as sitting height, sitting eye height, buttock-knee length, and thumb tip reach. The primary focus is avoiding any impingement on controls or control panels and allowing for egress (i.e., ejection seat) clearance. It is noteworthy that crash-worthiness is not necessarily considered in these anthropometric and ergonomic studies.

Senol presents the largest recent body of work regarding cockpit layout anthropometry. The bulk of this research focused on rotary-wing cockpits, although fixed-wing cockpits were included. It addresses the "dialogue between the operator and the device" with both quantitative and qualitative metrics: multi-criteria decision-making (MCDM) (quantitative) and card-sorting (qualitative metric).[37,38] MCDM is referenced in subsequent research evaluating positioning of analog indicators on display panels.[37] The focus shifts to pilot visual field and ability to reach necessary cockpit controls and displays. The research recommendations include that pilot selection may be necessary to limit cockpit design accommodations.[36] While both MCDM and card-sorting may be useful in evaluating ergonomics and anthropometrics, MCDM may yield the greatest benefit as a data management and presentation evaluation tool and is categorized as such.

Multiple Chinese research groups are active in cockpit ergonomics research, some to an exhaustive level of mathematical detail. Zhang and Sun go as far as discussing coordinate transformation between pilot torso and cockpit reference frames when discussing cockpit layouts and body movements required of aircrew. A thorough examination of different flight profiles and regimes is presented, decomposing each in-flight task into items requiring either pilot attention or inputs.[50] Chen et al. discuss differences between Russian, American, and Chinese cockpit designs, but focuses on Chinese aircraft characteristics and quantitative evaluations with multiple attribute decision-making.[5] Similarities may be drawn to Senol's MCDM metric categorized in data management and presentation.[37] Wang et al. evaluate cockpit ergonomics in a virtual CAD model, which could be very useful in the preliminary design review stages of a cockpit design lifecycle.[46] However, they do not present their evaluation criteria in detail. Their scope has been limited to commercial aircraft cockpits.

Table II. Table of HCI Evaluation Metrics.

METRIC	DESCRIPTION
Communication-Human Information Processing (CHIP)[39]	Risk communication and warning/ACAWS evaluation tool. Based on model for traffic signs, medicine and food labels, etc. Includes framework based on source, channel, attention, memory, attitudes, motivation, and behavior. Uses various methods to measure attention, including eye movement, Detection or Reaction Time (D-RT), and Self Reports questionnaires.
Detection or Reaction Time (D-RT)[39,48]	Direct method of measuring attention. Susceptible to false positives when used to judge if participants have detected a warning. Cheaper and easier when compared to eye movement measurements, but drawback in that the researcher does not gain information on the visual path taken to locate the warning.
Crew Station Design Tool (CSDT)[45]	Proprietary software tool to help designers optimize displays and controls layout in workstations, with a focus on fixed-wing aircraft. Prioritizes criteria such as frequency of use, sequence of use, and both.
Stanton Input Device Evaluation[41]	Evaluation of cognitive and physical performance of menu navigation devices.
Modulation Transfer Function (MTF)[19 (p. 380)]	Developed in CRT world, unclear if LED/Flat Panel Display would require modifications.
Modulation Transfer Function Area (MTFA)/TQF[19 (p. 381)]	Developed in CRT world, unclear if LED/Flat Panel Display would require modifications.
Snyder's Threshold Sensitivity Curve[19 (p. 381)]	Further adaption of MTF requiring psychophysical experiments; developed in CRT world, unclear if LED/Flat Panel Display would require modifications.
Haworth-Newman Avionics Display Readability Scale[28 (p. 97)]	Naval Postgrad School proposal; developed in CRT world, unclear if LED/Flat Panel Display would require modifications.
Perceivable Just Noticeable Differences (PJND)[19 (p. 160)]	Measure color and luminance difference, used in (relatively) recent Eurofighter development; developed in CRT world, unclear if LED/Flat Panel Display would require modifications.

Table III. Table of Relevant Data Management Evaluation Metrics.

METRIC	DESCRIPTION
Multi Criteria Decision-Making (MCDM)[37]	On a 0–100 scale, pilots are evaluated on misapprehending information on flight safety and the frequency of that information's use during flight. This is graded on 24 locations in the cockpit. Disadvantage is that the pilot's desires for location placement are not factored in, only the design engineer's.
Eye-Movement Patterns[16 (p. 346)]	Utilized eye-movement records to determine in which order pieces of text were read.
Cloze Tests[16 (pp. 346-347)]	Text-reading comprehension test concurrent while user is reading.
Comprehension Tests[16 (p. 351)]	Text-reading comprehension test after user has completed reading.
Johnson Criteria/Detect Identify Recognize[19 (p. 118)]	Standard practice for evaluating sensor-assisted vision.
USAF Tri Bar Test Pattern[19 (p. 379)]	Standard practice for evaluating display image quality.
Display Readability Rating[28 (p. 111)]	Modified Cooper-Harper.
Display Flyability Rating[28 (p. 111)]	Modified Cooper-Harper.
HUD Optical Measurements/HUD Photometric Measurements[28 (p. 114)]	Often restricted to laboratory environment.

Hess focuses indirectly on ergonomics by developing metrics for evaluating pedal force and feel systems in transport aircraft. Using these metrics in conjunction with Cooper-Harper ratings allows for an evaluation of "stick and rudder" cockpit control layouts.[17]

Human–Computer Interaction (HCI)

The ability of aircrew members to interact with the increasingly digital systems of modern aircraft is critical to optimal cockpit design and performance, which falls under the field of HCI. Singer and Dekker provide an insightful body of work for evaluating cockpit design focusing on HCI.[40] Singer's background as a military test pilot leverages a high degree of operational knowledge to the cockpit design evaluation problem. Although dated, they walk through an excellent synopsis of 2001 European commercial aircraft cockpit certification, identifying a gap between technical focus (which, they suggest, the European Union and Federal Aviation Administration can become fixated on) at the expense of operability, and rely entirely on subjective evaluations for human–machine interactions. These subjective evaluations are prone to pilot-to-pilot biases.[40] Singer's dissertation deviates from quantitative metrics on cockpit design validation, proposing a modified design process for commercial air transport aircraft based on flight test

Table IV. Table of Operations/CRM Evaluation Metrics.

METRIC	DESCRIPTION
NASA-TLX (Task Load Index)[15 (p. 541),39]	Mental workload measurement for multidimensional characteristics. Considered the most widely used metric because of ease in administering. Participants rate 6 different scales in 20 intervals, ratings are then converted to values of 0–100. Laboratory research-based. Dimensions are also evaluated on relevance, and then weighted. Sometimes used in simulations but limited application in real-world flight operations.
SWAT (Subjective Workload Assessment Technique)[22 (p. 533)]	More time-consuming than NASA-TLX, requiring an hour to fully implement. Also multidimensional. Unique feature is that it's based on psychological model of how judgments of mental workload are formed by participants. Rate on three dimensions, each scale having 3 points. (1-1-1 = lowest workload, 3-3-3 = highest workload).
Human Factors Analysis and Classification Tool (HFACS)[32,39]	Uses data gathered from accident investigations to develop human error classifications into operational error. Less useful as a design evaluation tool and more of a human error event analysis tool. Also lacks references to novel cockpit technologies.
Bedford Workload Scale[28 (p. 72)]	Modified Cooper Harper. Captures workload, does nothing for capturing performance.
Defense Research Agency Workload Scale (DRAWS)[19 (p. 89)]	Similar to TLX, scale 0–100 (and beyond for overload).
Jarret's Three Classes of Objective Assessment Techniques[19 (p. 89)]	Measure performance directly—difficult to quantify all tasks this way. Loading operator to maximum sustainable effort. Assessment of physiological variables (blink rate, heart rate, blood pressure, heart rate variation/arrythmia, sweat rate, muscle tension, and the concentration of adrenal hormone secretions in the blood and urine).
W/INDEX[29]	Workload analysis tool based on Wickens' Multiple Resource Theory.
China Lake Situation Awareness (CLSA)[13,28 (pp. 59-66)]	Subjective questionnaire.
Crew Situation Awareness (CSA)[13,28 (pp. 59-66)]	Observers rate crew coordination.
Situation Awareness Global Assessment Technique (SAGAT)[13,28 (pp. 59-66)]	Intrusive questionnaire in simulator scenarios.
Situation Awareness Probe (SAP)[13,28 (pp. 59-66)]	Questionnaire similar to instructor pilot questions during pilot training.
Situation Awareness Rating Technique (SART)[10,13,28 (pp. 59-66)]	Subjective analysis tool where operators rate a system design based on the demand for attentional resources, supply of resources, and understanding of overall situation provided in a given scenario.
Situation Awareness Subjective Workload Dominance (SA-SWORD)[13,28 (pp. 59-66)]	Paired judgment rating matrix that produces numerical output.
Situation Awareness Supervisory Rating Form (SASRF)[13,28 (pp. 59-66)]	Peer evaluation of other pilots/crew members.
Physiological Measurements[22 (p. 531)]	Cardiac activity, heart rate, blood pressure, brain activity, etc.

Table V. Table of Ingress and Egress Evaluation Metrics.

METRIC	DESCRIPTION
Time Measurement[12]	Egress time.
Available Safe Egress Time[50]	Commercial aircraft passenger safety and behavior modeling in emergency situations.

experience and empirical results.[39] Singer discusses multiple facets of human factors involved in crewed aircraft flight, including task saturation,[15] aircrew training,[32] situational awareness, reaction time, and human information processing.[48]

Stanton et al. thoroughly investigated and evaluated different methods of aircraft display control inputs: trackballs, rotary controllers, touch pads, and touch screens.[41] Their conclusions are varied for different tasks but identified touch screens as the most commonly "best rated" input devices for multiple input tasks.

The published work of Marstall et al. focuses on marketing their proprietary cockpit design. However, their previous research may serve to expand the knowledge base of cockpit display and instrument evolution, particularly with regards to improving legacy aircraft flight instruments.[21]

The research scope of Walters et al. was very limited, serving more as a white paper for their proprietary design tool rather than presenting research conclusions. It still is noteworthy for putting forward a framework for evaluating cockpit designs based on flight regime and function.[45]

Data Management and Presentation

A clear example of data management and presentation is depicted in **Fig. 1**. On the left side is the traditional "steam gauge" or "blind flying" panel universally accepted in aviation since its development in the 1930s by William Ocker and Jimmy Doolittle, until modern electronic displays supplanted analog gauges in commercial and military aircraft in the last 30 yr. On the right side is an example of a modern "glass cockpit" display of an Attitude Display Indicator (ADI) and Horizontal Situation Indicator (HSI). Noteworthy is the fact that both left and right presentations display exactly the same data relevant to aircraft operation (i.e., indicated airspeed, altitude, heading, navigational aid data referenced to a VOR navaid). It's simply two different methods of presenting the same data. Analogous to a digital vs. analog wristwatch, one or the other display presentation may be more comfortable to different population sets of aircrew.

Common aircraft data displays include the now ubiquitous (at least as far as commercial airline and military aircraft are concerned) Heads Up Display (HUD). The next evolution of the HUD, specifically in the realm of tactical combat aircraft, is Helmet Mounted Displays. Heads Down Displays include Multi-Function Display (MFD), and the aforementioned analog "steam gauges." Advisory Cautions and Warning System (ACAWS) audible aircraft alerts provide data presentation in an auditory capacity. ACAWS in an aircraft system should not be confused with the NASA Orion Advanced Caution and Warning System, which is a spacecraft application for use in NASA's next-generation crewed spacecraft beyond low Earth orbit to provide autonomous alert monitoring and relaying.

Thomas and Rantanen focus on human factors involving a pilot's ability to process air traffic information. Their approach segments into computer display, such as alerting algorithms and false alarms, and other human factors issues such as aircrew workload and display dimensionality. They ultimately identify a gap requiring quantitative analysis of newer technology and cockpit displays.[43]

Dehais et al. broach the topic of anesthesia induced by sterile cockpit operations, where the sterile auditory environment in a cockpit during certain flight regimes can lull an aircrew into inattention.[8] This is also discussed by Broom et al. but with a greater focus on Cockpit/Crew Resource Management.[3] Dehais focuses on higher workload flight regimes (i.e., approach and landing) where 40% of a population of general aviation pilots failed to detect an auditory, critical alarm. They propose case-based learning as a solution to inattentiveness or auditory alarm misperception. Other research is investigating the implementation of cockpit display of traffic information (CDTI) and how associated alerts can be better tuned based on pilot preference and how cockpit alerting system test methods can be refined.[31,43] Kolbeinsson et al. published a high

Fig. 1. Comparison of legacy steam gauge blind flying panel to attitude display indicator and horizontal situation indicator.

level investigation of different cockpit display icons with designs varying in shape, size, and color to denote additional information with a case study of aircraft "friend or foe" identification and threat level.[20]

One of Senol's previously discussed quantitative metrics, MCDM takes a quantitative approach to evaluating both anthropometrics and interaction between operators and cockpit devices in rotary wing aircraft. It appears to offer the greatest benefit as an evaluation technique categorized under Data Management & Presentation, although as with some metrics it may be useful applied across more than one category.[38]

Operations/Crew Resource Management (CRM)

Crew Resource Management can be defined as "cognitive, social and personal resource skills that complement technical skills and contribute to safe and efficient task performance".[7] CRM has a quantifiable impact on crew performance, but how does cockpit influence it? Recent evolutions of the Lockheed C-130 aircraft have removed the Flight Engineer crew position from the US Air Force aircrew, now relying on computer generated diagnostic codes to prompt the aircrew members for in-flight maintenance advisory items. While this yields benefits for streamlining aircrew training and staffing, it may not necessarily prove to be beneficial for CRM in workload intensive phases of flight. Similar examples are presented in the burgeoning arena of Remotely Piloted Aircraft and their associated crew stations.

A popular method of capturing workload is by subjective/operator opinion techniques, or subjective measures of mental workload.[22] The Bedford Workload Scale is essentially a modified Cooper Harper evaluation scale applied to workload, with the noteworthy constraint that it does nothing to capture performance.[33] NASA Task Load Index (NASA-TLX) is another widely technique that is applied in simulations but limited in real world flight operations due to required interruption to complete the questionnaire.[22] Farmer's Defense Research Agency Workload Scale (DRAWS) is similar to NASA-TLX on a scale of 0 to 100 and beyond for task overload.[19]

Jarrett categorizes three classes of objective assessment techniques:[19]

1. Measuring performance directly, which is difficult to quantify all tasks this way.
2. Loading operator to maximum sustainable effort.
3. Assessment of physiological variables (blink rate, heart rate, blood pressure, heart rate variation/arrythmia, sweat rate, muscle tension and the concentration of adrenal hormone secretions in the blood and urine).

Similarly, Megaw suggests empirical, analytical, psychophysiological, and the previously mentioned subjective/operator opinion techniques.[22] Indeed the advent of eye tracking technology, as well as psychophysiological data acquisition systems, have both become increasingly commonly used for capturing aircrew workload and performance in recent years.

It's noteworthy when Eggemeier and Wilson conclude that a battery of measurements is required to capture workload in multitask environments,[9] and R. Newman and Greeley propose using a combination of test and evaluation techniques and success criteria as no single metric defines acceptability.[28] W/INDEX stands out as a predictive workload analysis tool based on Wickens' Multiple Resource Theory.[29]

Numerous other metrics and techniques to assess operator and crew situational awareness are captured by Gawron et al. and R. Newman and Greeley.[13,28] These primarily take the form of assessment questionnaires and include the following:

1. China Lake Situation Awareness (CLSA), a subjective questionnaire;
2. Crew Situation Awareness (CSA), in which observers rate crew coordination;
3. Situation Awareness Global Assessment Technique (SAGAT), a well-known, objective, knowledge-based approach developed, but can be an intrusive questionnaire in simulator scenarios;
4. Situation Awareness Probe (SAP), a questionnaire similar to IP questions during pilot training;
5. Situation Awareness Rating Technique (SART);
6. Situation Awareness Subjective Workload Dominance (SA-SWORD), a paired judgement rating matrix that produces numerical output; and
7. Situation Awareness Supervisory Rating Form (SASRF), a peer evaluation of other pilots/crew members.

Crichton examined five principles for improving simulator-based training for teams involved in complex, technical work environments.[7] While not focused on CRM, it discussed similar nontechnical skills being applied to improve overall team performance, as well as identifying behavioral markers and evaluation metrics. Broom et al. discuss inattentiveness induced by a sterile auditory environment in a cockpit, with results measured in different sound environments.[3] Contrasting their approach from the Data Management effort of Dehais et al. was the focus on CRM issues in a sterile cockpit environment.[8]

Salas et al. investigated the lack of empirical studies supporting findings that CRM implementation is beneficial. This is noteworthy as the US Navy and US Air Force often cite their own internal statistics for CRM improving aircraft mishap rates significantly. However, Salas et al. may be the first published academic investigation into the impact of CRM.[35] While the focus of Miller and Hannen's research is on implementing a new rotorcraft user interface for cockpit information management not previously utilized, in doing so they broke down pilot-perceptible behaviors in several categories for analysis. Initial trials of subjective evaluations of cockpit layouts were supplemented with objective performance data.[24] In a separate study Russi-Vigoya and Patterson took the unique approach of investigating eye fixation of private pilots utilizing glass cockpits in flight simulations, showing common trends during failures and poor weather conditions.[34]

Ingress and Egress

The ultimate measurement of how well a cockpit is designed for ingress and egress, particularly emergency egress, is time, followed by required assistance. These are the two metrics set forth for by the Federal Aviation Administration but specifically pertaining to passengers on transport category aircraft.[12] Ejection seat technology features heavily in tactical military aircraft cockpit designs and remains a primary consideration due to the specific design requirements for ejection seat use (i.e., ensuring aircrew member's limbs are not impinged during ejection).

Stedmon et al. compare human behavior modeling between passenger airline and railroad environments, particularly noting the lack of research on passenger rail egress models and the abundance of passenger airline research.[42] While research focuses on aircrew egressing a cockpit specific environment would be of greater significance than passenger cabin egress, it still yields potential interest in commercial spaceflight (i.e., space tourism) applications. Zhang et al. goes into further detail on commercial aircraft passenger safety and behavior modeling in emergency situations. They discuss two specific models—the Fire Dynamics Simulator and Pathfinder—to measure safe egress from an Airbus A380 case study.[49]

Bienefeld and Grote analyzed commercial aviation cockpit and cabin crews and their behavior in simulated in-flight emergencies and developed a structured observation scheme to objectively evaluate crew performance. This could potentially be factored in to determining useful in how cockpit design facilitates or hinder crew performance during emergencies.[1]

DISCUSSION

No previous wide-ranging review focusing on aircraft cockpit design and performance evaluation metrics and techniques was found in the literature. As such, the information presented here attempts to summarize numerous evaluation methods across multiple aspects of cockpit design and performance. The metrics and techniques summarized here cover many of the commonly used preexisting subjective and objective approaches; however, this should not be considered a definitively comprehensive list.

Multiple research efforts, combined with research gaps identified by NASA and the US Navy, emphasize the importance of human-computer interaction during crewed flight. Quantitative evaluation metrics such as these allow for initial evaluation of emerging aircraft and spacecraft systems early in the design process. Table I, Table II, Table III, Table IV, and Table V present a brief overview of commonly used quantitative metrics focused on aircraft cockpit subsystems and human factors considerations. Each table presents the metrics and techniques cataloged into five categories covering aspects of cockpit design. These five categories are graphically depicted in **Fig. 2** in sequential order as an aircrew member may encounter them in aircraft operations.

As demonstrated in the literature, numerous metrics and methodologies exist to evaluate design effectiveness and performance of aircraft cockpit components and subsystems intended to aid human operators in task and mission

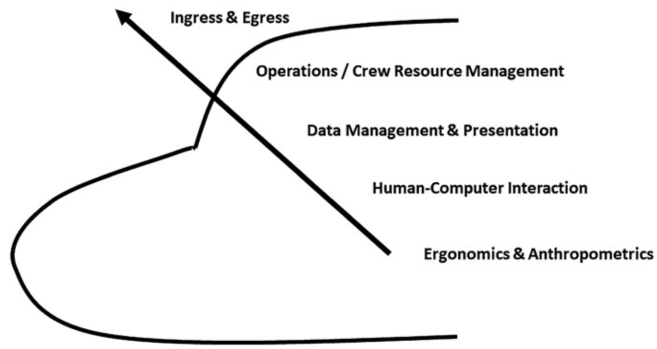

Fig. 2. Cockpit evaluation categories.

accomplishment. It would be useful to designers, systems engineers and the flight test community in evaluating and optimizing modern aircraft cockpit designs to combine these categories into a comprehensive quantitative evaluation metric to evaluate the cockpit system as a whole. By leveraging preexisting, traditionally used metrics as described here, one can quantify the effectiveness of various aircraft cockpit subsystems design and performance based on the human operator's ability to perform the intended tasks. However, to the best of our knowledge, no quantitative holistic method or metric for evaluating overall cockpit design and performance yet exists. In conclusion, it may be possible with further research to develop and validate such a holistic methodology to evaluate the integrated aircraft cockpit system performance as a means for improving the design and operations of the vehicle.

ACKNOWLEDGEMENTS

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

Authors and Affiliations: Eric M. Brighton, M.S., B.S., Aerospace Engineering Sciences (Ph.D. candidate), and David M. Klaus, Ph.D., M.S., Aerospace Engineering Sciences (Professor), University of Colorado, Boulder, Colorado, United States.

REFERENCES

1. Bienefeld N, Grote G. Shared leadership in multiteam systems: how cockpit and cabin crews lead each other to safety. Hum Factors. 2014; 56(2):270–286.
2. Bronk J. The mysterious case of the missing Russian Air Force. RUSI. 2022. [Accessed July 15, 2022]. Available from: https://rusi.org/explore-our-research/publications/commentary/mysterious-case-missing-russian-air-force.
3. Broom MA, Capek AL, Carachi P, Akeroyd MA, Hilditch G. Critical phase distractions in anaesthesia and the sterile cockpit concept. Anaesthesia. 2011; 66(3):175–179.
4. Chappelow JW. Error and accidents. In: Rainford D, Gradwell DP, Ernsting J, editors. Ernsting's aviation medicine. 4th ed. London (UK): CRC Press; 2006:349–358.
5. Chen J, Yu S, Wang S, Lin Z, Liu G, Deng L. Aircraft cockpit ergonomic layout evaluation based on uncertain linguistic multi-attribute decision-making. Adv Mech Eng. 2014; 6:698159.

6. Cohen D. Identification of advanced technology crew station decision points and information requirements. Defense Technical Information Center; 1993:356. Report No.: ADA326336. [Accessed 10 July 2023]. Available from: https://apps.dtic.mil/sti/citations/ADA326336.
7. Crichton MT. From cockpit to operating theatre to drilling rig floor: five principles for improving safety using simulator-based exercises to enhance team cognition. Cogn Technol Work. 2017; 19(1):73–84.
8. Dehais F, Causse M, Vachon F, Régis N, Menant E, Tremblay S. Failure to detect critical auditory alerts in the cockpit: evidence for inattentional deafness. Hum Factors. 2014; 56(4):631–644.
9. Eggemeier FT, Wilson GF. Performance-based and subjective assessment of workload in multi-task environments. In: Damos DL, editor. Multiple-task performance. London (UK): Taylor & Francis; 1991:217–276. [Accessed 10 July 2023]. Available from: https://www.taylorfrancis.com/chapters/edit/10.1201/9781003069447-13/performance-based-subjective-assessment-workload-multi-task-environments-thomas-eggemeier-glenn-wilson.
10. Endsley MR. Situation awareness measurement in test and evaluation. In: O'Brien TG, Charlton SG, editors. Handbook of human factors testing and evaluation. Mahwah (NJ): Lawrence Erlbaum Associates; 1996:159–80.
11. Fanchiang C. A quantitative human spacecraft design evaluation model for assessing crew accommodation and utilization [Ph.D. Dissertation]. Boulder (CO): University of Colorado Boulder; 2017.
12. Federal Aviation Administration. Federal aviation regulations. Washington (DC): Federal Aviation Administration; 2023. Sec. 25.803. Emergency evacuation. [Accessed 10 July 2023]. Available from https://www.ecfr.gov/current/title-14/chapter-I/subchapter-C/part-25/subpart-D/subject-group-ECFR88992669bab3b52/section-25.803.
13. Gawron V, Weingarten N, Hughes T, Adams S. Verifying situational awareness associated with flight symbology. Paper presented at the AIAA 37th Aerospace Sciences Meeting and Exhibit; January 11–14, 1999; Reno, NV. Reston (VA): American Institute of Aeronautics and Astronautics; 1999.
14. Glenn F, Boardway J, Wherry R Jr, Cohen D, Carmody M. The advanced technology crew station: development and validation of a workload assessment technique for cockpit function allocation. Defense Technical Information Center; 1993:57. Report No.: ADA279544. [Accessed 10 July 2023]. Available from https://apps.dtic.mil/sti/citations/ADA279544.
15. Hart SG, Staveland LE. Development of NASA-TLX (Task Load Index): results of empirical and theoretical research. Adv Psychol. 1988; 52:139–183.
16. Hartley J. Is this chapter any use? Methods for evaluating text. In: Wilson JR, Corlett EN, editors. Evaluation of human work. 3rd ed. Boca Raton (FL): Taylor & Francis; 2005:335–351.
17. Hess RA. Metrics for the evaluation of pedal force/feel systems in transport aircraft. J Aircr. 2008; 45(2):651–662.
18. Insinna V. At a budgetary crossroads, the US Navy's aviation wing must choose between old and new. Defense News. 2020. [Accessed October 20, 2022]. Available from https://www.defensenews.com/air/2020/06/01/at-a-budgetary-crossroads-the-us-navys-aviation-wing-must-choose-between-old-and-new/.
19. Jarrett DN. Cockpit engineering. Abingdon (UK): Routledge; 2005:89.
20. Kolbeinsson A, Falkman G, Lindblom J. Showing uncertainty in aircraft cockpits using icons. Procedia Manuf. 2015; 3:2905–2912.
21. Marstall J, Miller ME, Poisson RJ. Collaboration in the cockpit: human–system interaction beyond the autopilot. Ergon Des. 2016; 24(1):4–8.
22. Megaw T. The definition and measurement of mental workload. In: Wilson JR, Corlett EN, editors. Evaluation of human work. 3rd ed. Boca Raton (FL): Taylor & Francis; 2005:525–547.
23. Mejzak RS, Sparta ML, Warner NW. Crew system engineering methodology: process and display requirements. Paper presented at the IEEE/AIAA 10th Digital Avionics Systems Conference; October 14–17, 1991; Los Angeles (CA). New York (NY): IEEE; 1991:387–392.
24. Miller CA, Hannen MD. The rotorcraft pilot's associate: design and evaluation of an intelligent user interface for cockpit information management. Knowl Based Syst. 1999; 12(8):443–456.
25. Mizokami K. "Sixth generation" fighters jets are already taking shape. Popular Mechanics. 2017. [Accessed August 27, 2018]. Available from: https://www.popularmechanics.com/military/aviation/a25832/sixth-generation-fighter-jets-already-taking-shape/.
26. NASA. Human research roadmap, risk of inadequate human-computer interaction. [Accessed January 10, 2017]. Available from: https://humanresearchroadmap.nasa.gov/risks/risk.aspx?i=164.
27. Naval Air Systems Command. NAVAIR science and technology basic and applied research solicitation number: NAWCAD-BAA-17-03. [Accessed January 10, 2017]. Available from: https://www.fbo.gov/?s=opportunity&mode=form&id=854b996fbc57aab22547702b50d10132&tab=core&_cview=0.
28. Newman RL, Greeley KW. Cockpit displays: test and evaluation. Abingdon (UK): Routledge; 2016:59–76.
29. North RA, Riley VA. W/INDEX: a predictive model of operator workload. In: McMillan GR, Beevis D, Salas E, Strub MH, Sutton R, Van Breda L, editors. Applications of human performance models to system design. Boston (MA): Springer US; 1989:81–89. [Accessed July 10, 2023]. Available from: http://link.springer.com/10.1007/978-1-4757-9244-7_6.
30. Notaro J. Crew centered armament system for high technology cockpit. 1999:9–10. Report No.: ADA368287. [Accessed 10 July 2023]. Available from: https://apps.dtic.mil/sti/citations/ADA368287.
31. Pritchett AR, Vándor B, Edwards K. Testing and implementing cockpit alerting systems. Reliab Eng Syst Saf. 2002; 75(2):193–206.
32. Rigner J, Dekker S. Modern flight training – managing automation or learning to fly? In: Dekker S, Hollnagel E, editors. Coping with computers in the cockpit. 1st ed. Hants (UK): Ashgate; 1999:145–151. [Accessed 2022 Sept. 12]. Available from https://www.taylorfrancis.com/books/9780429864216.
33. Roscoe AH, Ellis GA. A subjective rating scale for assessing pilot workload in flight: a decade of practical use. Farnborough (UK): Royal Aerospace Establishment Farnborough; 1990. Report No.: TR 90019. [Accessed 10 July 2023]. Available from https://apps.dtic.mil/sti/citations/ADA227864.
34. Russi-Vigoya MN, Patterson P. Analysis of pilot eye behavior during glass cockpit simulations. Procedia Manuf. 2015; 3:5028–5035.
35. Salas E, Fowlkes JE, Stout RJ, Milanovich DM, Prince C. Does CRM training improve teamwork skills in the cockpit?: two evaluation studies. Hum Factors. 1999; 41(2):326–343.
36. Şenol MB. Anthropometric evaluation of cockpit designs. Int J Occup Saf Ergon. 2016; 22(2):246–256.
37. Şenol MB, Dağdeviren M, Çilingir C, Kurt M. Display panel design of a general utility helicopter by applying quantitative and qualitative approaches. Hum Factors Man. 2010; 20(1):73–86.
38. Şenol MB, Dagdeviren M, Kurt M, Cilingir C. Evaluation of cockpit design by using quantitative and qualitative tools. Paper presented at 2009 IEEE International Conference on Industrial Engineering and Engineering Management. December 8–11, 2009; Hong Kong, China. New York (NY): IEEE; 2009:847–851.
39. Singer G. Methods for validating cockpit design: the best tool for the task. Royal Institute of Technology, Dept. of Aeronautics; 2002. [Accessed July 10, 2023]. Available from https://www.diva-portal.org/smash/get/diva2:9102/FULLTEXT01.pdf.
40. Singer G, Dekker S. The ergonomics of flight management systems: fixing holes in the cockpit certification net. Appl Ergon. 2001; 32(3):247–254.
41. Stanton NA, Harvey C, Plant KL, Bolton L. To twist, roll, stroke or poke? a study of input devices for menu navigation in the cockpit. Ergonomics. 2013; 56(4):590–611.
42. Stedmon A, Lawson G, Lewis L, Richards D, Grant R. Human behaviour in emergency situations: comparisons between aviation and rail domains. Secur J. 2017; 30(3):963–978.
43. Thomas LC, Rantanen EM. Human factors issues in implementation of advanced aviation technologies: a case of false alerts and cockpit displays of traffic information. Theor Issues Ergon Sci. 2006; 7(5):501–523.
44. Volz KM, Dorneich MC. Evaluation of cognitive skill degradation in flight planning. J Cogn Eng Decis Mak. 2020; 14(4):263–287.
45. Walters B, Bzostek J, Small R, Stachowiak C. Comparing methods for placing controls and displays in a cockpit. Proc Hum Factors Ergon Soc Annu Meet. 2004; 48(20):2431–2435.

46. Wang L, Wei X, He X, Sun X, Yu J, et al. The virtual evaluation of the ergonomics layout in aircraft cockpit. Paper presented in 2009 IEEE 10th International Conference on Computer-Aided Industrial Design & Conceptual Design. November 26–29, 2009; Wenzhou, China. New York: IEEE; 2009:1438–1442.
47. Winslow L, Warner N, Thomasson T. Advanced Technology Crew Station (ATCS) design methodology. Washington (DC): U.S. Navy; 1989.
48. Wogalter MS, Hancock PA, Dempsey PG. On the description and definition of human factors/ergonomics. Proc Hum Factors Ergon Soc Annu Meet. 1998; 42(10):671–674.
49. Zhang Q, Qi H, Zhao G, Yang W. Performance simulation of evacuation procedures in post-crash aircraft fires. J Aircr. 2014; 51(3):945–955.
50. Zhang Y, Sun Y. Reuse of pilot motions for improving layout design of aircraft cockpit. J Comput. 2013; 8(9):2269–2276.

Operational Considerations for Crew Fatality on the International Space Station

Philip C. Stepaniak; Rebecca S. Blue; Stevan Gilmore; Gary E. Beven; Natacha G. Chough; Ann Tsung; Kathleen A. McMonigal; Edward L. Mazuchowski II; Joan A. Bytheway; Kjell N. Lindgren; Michael R. Barratt

BACKGROUND: While catastrophic spaceflight events resulting in crew loss have occurred, human spaceflight has never suffered an on-orbit fatality with survival of other crewmembers on board. Historical plans for management of an on-orbit fatality have included some consideration for forensic documentation and sample collection, human remains containment, and disposition of remains; however, such plans have not included granular detailing of crew or ground controller actions. The NASA Johnson Space Center Contingency Medical Operations Group, under authority from the Space and Occupational Medicine Branch, the Space Medicine Operations Division, and the Human Health and Performance Directorate, undertook the development of a comprehensive plan, including an integrated Mission Control Center response for flight control teams and Flight Surgeons for a single on-orbit crew fatality on the International Space Station (ISS) and subsequent events. Here we detail the operational considerations for a crew fatality should it occur during spaceflight onboard the ISS, including forensic and timeline constraints, behavioral health factors, and considerations for final disposition of decedent remains. Future considerations for differential survival and crewmember fatality outside of low-Earth orbit operations will additionally be discussed, including consideration of factors unique to planetary and surface operations and disposition limitations in exploration spaceflight. While the efforts detailed herein were developed within the constraints of the ISS concept of operations, future platforms may benefit from the procedural validation and product verifications steps described. Ultimately, any response to spaceflight fatality must preserve the goal of handling decedent remains and disposition with dignity, honor, and respect.

KEYWORDS: human spaceflight, crew fatality, low Earth orbit, International Space Station.

Stepaniak PC, Blue RS, Gilmore S, Beven GE, Chough NG, Tsung A, McMonigal KA, Mazuchowski EL II, Bytheway JA, Lindgren KN, Barratt MR. *Operational considerations for crew fatality on the International Space Station*. Aerosp Med Hum Perform. 2023; 94(9):705–714.

Human spaceflight requires highly precise events to take place in unforgiving operational environments. Even small missteps can result in catastrophic events; historically, loss of crew life has occurred in ground training events, launches, reentry, and landings.[43,53,56] At the National Aeronautics and Space Administration (NASA), protocols have been developed for planning, training, and coordination of responses in the aftermath of these types of contingencies. While catastrophic events resulting in crew loss have occurred, to date human spaceflight has never suffered an on-orbit fatality or a loss of a subset of crewmembers with differential survival of those onboard. Nonetheless, the possibility exists.

Prior plans for the management of an on-orbit fatality have included some consideration for human remains containment and disposition as well as the possibility of forensic sample collection, though such plans have not included dedicated preflight protocol training for crew or granular detailing of crew or ground controller actions.[29] Historical plans involving remains containment and disposition were largely untested

From NASA Johnson Space Center, Houston, TX, USA; the University of Texas Medical Branch School of Public and Population Health, Galveston, TX, USA; Forensic Pathology Associates, HNL Lab Medicine, Allentown, PA, USA; Sam Houston State University, Southeast Texas Applied Forensic Science (STAFS) Facility, Huntsville, TX, USA; and Liberty University Department of Biology and Chemistry, Lynchburg, VA, USA.

This manuscript was received for review in May 2023. It was accepted for publication in June 2023.

Address correspondence to: Dr. Rebecca S. Blue, M.D., M.P.H., Emergency, Aerospace, University of Texas Medical Branch, School of Public and Population Health, 301 University Blvd, Galveston, Texas, 77555-1110, United States; rblue.md@gmail.com.

DOI: https://doi.org/10.3357/AMHP.6300.2023

and equipment unvalidated for use in the microgravity environment.[28,29,31] Further, ground support personnel, including flight controllers, were rarely privy to details of decedent management protocols; in general, these topics were not discussed widely outside of expert teams.

Early probability studies estimated the incidence of a significant medical event for a three-person crew onboard the International Space Station (ISS) would be once every 5.5 yr and the incidence of an incapacitating event necessitating orbital evacuation was estimated at once every 33 yr.[31,55] For expanded ISS operations of six crewmembers, the incidence of a significant medical event was estimated at once every 3.2 yr and the incidence of an incapacitating medical event requiring evacuation at 1–3 events per 15 yr of continuous ISS operations.[10,31,55] More recent probabilistic analysis applied to ISS conditions, with a crew of six, current ISS medical capabilities, and missions lasting 180 d, predicts a 0.5% chance of loss of crew life.[1] This would predict a fatality in 1 out of 200 ISS crewmembers, or once every 10–15 yr. At the time of writing, around 250 people have flown to the ISS in just over 20 yr of operations—even current models predict at least one fatality and multiple evacuations for serious medical events over that timeline.[1] Actual operational experience has not borne these estimates out. Between 1971 and 2022, one evacuation and two early mission terminations have occurred during crewed spaceflight,[11,31,53] far fewer than the estimates outlined above.

A fatality onboard ISS, like that in any analogous high-profile austere and hazardous venue, would result in a tragic and disruptive event with heavy media coverage and public scrutiny.[3,4] Lack of preparedness for such an event could render a situation far worse as stakeholders would be forced to formulate responses and actions in real time. Thus, the value of preparedness for a crew fatality and aftermath cannot be overstated.[25] Terrestrially, analog expedition scenarios demonstrate the implications of inadequate planning for a team member fatality.[32,52,59] Insufficient supplies, inadequate skillsets and capabilities, and the psychological impact of the loss of a member of a small team can all contribute to poor outcomes after a fatality, ranging from disruption and worsened psychological trauma to disorganized responses, and even increased risk to surviving crewmembers.[5,51,52] A cogent, orderly plan to respond to a traumatic event, such as the loss of a crewmember, can instead ensure the safety of the surviving team members, allow for expedited response for activities that are time-sensitive, ease psychological distress through appropriate actions, and protect the privacy and dignity of the decedent, survivors, and their families. Further, a well-established protocol allows for the collection of forensic evidence such that causal and contributory factors related to the fatality may be identified, providing the opportunity to gain a full understanding of the event, identify lessons learned, and drive program iteration and implementation of preventive measures.

The NASA Johnson Space Center (JSC) Contingency Medical Group, under authority from the Space and Occupational Medicine Branch, the Space Medicine Operations Division, and the Human Health and Performance Directorate, undertook the development of a comprehensive plan, including an integrated Mission Control Center response, in an organized, contemporaneous timeline for flight control teams and Flight Surgeons for a single on-orbit crew fatality on the ISS and subsequent response. This project included the following:

- Development of a comprehensive plan and integrated response for the flight controllers[29];
- Ground validation of pronouncement and forensic sampling procedures;
- Verification of equipment specifications for forensic sampling supplies[14,28,29];
- Verification of equipment specifications for a human remains containment unit (HRCU), including validation study using ISS analog pressure, temperature, and humidity[14,28,29];
- Determination of an appropriate ISS stowage location for the HRCU; and
- Designation of responsible entities within the NASA JSC Flight Operations Directorate and ISS Program Office tasked with the responsibility of determining the final disposition of remains.

This collaborative effort involved stakeholders from NASA and its international partners, as well as military and academic institutions, to develop and validate operational considerations for a single crewmember fatality in this scenario. Following development, this effort was reviewed and approved by Directorate stakeholders for operational implementation; these validated procedures and verified equipment were subsequently manifested on the ISS.

Prior publication has discussed the detailed procedures surrounding forensic sample collection, preparation of decedent remains for disposition, and validation of an HRCU modified for the space environment.[29] Here we discuss in detail the operational considerations for a single crew fatality occurring during NASA-crewed spaceflight, highlighting the historical background and risks of spaceflight and a timeline for management of an onboard fatality to ensure an orderly and timely response for pronouncement, forensic sampling, preparation, stowage, and disposition of remains. Further, we will discuss factors considered to ensure the protection of the surviving crew and vehicle from potential contamination risk, goals and rationale for forensic sampling, and efforts to ensure that the decedent will be handled with dignity, honor, and respect at all times while gathering forensic data needed to assist in determining the cause of death. Protocol development was heavily influenced by coordination with the Behavioral Health and Performance Operations Group; thus, psychological considerations for crew and ground support team members will additionally be addressed. Finally, future implications for programmatic development and customization of protocols to address fatality, decedent remains disposition, and postmortem management will be discussed, with factors to be considered for future and exploration-class missions outside of low Earth orbit.

Historical Perspective

The possibility of crewmember fatality during spaceflight has garnered considerable attention in previous human spaceflight programs. NASA's Project Mercury and Project Gemini protocols were influenced heavily by the high-performance flight programs that preceded them, with protocols adopted in parallel to those used in military test flight projects.[17] Missions were relatively short and crew rescue or evacuation options were limited in the nascent human spaceflight efforts. During the Apollo Program, mission duration increased and risks evolved due to distance from Earth and limited to no evacuation options during substantial portions of each mission. Astronauts were aware of the risks that they were undertaking and simultaneously recognized the need to prioritize the protection and safety of any survivors against the natural desire to recover a deceased crewmember's remains. During a retrospective review of the Apollo Program, in providing recommendations for developing future lunar missions, former Apollo astronauts highlighted their own awareness of the lack of evacuation or rescue options available during lunar missions and strongly recommended that future crews be similarly prepared to leave behind a deceased crewmember, as retaining or recovering decedent remains could threaten the safety of survivors.[50] Additional recommendations from Apollo crewmembers included advanced and detailed planning for contingencies, including death during a mission, ensuring that all individuals (including crew, ground support, and families) would be prepared in the event of a spaceflight fatality and that educational and psychological services were available and familiar to astronauts and their families.[50] Similar recommendations were received from former Skylab Medical Operations Project crewmembers and project personnel.[35]

This need for planning and integration of support services, and the benefits of early activation of crew and employee support in the aftermath of disaster, was again highlighted after U.S. Space Shuttle mishaps.[41,56] Further, during the U.S. Space Shuttle Program there was some effort to improve upon the capability to return crew to Earth, primarily for the return of ill or incapacitated crewmembers, but potentially applicable to return of remains. This included efforts to improve the crew survivability envelope, such as the development of the Crew Escape System after the U.S. Space Shuttle *Challenger* disaster, and the interest in development of an emergency crew return vehicle during the 1980s and 1990s.[31,41,60]

With the return to capsule-based crew transport in current operations, crew capsule vehicles provide nominal transit to and from orbit and crew return capabilities in contingency scenarios. Return of decedent remains in a capsule vehicle poses significant challenges, including the maneuverability of remains within an HRCU to fit within capsule seats, incorporation of seat restraints with the HRCU, and ensuring the safety of surviving crewmembers exposed to remains in a volume-limited capsule.[3,17,29] Additional challenges include the lack of validation studies for decedent remains containment or relevant equipment in microgravity conditions and the limited refrigeration and freezer capabilities available on current operational vehicles.[29] On the ISS, small volume refrigeration and freezer capabilities do exist with temperature storage ranges of −160°C to +4°C.[17] However, the volume available is exceptionally limited and use of this space would require sacrifice of other payloads or items requiring refrigeration; further, return vehicles may lack refrigeration capability after departure from the ISS. Large-volume refrigeration capable of preserving a human body is not available onboard current launch vehicles or on the ISS.[29] In the absence of refrigeration, isolation of remains in an HRCU and further sequestering the HRCU from the crew (such as placement in the airlock or similar compartment that could be then sealed off from the primary habitable volume) could provide some protection for crewmembers from any loss of contamination or biohazardous exposure while simultaneously offering some degree of psychological protection.

Recent efforts into developing a robust human remains capability for use in a microgravity environment have been detailed elsewhere, including feasibility analysis regarding the incorporation of an HRCU into a return vehicle.[29] However, even if effective remains containment resources are available, there is still a need for continued iteration and development of processes regarding the preparation, containment, and return of human remains from spaceflight in current or future vehicles.

Timeline: Decedent Remains Management and Forensic Pathology

An onboard fatality may involve a single crewmember with a medical event or multiple crewmembers due to a larger mishap. Multiple fatalities would likely prompt urgent or emergent evacuation of any survivors, which may preempt forensic procedures or disposition of decedent remains. However, there are circumstances that could conceivably result in a single crewmember fatality with the remaining crew preserved, such as an acute medical illness or event (for example, a sudden cardiac event), injury (vehicular, environmental, etc.), or an event uniquely related to spaceflight factors [for example, a failure of critical hardware during extravehicular activity (EVA)]. In the case of a single crewmember fatality on orbit where the circumstances do not drive an emergent evacuation of ISS by surviving crewmembers, procedural goals include the collection of forensic data, management of remains to ensure containment and prevent contamination of the survivors' habitable environment, and, by providing effective isolation, ensure time for the determination of best options for disposition of remains.[5,29]

An ISS plan for management of a fatality must ensure a mature and orderly response coordinated across critical disciplines. Any plan must be flexible, as it is not possible to anticipate all circumstances surrounding a potentially fatal event on orbit. Extraneous circumstances will influence the execution of any plan or timeline; thus, training of the crew and established procedural tasks increase the likelihood that necessary actions can be accomplished, with appropriate prioritization, in the case of a fatality. Further, development of such procedural actions for ISS operations allows for the application of lessons learned toward future programs and vehicles, scaled appropriately to platform size and crew complement, remote nature of the operation, available communication and support, and possibility of evacuation and return to Earth.

In the case of an on-orbit fatality, initial actions would include confirmation of death and pronouncement, followed by possible forensic collection and preservation of samples (**Fig. 1**). The need for collection of samples must be considered in balance with contraindications to sampling, including safety of the crew (for example, if sample collection delays isolation of potentially dangerous biohazards), cultural and religious sensitivities, and the risk of worsening psychological trauma to crew from sampling procedures or other manipulation of remains.[5,38]

Compared to a controlled, terrestrial forensic effort, any attempt to pursue forensic pathology in the spaceflight environment after crewmember fatality will undoubtedly be complicated by spaceflight-specific factors.[2–4] While crew are provided some preflight medical skills training (such as phlebotomy and catheterization) upon which the forensic sampling procedures are based, and many sample collection techniques are familiar to crew due to similar research sample collection and preservation procedures, crewmembers lack formal forensic training and any procedural training prior to a mission will likely be minimal. Inexperience will be compounded by real-time stressors, including psychological considerations and the circumstances that led to a crew fatality (for example, an altered vehicular environment). Additional factors include microgravity and altered fluid dynamics (and related procedural impacts),[15] the closed vehicle atmosphere, unknown decomposition rates in spaceflight environments, the challenges inherent to validating procedures in the unique operational environment, and the variable but limited options for disposition of remains.[29]

The goals of forensic examination following a spaceflight crew fatality include photographic documentation, removal of personal effects and clothing, forensic sample collection and storage, preparation of the body for disposition, and placement in an HRCU.[29] Desirable forensic samples include hair, fingernails, urine, blood, and vitreous humor[38]; such samples allow for delayed qualitative analysis[21] and are balanced against spaceflight storage and transportation considerations (**Table I**). In the absence of large-volume refrigeration, sample collection should occur as early as possible, preferably within 4 h but certainly within 12 h of death, to minimize alteration of samples from decomposition[14,21,38] and to allow for early isolation of remains in appropriate containment to avoid unnecessarily biohazardous contamination of habitable space.[29] Sample accommodation in available small-volume ISS cold storage would require real-time coordination with appropriate ground controllers to identify best options and appropriate temperatures. In general, freezing would be preferred over refrigeration for longer sample stability.

To minimize manipulation of remains and associated biohazardous and psychological risk, it is likely that preparation of remains will be concurrent to or immediately following forensic sampling, with subsequent isolation and stowage of remains. Decomposition of human remains in a microgravity environment has not been validated, though decomposition in a nonrefrigerated terrestrial environment similar to the environment of the ISS can provide some context for expected timeline. In a room-temperature (~72°F, 22.2°C) environment, rigor mortis can occur within 3–6 h of death and remain present for 24–36 h. This timeline may be altered by environmental conditions (particularly temperature and humidity),[24,37] internal body temperature, and premortem decedent activity.[13,22,27] Initial autolysis and tissue degradation can be expected to occur within a few hours of death.[13,23] Within 24 h, autolytic changes

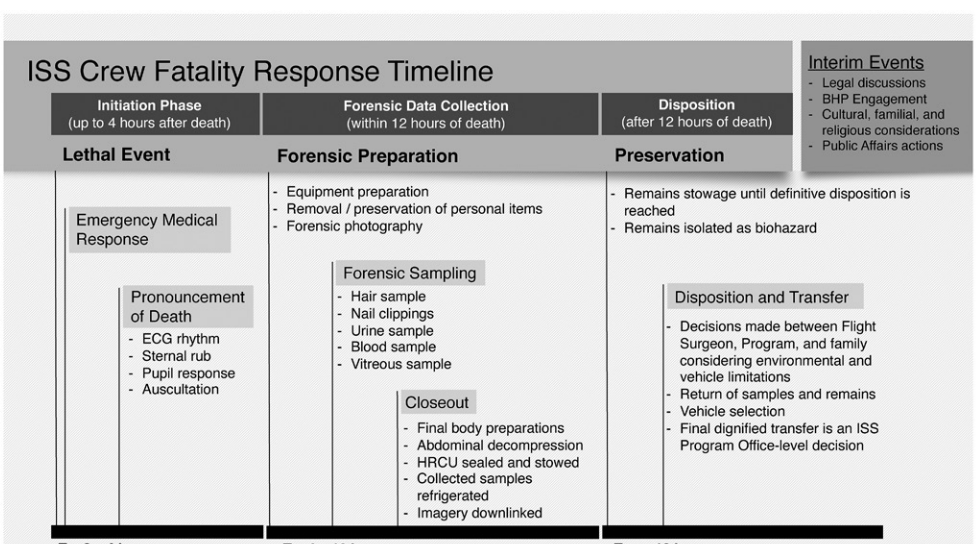

Fig. 1. ISS crew fatality response timeline. Following pronouncement of death, protocol timelines prioritize early sample collection and body preparations for stowage, to be completed no later than 12 h following death. Final disposition of remains will follow, with the ISS Program Office responsible for final determination of remains disposition. Discussions regarding legal, cultural, familial, and religious considerations, as well as behavioral health support plans and public affairs actions, will be concurrent with other timeline actions. BHP: Behavioral Health and Performance Team; ISS: International Space Station; ECG: electrocardiogram; HRCU: human remains containment unit.

Table I. Desirable Spaceflight Forensic Samples and Associated Rationale and Collection Considerations.[29,38]

SAMPLE	RATIONALE	COLLECTION CONSIDERATIONS
Blood	Provides expanded analysis capability compared to other samples [e.g., complete blood count (CBC), thyroid stimulating hormone (TSH), serum protein electrophoresis (SPEP), cortisol, glycosylated hemoglobin (HbA1c), acetone, cholinesterase, carbon monoxide level (CO), microbial cultures].	Anterior parasternal approach for ease of landmarks, adequate sampling volume. Increased likelihood of success compared to great vessels due to postmortem vascular collapse, fluid shifting, loss of pulsatile landmarks.
Urine	Corroborates some serum analyses, culture to rule out source of infection.	Crew already trained on urinary catheterization, equipment available. Should be performed early given potential postmortem incontinence.
Vitreous Humor	Preferred sample substance, more stable than blood for metabolic study. Remains stable and valid for longer periods of time.	Familiarity of decedent and intimate nature of vitreous sampling anticipated to be most likely sampling technique to be associated with psychological stress.
Hair	Stable specimen, allows for toxicological and xenobiotic analysis; further provides segmental analysis for timeline or chronicity of exposure.	Prioritization of scalp hair then forearm for sampling. Postmortem sampling preferably includes bulb extraction.
Fingernails	Collagen can provide insight in protein expression, long-term studies.	Standard nail clippers provisioned for collection

may become externally visible; more concerning for the habitable environment, development of decomposition-related volatiles would be expected by 24 h of decomposition.[36,61] Unless contained, in an enclosed, pressurized environment, production of volatiles such as methanethiol and hydrogen sulfide will adversely affect air quality and pose a health risk to remaining crew.[29] The presence of rigor can be expected to complicate forensic collection and remains stowage, and visible evidence of decomposition would certainly have psychological impact on any surviving crew; development and release of volatile compounds into the habitable environment is clearly undesirable. Thus, these issues would be high-priority drivers for timeline considerations. Ideally, any necessary manipulation of remains should occur as soon as possible; protocols developed for crew fatality on ISS prioritize forensic data collection and final remains preparations for stowage within 12 h of death to minimize exposure to advancing stages of decomposition.[5,29,38]

Behavioral Health Considerations

An in-flight crewmember fatality would necessitate that the remaining crew act as first responders, provide confirmation of death, complete forensic sampling procedures, consider and execute options for remains disposition, honor the fallen colleague, and grieve, along with remote family and friends, all while safely continuing the mission.[3,8] The complexity of these needs will undoubtedly lead to significant behavioral health and performance challenges. Due to pre-mission crew training requirements and schedule constraints, procedural training for actions following an on-orbit fatality is prone to be minimal, and crew are unlikely to be fully briefed on the scope or granular details of procedures until the aftermath of a crewmember fatality. All forensic sampling and crew disposition procedures are designed to be remote-guided by a Flight Surgeon,[29] which ensures that a trained ground support physician is available to assist while simultaneously offering real-time assessment of the crew to determine if a crewmember may need to take a break, refocus, or receive additional psychological support. Crew can opt out of any procedures and the Flight Surgeon has the authority to terminate any forensic sampling procedures to protect the health and safety of the surviving crew.

Even so, given mission demands, procedural timelines, and mission management expectations, it is doubtful that a crewmember will be immediately forthcoming with reporting emotional distress that may interfere with their ability to perform operational tasks, including postmortem procedures. It is expected that crewmembers would initially attempt to suppress their emotional reactions, as compartmentalization is a necessary and effective short-term coping skill that facilitates operational performance.[8] However, compartmentalization can lead to delayed and occasionally unexpected reactions of grief and trauma, and long-term compartmentalization can further interfere with the natural trauma recovery process. Natural human mourning and grief will occur and should be effectively addressed and facilitated when circumstances permit to determine if subsequent mission duties can be undertaken safely. Thus, ground support personnel would need to maintain high suspicion and awareness of crewmember emotional responses and provide increased opportunities for support as well as modifications of crew work schedules to ensure adequate time for grieving, rest, or utilization of the support framework.

The ISS has the benefit of preexisting architecture to enable real-time communication and evaluation by NASA's Behavioral Health and Performance team via established protocols for private medical and psychological conferences.[9,33] Given this pre-existing structure for behavioral support and the familiarity of such protocols to crew, integration of support after a fatality onboard the ISS would more likely to be successful than in operational settings with less established psychological support practices, or where communication delays or telemetry complexity may interfere with the availability of support services. Similarly, commercial operators may be more likely to experience challenges in integration of support when integration has not been prioritized throughout architectural and operational development.

It is worth noting that a death in space will affect the entire spaceflight community, including ground controllers, family, friends, governmental and private spaceflight organizations, and international partners, particularly in countries of crew origin. At NASA JSC, the Behavioral Health and Performance Operations Group and the Employee Assistance Program are trained to respond immediately to both crew and support personnel needs in the case of such a tragedy.[56] Aspects of such a response include:

- Consultation with mission crew surgeons, flight directors, and senior management for guidance and support.
- Consultation with astronaut family support providers and engagement, as desired or needed, with crew family members.
- Consultation with international partners, including coordination with subject matter experts on medical, cultural, religious, ethical, and legal matters.
- Provision of private psychological conferences with surviving crewmembers.
- Initiation of a Center-wide Employee Assistance Program crisis response.
- Enabling crew virtual participation in memorial services.
- Monitoring and facilitating grief in crew and ground support teams for the ongoing mission.

Pre-coordination of psychological support assets before a mission increases the ability for behavioral support personnel to engage with crew and others in the case of tragedy, as trust and friendship built over years of association allow for empathy and a better understanding of what each individual may need to optimally cope with the grieving process.[56]

At NASA, the Employee Assistance Program is tasked with providing Critical Incident Stress Management services to the entire workforce of the Agency in the aftermath of a catastrophic event, including providing a means for employees to understand and manage the emotional response to mishaps in a structured and supportive way, identifying highly impacted individuals, and promoting individual and team recovery and functionality.[56] The timing of services is dependent on the level of impact and the completion of mission operations related to the loss and follow-on investigations. Long-term follow-up is essential, including post-investigational or post-mission support, to ensure delayed psychological needs are met. While NASA's workforce tends to be resilient and hardy by nature, the dedication and investment in the crew and mission leads to significant emotional impact when there is a loss.[8,56] Comprehensive emotional first aid and ongoing behavioral health care can help to minimize any long-term negative psychological impact while improving workforce retention and resiliency.

Dignified Remains Disposition: Current and Future Considerations

Multiple factors must be considered when determining appropriate disposition for human remains following an on-orbit fatality. For a fatality occurring on the ISS, the ISS Program Office will hold the authority for final determination of remains disposition. However, onboard resources for containment, biohazard risk, and compatibility with return vehicle design will factor into decisions regarding the potential for return of human remains to Earth. Simultaneously, alternative disposition options pose additional challenges. If return to Earth is not feasible, some additional options for remains disposition include jettison into a reentry orbit such that remains are destroyed during atmospheric descent, jettison into a nondestructive, stable "disposal trajectory" orbit, or interment on an extraterrestrial surface. For a crew fatality occurring on the ISS, options would be limited to return of remains, jettison to a disposal trajectory, or destructive reentry.

Destructive reentry occurs when a descending object experiences atmospheric drag, with extreme heat generated by the friction between atmospheric gases and the object causing the object to combust. In the absence of thermal protection, reentering objects can be destroyed by this excessive heat. This process could potentially be used to provide a means of cremation of human remains. However, reentry thermal stress must be sufficient to ensure combustion and elimination of remains beyond an identifiable state. This is by no means guaranteed by all return trajectories; for example, after the U.S. Space Shuttle *Columbia* mishaps, identifiable remains were recovered from all crewmembers onboard despite unprotected reentry after the orbiter breakup.[42,56] In the case of the *Columbia,* orbiter breakup happened well after entry interface in an intended deorbit trajectory and thus remains were not exposed to full reentry stressors[56]; even so, this highlights the risk of incomplete elimination. Other uncrewed space vehicles have returned to Earth via destructive reentry only to have identifiable vehicle components recovered, in some cases from populated areas.[6,12,44] In the absence of guaranteed destruction, a desirable reentry trajectory would preferably ensure that any intact remains land in remote areas of the planet, ideally over an ocean, to minimize risk of rediscovery. However, trajectory prediction can be challenging, particularly in the absence of propulsive return.[57] Further, certain cultures and religions are strongly opposed to the practice of cremation, and crewmembers and families from such cultural experiences may be fundamentally opposed to destruction of remains in this manner. The risk of intact remains being discovered and identified after reentry violates the primary objective of ensuring the decedent will be handled with dignity, honor, and respect at all times.

Jettison of remains into a stable disposal trajectory similarly requires considerations of complex factors. Automated jettison (for example, via propulsive capsule or an automated airlock system) has historically been unavailable on crewed vehicles. However, NASA recently demonstrated an automated large-volume waste disposal capability using a commercially developed airlock module (the Bishop Air Lock, Nanoracks LLC, Houston, TX), able to jettison up 600 lb of ISS waste into a destructive reentry trajectory.[39] Even so, this nascent technology was not developed or intended for use in the case of remains disposition and would be subject to the limitations of destructive reentry described above.

In the absence of an automated capability, jettison would require either decompression of a habitable vehicle (for example, a crewed transit vehicle without an airlock) or an EVA with other crewmembers transporting remains out of an airlock (for example, on the ISS). Decompression of a nonairlocked vehicle would require that all surviving crewmembers have access to usable, working EVA suits with sufficient onboard consumables to reconstitute a habitable atmosphere after decompression and jettison of remains. Even if an airlock is available, decompression is always associated with risk; thus, the decision to jettison remains poses substantial risk to survivors regardless of vehicle architecture. Further, nonpropulsive jettison of remains (for example, transfer of remains out of the ISS airlock) would result in those remains entering essentially the same orbit as the crewed vehicle.[3] While this orbit will degrade over time, this will require tracking of the jettisoned remains to ensure there is no recontact or risk of impact to future vehicle traffic.[45,49] Placement in a low Earth orbit again risks the potential for future atmospheric reentry, incomplete destruction, and terrestrial rediscovery; placement in orbit around another object (for example, the sun) may be more appropriate given the decreased likelihood and frequency of recontact, but adds complexity, such as requiring some propulsive means and sufficient consumables for achieving the desired trajectory.

A return to the Moon via the NASA Artemis Program raises the possibility of crew fatality on a planetary surface and the potential for lunar interment. Similar possibilities may be feasible in future missions to Mars or other celestial bodies; however, disposition of remains on a planetary surface may be contrary to planetary protection statutes. The United Nations established a Treaty on Principles Governing the Activities of States in the Exploration and Use of Outer Space in 1966, in which protection requirements included prevention of potentially harmful biological contamination of celestial surfaces.[34] In 2020, a NASA Interim Directive declared that existing science suggests that biological contamination of the Moon is not a significant threat to future scientific investigations except in polar latitudes and perpetually shadowed regions of the surface; this effectively decreased the restrictions surrounding the deposition of biological material on the lunar surface in most regions.[18,47] In 2021, the Committee on Space Research similarly published their Policy on Planetary Protection, in which mission destinations are categorized based on concern for biological contamination.[19] Planetary protection, particularly control of forward contamination that may interfere with the future search for life in the solar system, remains a significant concern for interment of human remains on other planetary bodies such as Mars.[46]

Even in the absence of contamination concerns, there would be numerous challenges associated with surface interment. For example, the lunar surface consists of dusty, sharp, angular, and compact soil particulates with high glass content, known to be very abrasive, as well as frequent boulders and subsurface rock.[20,30] There is no wind on the lunar surface, so there is no smoothing of sharp and irregular regolith particles. Crewmember manipulation of regolith for remains interment risks abrading, cutting, or otherwise damaging suit components with associated risk to the safety of the crew. Future missions may include tools to assist in regolith manipulation, such as robotics[20]; even so, establishing an interment location (via subsurface excavation or building up of a cairn-type structure) would require significant work from surviving crewmembers, with additional EVA/surface operations and related risks[7,16] as well as associated depletion of consumables. Given that near-future missions to the Moon are likely to involve relatively small crew complements (2–4 crewmembers for initial Artemis Program missions),[40] this would be particularly burdensome on surviving crew and substantially increase the risk to those survivors. Further, with extreme temperatures and the lack of pressure and oxygen to support bacterial growth, human remains would not be expected to undergo natural decomposition on the lunar surface; this increases the risk that future lunar missions, particularly non-NASA missions, could rediscover or disrupt the interment site.

Other novel methods of remains disposition have been considered for future missions, though frequently such methods would require development or manifesting of nascent technologies for use in the space environment.[3,58] For example, terrestrial facilities to enable human composting have become legal in some parts of the United States in recent years[54]; future technologies may allow such practices to take place on planetary surfaces and yield compost material for surface plant growth or similar applications. Alkaline hydrolysis technologies use heated and pressurized alkaline solutions to rapidly dissolve biological tissues, yielding a sterilized effluent and a small volume of brittle calcified remains that can be returned, similar to cremation ashes, to families.[26,48] However, even terrestrially, these practices have met moral, cultural, and religious opposition[26]; these factors would need to be considered if such options were to be implemented in spaceflight. Regardless, these technologies are unavailable in near-term space operations.

In addition to disposition of remains, future missions and vehicle platforms must consider decedent management and support operations to ensure streamlined, cogent processes for management of a crewmember fatality. For example, missions in which multiple vehicles will be used (such as the Artemis Program, which intends to make use of a crew transit vehicle for transport to lunar orbit, a lunar space station, and a surface landing vehicle, with integration of vehicular architecture from both governmental and commercial providers),[40] all vehicles must coordinate compatibility of forensic samples and containment protocols across platforms. Chain of custody protocols should be established to ensure appropriate forensics handling across vehicles and after return to Earth.[58] Supplies for medical and forensic kits and sample preservation capabilities should be streamlined across platforms, and crew protocols should be specific to vehicle architecture and crew needs for a given reference mission. Feasibility of disposition options should take into consideration multivehicle mission architecture and compatibility of HRCUs or other equipment (for example, refrigeration) with each vehicle that may be affected or incorporated into a disposition strategy.[29] Similarly, limitations of resources or environmental constraints should be considered when determining the feasibility of any final disposition plan.

As always, incorporation of medical and psychological support capabilities better positions such resources to be used by crew should the need arise. This may be particularly complex when commercial providers are integrated with government-run mission architecture; development of a streamlined means of ensuring crewmember and ground support team psychological support may be instrumental in ensuring the resiliency of the workforce in the case of catastrophe. Early planning and implementation of decedent management protocols, manifestation of necessary equipment, and incorporation of support architecture during vehicle and mission design stages will best protect for a smooth and coordinated approach to management of an on-orbit fatality, minimizing physical risk and psychological trauma to surviving crewmembers and support teams while ensuring dignity and respect for the decedent.

Decades of in-flight incidents and close calls demonstrate the risk of fatal events during spaceflight and the need for contingency plans inclusive of protocols to manage the unexpected. Any loss of a crewmember during a mission will have devastating and widespread impact to the surviving crew, family, and ground support team members, while the physical constraints of microgravity and spaceflight operations limit resources and the feasibility of responses. This effort was intended to provide guidance and pre-establish protocols for use in the case of an on-orbit crewmember fatality. While knowledge gaps and continued areas for improvement were identified, the effort resulted in the on-orbit provision of equipment for decedent remains management and the establishment of operational products intended to assist crew and ground operators in the case of a catastrophic event. While the efforts detailed herein were developed within the constraints of the ISS concept of operations, future platforms may benefit from the procedural validation and product verifications steps described. Ultimately, any response to spaceflight fatality must preserve the goal of handling decedent remains and disposition with dignity, honor, and respect. This project lays the groundwork for current programs to prepare for such an event while enabling future platforms to adopt and expand upon these concepts for exploration missions.

ACKNOWLEDGMENTS

We would like to recognize the following individuals from NASA/Johnson Space Center (JSC) for their technical, bioengineering, and medical expertise: TJ Creamer, Michael Misiora, and Michael Rapley of the Flight Operations Directorate; Drs. Valerie Ryder and Spencer Williams of the Toxicology and Environmental Chemistry Laboratory; Drs. Albert Holland and Jana Tran of the Behavioral Health and Performance Operations Group; Randall Suratt of the Legal Office; Travis Houser, Robert Patlach, Rachel Richardson, and Steven Uhl of the NASA Mission Operations Branch; Ted Duchesne, NASA Mission Operations Branch and Director of Medical Operations, Axiom Space; Lorraine Gibson Benavides and Brian Balu of the Systems and Project Management Branch; and Dr. Michael Pedley of the Materials and Processes Branch.

Trade names and trademarks are used in this report for identification only. Their usage does not constitute an official endorsement, either expressed or implied, by the National Aeronautics and Space Administration (NASA).

This project was funded by the NASA/JSC HH&P Directorate and the active data collection phases were undertaken from November 2017 through December 2019. Efforts were coordinated with multiple stakeholders, including NASA JSC (Houston, TX), the Armed Forces Medical Examiner System (AFMES) and Air Force Mortuary Affairs Operation (Dover Air Force Base, DE); the Sam Houston State University (SHSU) Department of Chemistry and their Applied Anatomical Research Center/Southeast Texas Applied Forensic Science (STAFS) Facility (Huntsville, TX); the University of Texas Medical Branch (UTMB) School of Preventive Medicine and Population Health (Galveston, TX); Kellogg-Brown-Root (KBR) (Houston, TX); Isovac Products LLC (Romeoville, IL); and the NASA Multilateral Medical Operations Panel (MMOP) international partners from the Russian Federation Space Agency (RFSA), European Space Agency (ESA), Japan Aerospace Exploration Agency (JAXA), and the Canadian Space Agency (CSA).

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

Authors and Affiliations: Philip C. Stepaniak, M.D., M.S., Stevan Gilmore, M.D., M.P.H., Gary E. Beven, M.D., Kathleen A. McMonigal, M.D., Kjell N. Lindgren, M.D., M.P.H., and Michael R. Barratt, M.D., M.S., NASA Johnson Space Center, Houston, TX, USA; Rebecca S. Blue, M.D., M.P.H., Natacha G. Chough, M.D., M.P.H., and Ann Tsung, M.D., M.P.H., University of Texas Medical Branch School of Public and Population Health, Galveston, TX, USA; Edward L. Mazuchowski II, M.D., Ph.D., Forensic Pathology Associates, HNL Lab Medicine, Allentown, PA, USA; and Joan Bytheway, Ph.D., D-ABFA, Sam Houston State University, Southeast Texas Applied Forensic Science (STAFS) Facility, Huntsville, TX, USA, and the Department of Biology and Chemistry, Liberty University, Lynchburg, VA, USA.

REFERENCES

1. Antonsen EL, Myers JG, Boley L, Arellano J, Kerstman E, et al. Estimating medical risk in human spaceflight. NPJ Microgravity. 2022; 8(1):8.
2. Bacal K, Smart K. Heavenly Bodies: Part One. Spaceflight Quarterly. 2011; 53(7):260–264.
3. Bacal K, Smart K. Heavenly Bodies: Part Two. Spaceflight Quarterly. 2011; 53(8):304–308.
4. Banks R, Aunon S, Harding R, Mumbower A Spacecraft accident investigation. In: Barratt M, Baker E, Pool S, editors. Principles of clinical medicine for space flight. S.l. New York: Springer-Verlag; 2019.
5. Barratt M, Lindgren K, Stepaniak P, McMonigal K, Beven G, et al. Timeline overview: procedural approach to managing inflight fatality [Abstract 276]. Aerosp Med Hum Perform. 2021; 92(6):468–469.
6. Beck J, Holbrough I, Merrifield J, Lemmens S. Probabilistic comparison of destructive re-entry tools. Darmstadt, Germany: ESA Space Debris Office; 2021. [Accessed 10 July 2023]. Available from https://conference.sdo.esoc.esa.int/proceedings/sdc8/paper/279.
7. Belobrajdic B, Melone K, Diaz-Artiles A. Planetary extravehicular activity (EVA) risk mitigation strategies for long-duration space missions. NPJ Microgravity. 2021; 7(1):16.
8. Beven G, Holland A, Picano J, Passmore R, Moomaw R, Reese J. Operational considerations for death in space: behavioral health and performance aspects [Abstract 278]. Aerosp Med Hum Perform. 2021; 92(6):469.
9. Beven G, Vander Ark S, Holland A. Psychological support operations and the ISS one-year mission [Abstract 140]. Aerosp Med Hum Perform. 2016; 87(3):208.
10. Billica RD, Simmons SC, Mathes KL, McKinley BA, Chuang CC, et al. Perception of the medical risk of spaceflight. Aviat Space Environ Med. 1996; 67(5):467–473.
11. Blue R, Clark J, Duchesne T, Pattarini J, Menon A. Human spaceflight mishaps and incidents: an overview. In: Davis J, Stepanek J, Fogarty J, Blue R, editors. Fundamentals of aerospace medicine. Philadelphia: Wolters Kluwer; 2020.
12. Byers M, Wright E, Boley A, Byers C. Unnecessary risks created by uncontrolled rocket reentries. Nat Astron. 2022; 6(9):1093–1097.

13. Byers SN. Introduction to forensic anthropology. 5th ed. New York: Routledge, Taylor & Francis Group; 2017.
14. Bytheway J, Stepaniak P, Lindgren K, McMonigal K, Mazuchowski E, et al. Operational considerations for death in space: human decomposition [Abstract 165]. Aerosp Med Hum Perform. 2020; 91(3):184.
15. Campbell MR, Billica RD, Johnston SL, Muller MS. Performance of advanced trauma life support procedures in microgravity. Aviat Space Environ Med. 2002; 73(9):907–912.
16. Chappell S, Norcross J, Abercromby A, Bekdash O, Benson E, Jarvis S. Risk of injury and compromised performance due to EVA operations. Houston (TX): NASA Johnson Space Center; 2017. Evidence Report. [Accessed 10 July 2023]. Available from https://humanresearchroadmap.nasa.gov/evidence/reports/EVA.pdf.
17. Chough N, Stepaniak P, McMonigal K, Barratt M, Lindgren K, et al. Operational considerations for death in space: historical background, aspects, and risks of spaceflight [Abstract 275]. Aerosp Med Hum Perform. 2021; 92(6):468.
18. Committee on Planetary Protection, Space Studies Board, Board on Life Sciences, Division on Engineering and Physical Sciences, Division on Earth and Life Studies, National Academies of Sciences, Engineering, and Medicine. Report series: Committee on Planetary Protection: planetary protection for the study of lunar volatiles. Washington (DC): National Academies Press; 2020. [Accessed 28 November 2022]. Available from https://www.nap.edu/catalog/26029.
19. Committee on Space Research. COSPAR policy on planetary protection. Committee on Space Research; 2021. Policy. [Accessed 10 July 2023]. Available from https://cosparhq.cnes.fr/assets/uploads/2021/07/PPPolicy_2021_3-June.pdf.
20. Detwiler M, Foong C, Stocklin C. Conceptual design of equipment to excavate and transport regolith from the lunar maria. Cape Canaveral (FL): Kennedy Space Center; 1990. CR No.: 19920010134. [Accessed 10 July 2023]. Available from https://ntrs.nasa.gov/citations/19920010134.
21. Dinis-Oliveira RJ, Vieira DN, Magalhães T. Guidelines for collection of biological samples for clinical and forensic toxicological analysis. Forensic Sci Res. 2017; 1(1):42–51.
22. Dix J, Graham M. Time of death, decomposition, and identification: an atlas. Boca Raton: CRC Press; 2000.
23. Gill-King H. Chemical and ultrastructural aspects of decomposition. In: Haglund WD, Sorg MH, editors. Forensic taphonomy: the postmortem fate of human remains. Boca Raton: CRC Press; 1997.
24. Haglund WD, Sorg MH, editors. Forensic taphonomy: the postmortem fate of human remains. Boca Raton: CRC Press; 1997.
25. Hamilton D, Smart K, Melton S, Polk JD, Johnson-Throop K. Autonomous medical care for exploration class space missions. J Trauma. 2008; 64(4):S354–S363.
26. Hansen K. Choosing to be flushed away: a national background on alkaline hydrolysis and what Texas should know about regulating “liquid cremation.” Tex Tech Estate Plan Community Prop Law J, 2012; 5. [Accessed 10 July 2023]. Available from http://hdl.handle.net/2346/73598.
27. Hayman J, Oxenham M. Human body decomposition. Amsterdam: Elsevier; 2016.
28. Houser T, Chough N, Stepaniak P, McMonigal K, Lindgren K, et al. Operational considerations for death in space: hardware considerations for preparation, stowage, and potential return of remains [Abstract 185]. Aerosp Med Hum Perform. 2021; 92(6):437.
29. Houser T, Lindgren K, Mazuchowski E, Barratt M, Haines D, et al. Remains containment considerations for death in low-earth orbit. Aerosp Med Hum Perform. 2023; 94(5):368–376.
30. Johnston R, Dietlein L, Berry C, Parker J, West V. Biomedical results of Apollo. Washington (DC): National Aeronautics and Space Administration; 1975. TR No.: NASA-SP-368. [Accessed 10 July 2023]. Available from https://ntrs.nasa.gov/search.jsp?R=19760005580.
31. Johnston S, Smart K, Pattarini J. Medical evacuation risk and crew transport. In: Barratt M, Baker E, Pool S, editors. Principles of clinical medicine for space flight. S.l. New York: Springer-Verlag; 2019:327–353.
32. Lamberth PG. Death in Antarctica. Med J Aust. 2001; 175(11–12): 583–584.
33. Landon L, Vessey W, Barrett J. Risk of performance and behavioral health decrements due to inadequate cooperation, coordination, communication, and psychosocial adaptation within a team. Houston (TX): NASA Johnson Space Center; 2016. Evidence Report. [Accessed 7 February 2023]. Available from https://humanresearchroadmap.nasa.gov/evidence/reports/Team.pdf?rnd=0.596982162723775.
34. Legal Subcommittee of the United Nations Office for Outer Space Affairs. Treaty on principles governing the activities of states in the exploration and use of outer space, including the Moon and other celestial bodies. 1966. [Accessed 10 July 2023]. Available from https://www.unoosa.org/oosa/en/ourwork/spacelaw/treaties/introouterspacetreaty.html.
35. Lindgren K, Mathes K, Scheuring R, Gillis D, Polk J, et al. The Skylab Medical Operations Project: recommendations to improve crew health and performance for future exploration missions. Houston (TX): NASA Johnson Space Center; 2009. TM No.: NASA/TM-2009-214790. [Accessed 10 July 2023]. Available from https://ntrs.nasa.gov/api/citations/20090034952/downloads/20090034952.pdf.
36. Love J, Marks M. Taphonomy and time: estimating the postmortem interval. In: Steadman DW, editor. Hard evidence: case studies in forensic anthropology. Upper Saddle River (NJ): Prentice Hall; 2009.
37. Mann RW, Bass WM, Meadows L. Time since death and decomposition of the human body: variables and observations in case and experimental field studies. J Forensic Sci. 1990; 35(1):103–111.
38. Mazuchowski E, Stepaniak P, McMonigal K, Bytheway J, Lindgren K, et al. Operational considerations for death in space: forensic pathology investigations [Abstract 277]. Aerosp Med Hum Perform. 2021; 92(6):469.
39. Nanoracks LLC. Nanoracks Bishop Airlock enables responsible waste disposal from the ISS. 2022; [Accessed 10 March 2023]. Available from https://nanoracks.com/nanoracks-bishop-airlock-enables-responsible-waste-disposal/.
40. National Aeronautics and Space Administration. Artemis II: NASA’s first flight with crew important step on long-term return to the Moon, missions to Mars. 2018, [Accessed 10 July 2023]. Available from https://www.nasa.gov/feature/nasa-s-first-flight-with-crew-important-step-on-long-term-return-to-the-moon-missions-to.
41. National Aeronautics and Space Administration. Columbia Accident Investigation Board report. Vol. 1. Washington (DC): National Aeronautics and Space Administration; 2003. [Accessed 10 July 2023]. Available from https://sma.nasa.gov/SignificantIncidents/assets/columbia-accident-investigation-board-report-volume-1.pdf.
42. National Aeronautics and Space Administration. Columbia crew survival investigation report. Houston (TX): National Aeronautics and Space Administration; 2008. TR No.: NASA/SP-2008-565. [Accessed 10 July 2023]. Available from https://www.nasa.gov/pdf/298870main_SP-2008-565.pdf.
43. National Aeronautics and Space Administration Safety and Mission Assurance; Flight Safety Office. Significant incidents and close calls in human spaceflight. 2019. [Accessed 10 July 2023]. Available from https://sma.nasa.gov/SignificantIncidents/.
44. National Research Council (U.S.), editor. Limiting future collision risk to spacecraft: an assessment of NASA’s meteoroid and orbital debris programs. Washington (DC): National Academies Press; 2011. [Accessed July 10, 2023]. Available from https://nap.nationalacademies.org/catalog/13244/limiting-future-collision-risk-to-spacecraft-an-assessment-of-nasas.
45. Nicolls M, McKnight D. Collision risk assessment for derelict objects in low Earth orbit. Houston (TX); First International Orbital Debris Conference; 2019. [Accessed 9 March 2023]. Available from https://www.hou.usra.edu/meetings/orbitaldebris2019/orbital2019paper/pdf/6096.pdf.
46. Office of Safety and Mission Assurance. Biological planetary protection for human missions to Mars. 2020. [Accessed 24 February 2023]. Available from https://nodis3.gsfc.nasa.gov/OPD_docs/NID_8715_129_.pdf.
47. Office of Safety and Mission Assurance. Planetary protection categorization for robotic and crewed missions to the Earth’s Moon. 2020. [Accessed 24 February 2023]. Available from https://nodis3.gsfc.nasa.gov/OPD_docs/NID_8715_128_.pdf.

48. Olson PR. Flush and bone: funeralizing alkaline hydrolysis in the United States. Science, Technology, & Human Values. 2014; 39(5):666–693. [Accessed 28 November 2022]. Available from http://journals.sagepub.com/doi/10.1177/0162243914530475.
49. Parodi J, Ewert M, Trieu S, Young J, Pace G, et al. A review of existing policies affecting the jettison of waste in low Earth orbit and deep space. Lisbon (Portugal); 50th International Conference on Environmental Systems; 2021. [Accessed 9 March 2023]. Available from https://ttu-ir.tdl.org/bitstream/handle/2346/87276/ICES-2021-366.pdf?sequence=1&isAllowed=y.
50. Scheuring RAJ. The Apollo Medical Operations Project: recommendations to improve crew health and performance for future exploration missions and lunar surface operations. Houston (TX): NASA Johnson Space Center; 2007. TM No.: NASA/TM–2007–214755. [Accessed 6 July 2019]. Available from https://ntrs.nasa.gov/search.jsp?R=20070030109.
51. Shaw MTM, Leggat PA. Illness and injury to travelers on a premium expedition to Iceland. Travel Med Infect Dis. 2008; 6(3):148–151.
52. Shaw MTM, Leggat PA. Life and death on the Amazon: illness and injury to travelers on a South American expedition. J Travel Med. 2003; 10(5): 268–271.
53. Shayler D. Disasters and accidents in manned spaceflight. New York: Springer; 2000.
54. State of California. Assembly Bill No. 351: Reduction of human remains and disposition of reduced human remains. 2022. [Accessed 11 July 2023]. Available from https://trackbill.com/bill/california-assembly-bill-351-reduction-of-human-remains-and-the-disposition-of-reduced-human-remains/2007438/.
55. Stepaniak PC, Hamilton GC, Olson JE, Gilmore SM, Stizza DM, Beck B. Physiologic effects of simulated + Gx orbital reentry in primate models of hemorrhagic shock. Aviat Space Environ Med. 2007; 78(4, Suppl.): A14–A25.
56. Stepaniak PC, Lane H, Davis J. Loss of signal: aeromedical lessons learned from the STS-107 Columbia space shuttle mishap. Houston (TX): NASA Johnson Space Center; 2014. Report No.: SP No: NASA/SP-2014-616.
57. Trisolini M, Colombo C. Re-entry prediction and demisability analysis for the atmospheric disposal of geosynchronous satellites. Adv Space Res. 2021; 68(11):4321–4335.
58. Tsung A. Death in space protocol considerations: ISS, Gateway, Orion, lunar, Mars and beyond [Abstract 279]. Aerosp Med Hum Perform. 2021; 92(6):469–470.
59. Watson A. Preparing for a tropical expedition. Aust Fam Physician. 1998; 27(1–2):55–58.
60. Weaver L, Booher C, Cioni J, Perner C, Craig J. Assured crew return vehicle: man-systems integration standards. Washington (DC): National Aeronautics and Space Administration; 1992. Report No.: NASA STD 3000, Volume VI, NASA-CR-193065. [Accessed 11 July 2023]. Available from https://ntrs.nasa.gov/api/citations/19930017140/downloads/19930017140.pdf.
61. Woollen KC. Chilled to the bone: an analysis on the effects of cold temperatures and weather conditions altering the decomposition process in pig (sus scrofa) remains [MS]. Illinois State University; 2019. [Accessed 23 February 2023]. Available from https://ir.library.illinoisstate.edu/etd/1059.

Delayed Drowsiness After Normobaric Hypoxia Training in an F/A-18 Hornet Simulator

Nikke Varis; Antti Leinonen; Jesper Perälä; Tuomo K. Leino; Lauri Husa; Roope Sovelius

BACKGROUND: In military aviation, due to high-altitude flight operations, hypoxia training is mandatory and nowadays is mainly done as normobaric hypoxia training in flight simulators. During the last decade, scientific data has been published about delayed recovery after normobaric hypoxia, known as a "hypoxia hangover." Sopite syndrome is a symptom complex that develops as a result of exposure to real or apparent motion, and it is characterized by yawning, excessive drowsiness, lassitude, lethargy, mild depression, and a reduced ability to focus on an assigned task.

CASE REPORT: In this study, we present the case of a 49-yr-old pilot who participated in normobaric hypoxia refreshment training in an F/A-18C Hornet simulator and experienced delayed drowsiness, even 3 h after the training.

DISCUSSION: This case report demonstrates the danger of deep hypoxia. Hypoxia training instructions should include restrictions related to driving a car immediately after hypoxia training. In addition, hypoxia may lower the brain threshold for sopite syndrome.

KEYWORDS: hypoxia training, sopite syndrome, normobaric, simulator sickness.

Varis N, Leinonen A, Perälä J, Leino TK, Husa L, Sovelius R. ***Delayed drowsiness after normobaric hypoxia training in an F/A-18 Hornet simulator*****. Aerosp Med Hum Perform. 2023; 94(9):715–718.**

Motion sickness can occur when a person is exposed to a visual or vestibular mismatch. The primary symptoms are nausea, vomiting, pallor, and a cold sweat. Such sickness is usually provoked by traveling by boat, car, or airplane, but it can also result from simulators, virtual reality, or space travel.[6] It is known that motion can also cause yawning and lethargy, and these can sometimes be the sole manifestations of motion sickness. These symptoms were first described as "sopite syndrome" by Graybiel and Knepton in 1976.[8]

Sopite syndrome has been later defined as a symptom complex that develops as a result of exposure to real or apparent motion, and it is characterized by excessive drowsiness, lassitude, lethargy, mild depression, and a reduced ability to focus on an assigned task.[13] It is considered distinct from "regular" motion sickness because it has different cardinal symptoms (drowsiness vs. nausea) and a different time course. Sopite syndrome usually appears before nausea and persists longer.[10] Cognitive performance has been noticed to decline, even when motion sickness and soporific symptoms are mild.[15] In aviators, sopite syndrome may persist without being recognized and it may threaten flight safety.[10] Yawning has been shown to be a viable behavioral marker that can be used to recognize the onset of soporific effects.[14]

It is still unclear how motion sickness develops, but the most widely accepted theory is the sensory conflict theory. It proposes that when the motion detected by vestibular, visual, and proprioceptor systems conflicts with the expected or previously learned motion, the mismatch of neural signals may result in motion sickness. This is supported by experienced pilots having more simulator sickness during flight simulator training than student pilots, since the latter have not yet become accustomed to the real motion of aircraft.[6] Subjects who have lost their normal vestibular function have been noted to be free of such symptoms.[7] It is speculated that sopite syndrome is evoked by

From the Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland, and the National Defence University and the Aeromedical Centre, Centre for Military Medicine, Helsinki, Finland.

This manuscript was received for review in February 2023. It was accepted for publication in June 2023.

Address correspondence to: Dr. Nikke Varis, Lääkärinkatu 1, Tampere, Pirkanmaa 33520, Finland; nikke.v@hotmail.com.

DOI: https://doi.org/10.3357/AMHP.6238.2023

the inhibition of the noradrenergic neurons of the locus coeruleus.[16]

In military aviation, due to high-altitude flight operations, hypoxia training is mandatory and nowadays is often done as normobaric hypoxia training in flight simulators. The Finnish Air Force has conducted normobaric hypoxia training since 2008.[11] During the last decade, scientific data has been published about delayed recovery after normobaric hypoxia; this is called a "hypoxia hangover."[21] In this case report, we present a case of delayed drowsiness that occurred after normobaric hypoxia training.

CASE REPORT

A 49-yr-old male pilot participated in normobaric hypoxia refreshment training in an F/A-18C Hornet simulator. He had completed chamber hypobaric hypoxia training in the U.S. Navy and simulator hypoxia refreshment training in both BAE Hawk and F/A-18C Hornet simulators at 3-yr intervals. His previous hypoxia training sessions had been uneventful. The pilot had completed an annual aeromedical flight physical that noted a near-vision correction requirement and the need for medication for both hypercholesterolemia and gastroesophageal reflux disease. He had experienced motion sickness in a car as a child and had once experienced airsickness (including vomiting) during early flight training with a Hawk jet trainer. This Hawk flight also included yawning and lethargy before the vomiting. However, he had adapted to the sensory mismatch of military flying and had had no motion sickness for over 20 yr. Over the three nights before the hypoxia training, he had 7 h, 8 h, and 8 h of sleep and felt well-rested.

The hypoxia training was performed at 1230 h in a fixed-based tactical F/A-18C Hornet Weapons Tactics and Situational Awareness Training System simulator (Boeing Corporation, Chicago, IL, USA). The pilot's flight gear consisted of a flight helmet with a mask (Gentex Corporation, Zeeland, MI, USA) and a flight vest with a regulator (as is normally worn by pilots while flying fighter aircraft). Forehead peripheral oxygen saturation (S_pO_2), minute ventilation, and wireless electrocardiogram were monitored during the experiment by the senior flight surgeon (J.S.). Minute ventilation, S_pO_2, and subjective symptoms were manually saved to a data sheet by an experienced flight nurse. The flight instructor and the senior flight surgeon used audio-visual monitoring of the pilot. During hypoxia training, four gas mixtures were used with different concentrations of O_2: 8%, 6%, 21% (equal to sea level), and 100% (emergency oxygen). The gas change was done manually by using a gas selection box (Hypcom, Tampere, Finland). Physiologically, 8% O_2 simulates a cabin altitude of 6200 m (20,341 ft) and 6% O_2 simulates a cabin altitude of 7900 m (25,919 ft).

The training included two set-ups of the same simulated visual identification flight with a mask on and the sudden onset of different O_2 concentrations (8% and 6% O_2). At the beginning of both set-ups, the pilot was breathing air, but the flight surgeon switched on 8% or 6% O_2 during tactical maneuvering. The pilot was instructed to continue the flight mission until he recognized hypoxia symptoms or saw a system warning (a master caution and OBOGS DEGD light), and then execute hypoxia emergency procedures. The emergency procedures in hypoxia were: 1) a green ring pull, i.e., releasing emergency O_2 (100%); 2) turning the OXY FLOW KNOB off, i.e., turning the main O_2 valve off; 3) an emergency descent at a 20° nose-down attitude; and 4) sending a transponder code 7700 (an emergency squawk).

During the first set-up, when the pilot was exposed to 8% O_2, he noticed symptoms of hypoxia 74 s after the hypoxic mixture gas was induced. The symptoms were lightheadedness, deep breathing ($16 L \cdot min^{-1}$), and increased heart rate (98 bpm). At this point, his S_pO_2 was 78%. The pilot consciously wanted to experience deeper hypoxia and continued the set-up mission after hypoxia recognition without emergency procedures. He cleared this intention with the senior flight surgeon via radio. After 5 min, the pilot experienced tunnel vision but was able to fly, making visual identification of unidentified aircraft and using throttle adjustments to keep a visual identification position with euphoric sensation. After 5 min 55 s (355 s), the senior flight surgeon noticed the pilot's slow speech and that his left hand on the throttle started to twitch. The master caution light, the sound warning, and the OBOGS DEGD text appeared because the flight surgeon aborted the set-up. Although S_pO_2 was 59%, the pilot was able to execute all emergency procedures. The simulated flight was frozen after an emergency descent at low altitude and level flight for 3 min in order to give feedback and instructions for the next set-up.

During the next set-up with a gas mixture of 6% O_2, the pilot noticed the same hypoxic symptoms after 43 s with S_pO_2 78%, and all emergency procedures were executed after 61 s with S_pO_2 further decreasing to 69%. Ventilation increased significantly from $14 L \cdot min^{-1}$ to $21 L \cdot min^{-1}$ during hypoxia. After the second set-up, a return-to-base flight was made at low altitude. The flight performance was standard level and the landing under Visual Flight Rules conditions was normal. The pilot did not experience any nausea or motion sickness during the simulator training and the simulated flight did not include intensive maneuvering.

During debriefing, 15 min after the hypoxia simulator training, the pilot felt normal and was not pale. The instruction pilot and senior flight surgeon emphasized the importance of aborting the flight mission immediately after hypoxia recognition in order to increase the time of useful consciousness for emergency procedures. The pilot was driving his car home 1 hr after the hypoxia training and, during the drive, he felt extreme lethargy and was yawning 2–3 times per min for 2 h. He considered pulling the car aside but drove all the way home. The lethargy and yawning were gone 3 h after the hypoxia training, and he felt normal the following morning.

DISCUSSION

Most of the symptoms caused by simulator sickness should alleviate quickly after the training is over, but around 10% of pilots experience aftereffects that persist for several hours, which may increase the risk of safety hazards.[1,6] Tiredness and fatigue are the most common adverse effects after normobaric hypoxia training.[22] Therefore, the Finnish Air Force is using a 12-h grounding from flight duty after hypoxia training. Also, car-driving problems after hypoxia training have been reported previously.[22] For safety, hypoxia training instructions should include restrictions on driving a car immediately after hypoxia training. This is supported by a recent study, which showed a delayed neurocognitive recovery after a hypoxic exposure.[2]

The pilot reported yawning and extreme tiredness 1–3 h after normobaric hypoxia training. The pilot had experienced motion sickness and sopite syndrome after Hawk IMC aerobatics during his early flight career. The symptoms in this case report matched sopite syndrome without cybersickness symptoms. However, it is not possible to determine with certainty whether symptoms were delayed sopite syndrome, hypoxia-induced drowsiness, or a combination of both. The symptoms may mirror an autonomous nervous system balance change, leading to inhibition of noradrenergic pathways, especially in the reticular formation brain area.[16]

There has been a previous report of a 23-yr-old student pilot experiencing such extreme tiredness during T-6B aerobatic training that he almost fell asleep.[5] They practiced adaptation for 7 d with a Barany chair, which resolved the nausea symptoms, but the drowsiness persisted and this ended his flight career. Sopite syndrome has also been described during a parabolic flight.[20] A 35-yr-old participant had symptoms of nausea, irritation, and drowsiness that were provoked by intermittent periods of weightlessness. At the end of the flight, the symptoms worsened to the point that she was almost unconscious, and the mood changes lasted for several hours. Interestingly, the participant had received a subcutaneous scopolamine injection prior to the parabolic flight.

On average, Finnish military pilots recognize their hypoxia symptoms at the S_pO_2 saturation level of 73% with 6% O_2 exposure.[11] S_pO_2 is known to weakly predict, for example, working memory impairment.[12] During normobaric hypoxia training, the exposure time is a more important parameter than S_pO_2, although, for example, the U.S. Navy uses 60% S_pO_2 as an abort point. It took 18 s for the case pilot to execute all the hypoxia emergency procedures. This highlights the importance of making an early decision to abort a flight mission and having the cognitive ability to change one's mental focus from an operational flight task to emergency procedures, creating a safety margin before the onset of more severe cognitive impairment when approaching the time of useful consciousness.[9] If a pilot does not execute hypoxia emergency procedures immediately, there is a risk that he or she will lose consciousness in real flights. In this case report, the pilot would not have been able to abort the flight in the first set-up without the senior flight surgeon. This highlights the reduced ability to make decisions during deep hypoxia. Our experience from over 900 normobaric hypoxia training sessions in an F/A-18 Hornet simulator is that the pilot can even fly the aircraft in deep hypoxia, but the pilot's situational awareness (SA 2 and 3 levels) and cognitive ability are decreased. Even in deep hypoxia, pilots can follow direct orders to start emergency procedures (like in our case) or follow a lead aircraft (i.e., they can perform a supported emergency descent as Dash 2 in formation).

Hyperventilation is one of the reasons for nonpressure hypoxia-like physiological episodes in flight. It is even possible that the majority of reported physiological episodes are caused by hyperventilation symptoms[3] that are recognized because of mandatory hypoxia training in military aviation. Some of what seem to be hypoxia symptoms reported in this case report are actually hyperventilation-induced symptoms.[18] This can be one explanation for why hypoxia symptoms in the same individuals can vary from one hypoxia training session to another. Pilots with a slow ventilation rate during hypoxia may lack previously learned symptoms and have difficulties in identifying hypoxia due to the lack of hyperventilation-induced hypocapnia symptoms.

Hypoxia impairs working memory, increases reaction time, and deteriorates executive functions.[4,12,19] In addition, hypoxia has a long-lasting effect on the pilot's flight performance even if hypoxia emergency procedures are executed without delay. The reaction time and regional cerebral saturation do not return to baseline levels until 24 h after hypoxia exposure.[17]

In conclusion, this case report demonstrates delayed drowsiness after normobaric hypoxia training. Yawning and extreme lethargy were even seen 3 h after the hypoxia training. A hypoxia hangover may also involve an autonomous nervous system balance change, leading to the inhibition of noradrenergic neurons. More research is needed in order to understand the complicated relationship between hypoxia and body homeostasis maintenance.

ACKNOWLEDGMENTS

The authors acknowledge flight nurse Nina Eklund, R.N., senior flight surgeon Jarmo Skyttä, M.D., and flight instructor Tuomo Asmundela for their valuable work during the hypoxia training.

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

Authors and Affiliations: Nikke Varis, M.D., and Jesper Perälä, M.D., Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; Antti Leinonen, M.D., School of Medicine, University of Eastern Finland, Kuopio, Finland; Tuomo K. Leino, M.D., National Defence University and Aeromedical Centre, Centre for Military Medicine, Helsinki, Finland; Lauri Husa, M.D., Department of Anesthesiology, University of Helsinki, Finland; and Roope Sovelius, M.D., Aeromedical Centre, Centre for Military Medicine, Helsinki, Finland.

REFERENCES

1. Baltzley DR, Kennedy RS, Berbaum KS, Lilienthal MG, Gower DW. The time course of postflight simulator sickness symptoms. Aviat Space Environ Med. 1989; 60(11):1043–1048.
2. Blacker KJ, McHail DG. Time course of recovery from acute hypoxia exposure as measured by vigilance and event-related potentials. Physiol Behav. 2021; 239:113508.
3. Connolly DM, Lee VM, McGown AS, Green NDC. Hypoxia-like events in UK typhoon aircraft from 2008 to 2017. Aerosp Med Hum Perform. 2021; 92(4):257–264.
4. Dart T, Gallo M, Beer J, Fischer J, Morgan T, Pilmanis A. Hyperoxia and hypoxic hypoxia effects on simple and choice reaction times. Aerosp Med Hum Perform. 2017; 88(12):1073–1080.
5. Gemender MS, Sholes PC, Haight SP. Sopite syndrome identified in a student naval aviator. Aerosp Med Hum Perform. 2018; 89(9):848–850.
6. Geyer DJ, Biggs AT. The persistent issue of simulator sickness in naval aviation training. Aerosp Med Hum Perform. 2018; 89(4):396–405.
7. Graybiel A, Clark B, Zarriello JJ. Observations on human subjects living in a "slow rotation room" for periods of two days. Arch Neurol. 1960; 3(1):55–73.
8. Graybiel A, Knepton J, Graybiel A, Knepton J. Sopite syndrome: a sometimes sole manifestation of motion sickness. Aviat Space Environ Med. 1976; 47:873–882.
9. Johnston BJ, Iremonger GS, Hunt S, Beattie E. Hypoxia training: symptom replication in experienced military aircrew. Aviat Space Environ Med. 2012; 83(10):962–967.
10. Lawson BD, Ead AMM. The sopite syndrome revisited: drowsiness and mood changes during real or apparent motion. Acta Astronaut. 1998; 43(3-6):181–192.
11. Leinonen A, Varis N, Kokki H, Leino TK. Normobaric hypoxia training in military aviation and subsequent hypoxia symptom recognition. Ergonomics. 2021; 64(4):545–552.
12. Malle C, Quinette P, Laisney M, Bourrilhon C, Boissin J, et al. Working memory impairment in pilots exposed to acute hypobaric hypoxia. Aviat Space Environ Med. 2013; 84(8):773–779.
13. Matsangas P, McCauley ME. Sopite syndrome: a revised definition. Aviat Space Environ Med. 2014; 85(6):672–673.
14. Matsangas P, McCauley ME. Yawning as a behavioral marker of mild motion sickness and sopite syndrome. Aviat Space Environ Med. 2014; 85(6):658–661.
15. Matsangas P, McCauley ME, Becker W. The effect of mild motion sickness and sopite syndrome on multitasking cognitive performance. Hum Factors. 2014; 56(6):1124–1135.
16. Nishiike S, Takeda N, Kubo T, Nakamura S. Noradrenergic pathways involved in the development of vertigo and dizziness-a review. Acta Otolaryngol Suppl. 2001; 545:61–64.
17. Phillips JB, Hørning D, Funke ME. Cognitive and perceptual deficits of normobaric hypoxia and the time course to performance recovery. Aerosp Med Hum Perform. 2015; 86(4):357–365.
18. Shaw DM, Cabre G, Gant N. Hypoxic hypoxia and brain function in military aviation: basic physiology and applied perspectives. Front Physiol. 2021; 12:665821.
19. Takács E, Czigler I, Pató LG, Balázs L. Dissociated components of executive control in acute hypobaric hypoxia. Aerosp Med Hum Perform. 2017; 88(12):1081–1087.
20. Van Ombergen A, Lawson BD, Wuyts FL. Motion sickness and sopite syndrome associated with parabolic flights: a case report. Int J Audiol. 2016; 55(3):189–194.
21. Varis N, Leinonen A, Parkkola K, Leino TK. Hyperventilation and hypoxia hangover during normobaric hypoxia training in Hawk simulator. Front Physiol. 2022; 13:942249.
22. Varis N, Parkkola KI, Leino TK. Hypoxia hangover and flight performance after normobaric hypoxia exposure in a Hawk simulator. Aerosp Med Hum Perform. 2019; 90(8):720–724.

Acute Myocardial Infarction in a Young Bodybuilder Fighter Pilot

Sasirajan Jeevarathinam; Saleh Al Sabei; Yousuf Al Wardi

BACKGROUND: Although advanced coronary artery disease in young, healthy fighter pilots is uncommon, an acute cardiac event in flight could be catastrophic.

CASE REPORT: After a gym workout, a 31-yr-old F-16 pilot reported severe central chest pain, one vomiting episode, and excessive sweating but no radiation of pain. Electrocardiograph showed ST elevation in V2-V6. Coronary arteriography showed a thrombotic lesion at the proximal left anterior descending (LAD) artery (90%) and one occluded LAD branch with thrombus; the rest of the arteries were normal and ejection fraction was 55%. Primary percutaneous coronary intervention to LAD with one drug-eluting stent was done. The pilot was discharged in stable hemodynamic condition with medication advice. Assessment revealed no significant cardiac risk factors. He did not seek medical care for two central chest pain episodes following a gym workout prior to this event because rest relieved the pain. He gave a history of using commercial protein supplements for bodybuilding in the past 6 yr.

DISCUSSION: In this case report, the impact of aggressive gym workouts and chronic use of commercially available bodybuilding protein supplements on cardiovascular health is discussed, as well as aeromedical dilemmas related to this pilot's career. This case sparks debate about whether a highly motivated young pilot with an unexpected cardiac event should be subjected to regular intensive cardiac evaluation throughout his remaining flying career, with permanent flying limitations, or be motivated to pursue a career shift to facilitate noncomplicated career rehabilitation.

KEYWORDS: myocardial infarction, fighter pilot, protein supplements, aggressive gym workouts.

Jeevarathinam S, Sabei SA, Wardi YA. *Acute myocardial infarction in a young bodybuilder fighter pilot*. Aerosp Med Hum Perform. 2023; 94(9):719–722.

It is well-known fact that fighter pilots are selected from the elite of potential cadets possessing high cardiovascular and physical fitness, strong mental drive, and exceptional academic records. Hence the probability of presence of advanced coronary artery disease (CAD) in a young, healthy fighter pilot is remote. But, if it occurs, it may be catastrophic provided an acute cardiac event develops in-flight. CAD is known to account for approximately one third of all global deaths, and acute myocardial infarction (MI) is the most severe form of CAD. The most common etiologies for MI in young people are lifestyle modifications, including: sedentary lifestyle; change in dietary habits; stressful and long working hours; strong family history of heart disease; smoking; and development of other comorbid conditions such as diabetes and hypertension at an early age.[7] Recently, the younger generation is showing an increasing trend toward bodybuilding and the use of various protein supplements and anabolic steroids for faster results. Although an association between bodybuilding and MI has been reported in the literature, no exact mechanism has been identified. It has been stated that vigorous physical activity can also acutely and transiently increase the risk of acute MI and sudden cardiac death in susceptible individuals.[14] It is estimated that only 4–17% of MI incidents in men are linked to physical exertion, with much lower rates observed for women.[6] It is postulated that to increase protein synthesis and induce muscle growth, strenuous isotonic exercise or the use of performance enhancers

From the Royal Air Force of Oman, Muscat, Sultanate of Oman.

This manuscript was received for review in April 2023. It was accepted for publication in June 2023.

Address correspondence to: Medical Center - RAFO Seeb, P.O. Box 732, Seeb, COP Seeb 111, Oman; drsasirajan@gmail.com.

DOI: https://doi.org/10.3357/AMHP.6271.2023

and protein supplements (or a combination of both) can cause MI.[8] This is an interesting case of a MI in a young fighter pilot who was taking protein supplements (whey protein and amino acids) for bodybuilding.

CASE REPORT

A 31-yr-old male fighter pilot with about 950 h of F-16 flying was brought to the base medical center with severe central chest pain following a gym workout and an episode of vomiting and excessive sweating. No radiation of pain was stated. Electrocardiograph showed ST elevation in V2-V6. After initiating primary cardiac care, he was transferred to a tertiary hospital for further management. Coronary arteriography revealed a 90% thrombotic lesion at proximal left anterior descending (LAD) artery, and one of the LAD branches was occluded with thrombus; the rest of the other arteries were normal and ejection fraction was 55%. Troponin T was raised and all other parameters (lipid profile, liver function test, renal function test, and coagulation profile) were within normal limits. Primary percutaneous coronary intervention to LAD artery with one drug-eluting stent was done. He was discharged in stable hemodynamic condition with medication advice. With regards to cardiac risk assessment, he is a nonsmoker, nonalcoholic, and physically active. There is no family history of young-age heart disease or sudden cardiac death. No red flag signs in the noted blood parameters were suggestive of undergoing atherosclerosis. Thrombophilia screening was negative. Homocysteine levels were within normal limits. He gave a history of central chest pain episodes following gym workouts: two times (once weekly) prior to this event, both of which were relieved by rest between 30 min and 3 h. He did not seek medical care nor report to the medical department. He gave a history of intake of commercial protein supplements for bodybuilding in the past 6 yr. He was taking a random proportion mixture of whey protein and amino acids 1–3 times per wk. His intake was unguided, unmonitored, and unregulated by a professional expert. As far as his workout history prior to the event, he was working out 3–4 times per wk, each session lasting about 120 min and involving a mix of cardio, isotonic, and isometric exercises. His intention was to build up his body musculature, and he categorized his workout as "moderate to severe". He was bearing weights in the range of 50–120 kgs, depending on the involved body region. He is presently stable and asymptomatic. He is on regular cardiology follow-up. He has now limited his exercise regimen to 60 min per session involving warm-ups, cycling, and bearing weights up to a maximum of 60 kgs. He is no longer consuming any commercial protein supplements.

After the cardiac event, the pilot's flying duties were downgraded. During his observation period of 1 yr, he was subjected to periodical and comprehensive cardiological follow-up at a cardiology center, with all relevant investigations (echocardiography, cardiac magnetic resonance imaging, treadmill test, Holter test) complemented by successful modification of cardiac risk factors using appropriate medications and no other comorbidities. Subsequently, his case was discussed in an aviation medicine waiver panel for clinical review and aeromedical disposition. He was documented to be asymptomatic with good-effort tolerance, normal cardiac functional status, and controlled cardiac risk factors. This young pilot was strongly motivated to pursue his piloting career despite being aware of a few permanent career limitations and the need for periodical, detailed cardiological evaluation throughout his career. He was deemed to be permanently unfit for fighter flying duties and instructor duties. He was considered fit to resume flying duties in fixed-wing aircrafts as or with an experienced copilot. He was also advised to continue periodical cardiologist follow-up and aviation-compatible medications as per standard clinical recommendations. He will be reviewed in a waiver panel at periodical intervals with updated cardiologist reports and appropriate investigations, such as angiography, echocardiography, Holter, and treadmill test reports. Presently, the pilot is keen and highly enthusiastic to pursue a career in military drone-flying duties.

DISCUSSION

A young fighter pilot with no known significant cardiac risk factors in the post ST segment elevation MI – percutaneous coronary intervention done status, with a history of chronic commercial protein supplement intake and aggressive gym workout for bodybuilding, poses the following aeromedical dilemmas and challenges.

It is widely accepted fact that physical activity and exercise training delay the development of atherosclerosis and reduce the incidence of coronary heart disease events. Despite this fact, we could find few case reports[7,8,12] in recent literature and media news involving professionals in different fields indicating the occurrence of young-age MI in those exposed to aggressive gym workouts. In one of the published scientific statements of the American Heart Association,[14] it is stated that chronic extreme exercise training and competing in endurance events may lead to heart damage and rhythm disorders. It is also stated that vigorous physical activity, particularly when performed suddenly by unaccustomed individuals or involving high levels of anaerobic metabolism, may transiently increase the risk of acute MI and sudden cardiac death.

The mechanism by which vigorous exercise provokes such events is not defined, but suggested triggering mechanisms include: increased wall stress from increases in heart rate and blood pressure; exercise-induced coronary artery spasm in diseased artery segments; and increased flexing of atherosclerotic epicardia coronary arteries, leading to plaque disruption and thrombotic occlusion.[14] It is also stated that vigorous exercise could provoke acute coronary thrombosis by deepening existing coronary fissures, augmenting catecholamine-induced platelet aggregation, or both.[14]

In one of the research studies,[4] it is stated that spontaneous coronary plaque fissures are common and have been reported in 17% of people dying of noncoronary atherosclerosis.

This observation suggests that mildly fissured coronary plaques require some exacerbating event, such as vigorous physical activity, to induce coronary thrombosis. Increased platelet activation has been reported in sedentary individuals who engage in unaccustomed high-intensity exercise, but not in physically conditioned individuals.[9,11] The predominant pathological cause of exercise-related events in adults is occult CAD.[14] Compelling evidence indicates that vigorous physical activity acutely increases the risk of cardiovascular events among young individuals and adults with occult heart disease.[3,14,15]

In a published scientific statement by the American Heart Association,[5] the conceptual overview of dose-response association between physical activity volume and cardiovascular health outcomes is highlighted. The prevailing dogma, which is also strongly supported by epidemiological evidence,[1,16] suggests a curvilinear relationship between exercise volume and cardiovascular health risks. This indicates that individuals performing none to very low volumes of exercise training have the highest risk for adverse outcomes, whereas the individuals who exercise the most have the lowest risk.[5] The observation that very high volumes of physical activity may yield lower risk reductions than moderate to high activity volumes resulted in the extreme exercise hypothesis, which postulates a U-shaped relationship between physical activity volumes and health outcomes and is characterized by partial loss of exercise-induced health benefits among the most active individuals.[5] However, only limited data are available to support this hypothesis.[6,10,13] Despite all these, there is currently no compelling evidence to reject the curvilinear association between exercise volumes and cardiovascular health outcomes.

Literature review revealed around 8–10 case reports[7,8,12] of cardiac events in bodybuilders who were under some commercial supplements. A mouse study conducted at the Washington University School of Medicine[17] claims that high-protein diets boost artery-clogging plaque, which dangerously increases the risk of heart disease. The most commonly abused supplements among bodybuilders are whey protein, amino acids, and anabolic androgenic steroid tablets. These are mostly prescribed by peer groups or untrained gym professionals without judging their adverse effects.

Literature review of case reports of bodybuilders who experienced MI revealed that the most commonly abused supplement was anabolic androgenic steroid, followed by a whey protein and amino acid combination. Their usage duration ranged from 5–10 yr, with one case reporting MI within 21 d of usage. The clinical presentation is documented to be from sudden cardiac death to ST segment elevated MI. No exact mechanism of action has been identified. Some postulate that strenuous isotonic exercise alone can produce plaque rupture and lead to acute MI, while others blame the coexistence of high-risk attitudes toward over-the-counter medications and supplements.[8] Documented adverse effect of anabolic androgenic steroids on the myocardium[2] may include: decreased left ventricular (LV) ejection fraction; decreased LV diastolic function; significantly more LV hypertrophy, suggesting an anabolic effect on cardiac muscle mass; and increased coronary atherosclerosis. Most of the effects get reversed upon discontinuation. Use of whey protein powder is speculated to be the associated risk factor for coronary thrombus formation in a similar pathophysiologic mechanism in case reports involving whey protein intake.[7,8,12]

To summarize, it is very difficult to pinpoint the exact mechanism of coronary artery occlusion, provided that there are no known risk factors for atherosclerosis in our case and also we do not have data concerning whether there was any plaque burden below the thrombi area. However, on corroborating the evidence from similar case reports to the details of our case, we postulate that there is a strong possibility of chronic unregulated and unmonitored intake of whey protein and amino acids playing a significant role in plaque formation and/or transformation from stable to vulnerable plaque. The precipitating factor might have been aggressive gym workouts exacerbating mildly fissured plaques to induce coronary thrombosis.

The most prominent aeromedical disposition dilemma is: what will the future flying career of a young, motivated, and experienced fighter pilot with an unexpected cardiac event be? In most air forces around the world, there is no hope of him returning to fighter flying duties. So, what is the next best possible career option? Restreaming to transport or helicopter is possible, but he may be flying with some permanent limitations on his flying privileges (e.g., being allowed to fly only as a copilot). The chance of him becoming an instructor is very remote. In addition, he will be subjected to periodic detailed cardiac evaluation throughout his remaining flying career. There is a high chance that permanent limitation of flying privileges and intensive periodic cardiac follow-up evaluation might add to the peer pressure impact on pilot motivation toward his flying duties, as his colleagues and juniors might bypass him administratively. This sparks a debate about whether it is wise to motivate such a young person for an early career shift to facilitate satisfactory career rehabilitation. So, what are the options ahead to balance both career and passion? Some options include becoming a drone pilot or simulator instructor, or accepting non-flying administrative duties. In our case, the pilot is presently motivated to pursue his career in military drone-flying duties and wishes to seek an upgrade in flying privileges in due course of time, depending upon his cardiac stability in the coming years.

To conclude, chronic supra-physiological protein supplements and isotonic strenuous exercises might be the cause of MI in bodybuilders like in our case. More case reports and prospective studies among bodybuilders might clarify the cause-effect relationship of commercial protein supplements and MI. We recommend some squadron-level strategies to prevent such cardiac events in aircrew. It is ideal to do preparticipation screening and recommend prudent exercise programs to aircrew who intend to involve bodybuilding in their exercise regimen. It is important to educate the aircrew about the health implications of chronic, unregulated intake of the commercial protein supplements whose use has become quite frequent these days. Aircrew should have awareness to maintain physical fitness through regular physical activity rather than sporadic unaccustomed high intensity exercises.

And lastly, the most important is to encourage timely reporting of prodromal symptoms to prevent serious effects.

This case report highlights the rarely described risk factors which might contribute to the development of CAD and contributes to better understanding of the aeromedical disposition dilemmas in young aircrew for suitable long-term career rehabilitation.

ACKNOWLEDGEMENTS

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

Authors and Affiliations: Sasirajan Jeevarathinam, M.B.B.S., M.D., DAvMed, Saleh Al Sabei, M.D., DavMed, and Yousuf Al Wardi, M.D., DAvMed, Royal Air Force of Oman, Muscat, Sultanate of Oman.

REFERENCES

1. Arem H, Moore SC, Patel A, Hartge P, Berrington de Gonzalez A, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. JAMA Intern Med. 2015 Jun 175(6): 959–967.
2. Baggish AL, Weiner RB, Kanayama G, Hudson JI, Lu MT, et al. Cardiovascular toxicity of illicit anabolic-androgenic steroid use. Circulation. 2017; 135(21):1991–2002.
3. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? J Am Coll Cardiol. 2003; 42(11):1959–1963.
4. Davies MJ, Bland JM, Hangartner JR, Angelini A, Thomas AC. Factors influencing the presence or absence of acute coronary artery thrombi in sudden ischaemic death. Eur Heart J. 1989 Mar 10(3):203–208.
5. Franklin BA, Thompson PD, Al-Zaiti SS, Albert CM, Hivert MF, et al. Exercise-related acute cardiovascular events and potential deleterious adaptations following long-term exercise training: placing the risks into perspective-an update: a scientific statement from the American Heart Association. Circulation. 2020; 141(13):e705–e736.
6. Goodman J, Thomas S, Burr JF. Physical activity series: cardiovascular risks of physical activity in apparently healthy individuals: risk evaluation for exercise clearance and prescription. Can Fam Physician. 2013; 59(1):46–49, e6–e10. [Accessed June 12, 2023]. Available from https://www.cfp.ca/content/59/1/46.long
7. Jain V, Goel G. Acute myocardial infarction in young newbie bodybuilder using multiple steroid and protein supplements. J Cardiol Cases. 2019; 21(4):134–136.
8. Kayapinar O, Ozde C, Koc Ay E, Keskin M, Kaya A. Anterior myocardial infarction in a 26-year-old body builder with concomitant use of whey protein powder and amino acid capsules. Acta Cardiol Sin. 2018; 34(4): 359–362.
9. Kestin AS, Ellis PA, Barnard MR, Errichetti A, Rosner BA, Michelson AD. Effect of strenuous exercise on platelet activation state and reactivity. Circulation. 1993; 88(4):1502–1511.
10. Lear SA, Hu W, Rangarajan S, Gasevic D, Leong D, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. Lancet. 2017; 390(10113):2643–2654.
11. Li N, Wallén NH, Hjemdahl P. Evidence for prothrombotic effects of exercise and limited protection by aspirin. Circulation. 1999; 100(13): 1374–1379.
12. Rencuzogullari I, Börekçi A, Karakoyun S, Cagdas M, Karabağ Y, et al. Coronary thrombosis in three coronary arteries due to whey protein. Am J Emerg Med. 2017 Apr 35(4):664.e3–e4.
13. Schnohr P, O'Keefe JH, Marott JL, Lange P, Jensen GB. Dose of jogging and long-term mortality: the Copenhagen City Heart Study. J Am Coll Cardiol. 2015; 65(5):411–419.
14. Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, et al. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. Circulation. 2007; 115(17):2358–2368.
15. Thompson PD, Funk EJ, Carleton RA, Sturner WQ. Incidence of death during jogging in Rhode Island from 1975 through 1980. JAMA. 1982; 247(18):2535–2538.
16. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. Lancet. 2011; 378(9798):1244–1253.
17. Zhang X, Sergin I, Evans TD, Jeong SJ, Rodriguez-Velez A, et al. High-protein diets increase cardiovascular risk by activating macrophage mTOR to suppress mitophagy. Nat Metab. 2020; 2:110–125. Erratum in: Nat Metab. 2020; 2:991.

An American Perspective on the Legacy of Anatoly I. Grigoriev in Space Medicine

Arnauld E. Nicogossian; Charles R. Doarn

INTRODUCTION: Academician Anatoly Ivanovich Grigoriev was a physician, member of the Russian Academy of Sciences Presidium, and a celebrated leader of science in the Soviet Union and Russia—but in the United States, he will be remembered as a friend and mentor. His contributions to space and medicine of extreme environments had a profound impact on human space exploration. He fostered collaboration in many areas of space–human factors, especially in the areas of renal function, endocrinology, and fluids and electrolytes. The joint efforts between NASA and the Soviet/Russian Space Program constitute the foundation for mutual respect and scientific endeavors that continue to transcend the world's political events.

DISCUSSION: This article briefly summarizes Grigoriev's contributions in our long and historical collaboration in human spaceflight. Multiple sources were used, with much drawn from firsthand knowledge through our personal interfaces and working collaboration.

KEYWORDS: spaceflight, history, space medicine, international, legacy.

Nicogossian AE, Doarn CR. *An American perspective on the legacy of Anatoly I. Grigoriev in space medicine*. Aerosp Med Hum Perform. 2023; 94(9):723–727.

Anatoly Ivanovich Grigoriev was born March 23, 1943, in Medelivka, Zhytomyr Oblast, Union of Soviet Socialist Republics (USSR). He was married to Dorokhova Bella Radikovna, a physician biochemist with the Institute of Medical and Biomedical Problems (IBMP), Russian Academy of Sciences (RAS). Together with his spouse, Bella, and their children, he was always a welcoming and exceptional host to his Russian and international colleagues.

In 1966, Grigoriev attended the Pirogov Russian National Research Medical University and became a physician with a keen interest in nephrology. He was a student and research assistant to Professor Anton Yakovlevich Pytal, head of the urological clinic of the 2nd Institute of Medicine. Eventually, he joined the current IBMP and worked with Academicians Vasily Vasilievich Parin and Oleg Georgievich Gazenko.

IBMP, in collaboration with the USSR Air Force Institute of Aerospace Medicine, Academies of Sciences and Medicine, and the Ministry of Health, provided the biomedical training and support of cosmonauts assigned to flight on Salyut stations, the Mir station, the Soyuz, and eventually the U.S. Space Shuttle and the current International Space Station (ISS). Academician Grigoriev, together with Academician Oleg Gazenko, developed and managed the biological research satellite Bion program, contributing to the international collaboration under the auspices of the USSR Academy of Sciences Interkosmos program.[7]

The Bion satellites were used to conduct research on the adaptation of living systems of different evolutionary levels to the influence of gravity. This included the implementation of unique terrestrial simulation experimentation, which provided a greater understanding of the changes in body systems and their interactions under the influence of extreme spaceflight.[9]

At IBMP, Grigoriev defended his candidate's dissertation ("The effect of long-term experimental hypokinesia and spaceflight conditions on the functional state of human kidneys")

From George Mason University, Arlington, Virginia, USA, and the Department of Environmental and Public Health Sciences, University of Cincinnati, College of Medicine, Cincinnati, Ohio, USA.

This manuscript was received for review in March 2023. It was accepted for publication in June 2023.

Address correspondence to: Charles R. Doarn, M.B.A., FATA, FAsMA, 231 Albert Sabin Way, SRU Suite 1466, Cincinnati, OH 45267; charles.doarn@uc.edu.

DOI: https://doi.org/10.3357/AMHP.6252.2023

in 1971 and his Ph.D. dissertation ("The regulation of water-electrolyte metabolism and kidney function in humans during space flights") in 1981. His career with IBMP spanned several decades, and he assumed a variety of increasing roles both in management and with the RAS (see **Table I**).

Academician Grigoriev fostered a close relationship with the cosmonauts in preparation for flight, especially with Valeri Polyakov, M.D., who still holds the longest record of a single stay in low Earth orbit of 437.749 d. He developed and tested new methods for mitigating the physiological effects of the space environment by collaborating with Academician Guy Severin and Professor Arnold Barer.[8]

For many years, Academician Grigoriev actively participated in various international scientific societies, commissions, and working groups (see **Table II**). These activities served the international space medicine community and human spaceflight well. His tireless contributions to space medicine and life sciences research were acknowledged by a variety of national and international prestigious awards, which are highlighted in **Table III**.

International Cooperation

During the height of the Cold War and Space Race, Soviet and NASA physicians and scientists worked closely together on a variety of issues related to human spaceflight and space medicine which were considered humanitarian activities. This included sharing of knowledge, joint research initiatives, and a joint spaceflight. As a senior physician, academician, and leader in Soviet/Russian space medicine, Grigoriev was at the forefront of these international collaborations.

NASA/USSR/Russia joint biomedical working group. In the early 1970s, there was interest in establishing a joint working group between the United States and the USSR. This group was established as the Joint Working Group (JWG) on Space Biology and Medicine.[2] In 1994, this group was reconstituted as a U.S./Russia JWG. Academician Grigoriev worked closely with his U.S. counterparts in sponsoring and supporting the Apollo-Soyuz Test Project, Spacebridge (telemedicine) in the aftermath of the 1988 earthquake in Soviet Armenia, and the second publication of *Foundations of Space Biology and Medicine*. Some of the key activities of the JWG were the bed rest studies to standardize crew selection medical protocols.

Apollo-Soyuz test project. The docking of the Apollo capsule and the Soyuz demonstrated in 1975 that two nations with different geopolitical philosophies, technologies, and approaches to medical standards, as well as language and culture, could work closely together.[11] This effort set the stage for future collaboration using the Space Shuttle, Mir orbital station, and the ISS.

Spacebridge to Armenia and follow-on Spacebridge projects. In the aftermath of a massive earthquake in Soviet Armenia in 1988, the JWG developed a program using telemedicine to connect patients in Yerevan, Armenia, with physicians in Moscow and the United States. This program was extended to Ufa, Russia, after a train accident.[6] This initial effort led to two more successful telemedicine programs in which Academician Grigoriev was involved. The following two events demonstrated his continued support of this JWG program: 1) a 1994 live telemedicine demonstration at a hearing at the U.S. Senate led by Senator John D. "Jay" Rockefeller, who was joined by Academician Grigoriev and NASA's Drs. Harry Holloway and Arnold Nicogossian; and 2) a 1996 live telemedicine demonstration held during the American Medical Association's 150th

Table I. Academician Grigoriev's Career Developments.

YEAR	RECOGNITIONS AND HONORS
1970–1973	Researcher
1973–1979	Senior Fellow
1979–1982	Head of Laboratory
1982–1983	Head of Department
1983–1988	Deputy Director
1986	Appointed Professor
1988	Corresponding Member of the USSR Academy of Medical Sciences
1988–2008	Director of the Institute for Medical and Biological Problems*
2008–2023	Senior Science Advisor, Institute for Medical and Biological Problems
1990	Corresponding Member of the Academy of Sciences of the USSR
1993–2005	Chair, Scientific Council for Space Medicine of the Russian Academy of Medical Sciences
1989–2011	Co-Chair U.S./Russia/USSR Joint Working Group on Space Biology and Medicine
1993–2023	Co-Chair of the Ministry of Health and Ministry of Defense Medical Commission for Cosmonaut Flight Certification
1993	Member of the Russian Academy of Medical Sciences
1996–2008	Chief Medical Officer, Russian Space Program
2000–2021	Co-Chair, Multilateral Medical Policy Board
1989–2008	Editor-in-Chief, *Aviakosmicheskaya I Ekologicheskaya Meditsina*
2009–2022	Editor-in-Chief, *Human Physiology*, a journal of the RAS
2001–2022	Counselor of the RAS, Chairman of the Scientific Council "Space biology and physiology"
2008–2017	Vice President of the RAS
2013–2022	Board of Trustees of the Russian Science Foundation

*Election as director was due to reorganization and the status of the State Scientific Center of the Russian Federation.

Table II. Commissions and Committees (Start Date Until 2023).

YEAR	COMMISSION/COMMITTEE	ROLE
1983–2008	Medical Support of Space Flight on the Orbital Stations Salyut and Mir	Head
1983–1990	Soviet-French Working Group on Space Biology and Medicine	Co-Chair
1989–1992	Soviet-Russia-U.S. Working Group on Space Biology and Medicine	Co-Chair
1992–1994	Joint Russia-U.S. Working Group on Space Life Science and Life Support Systems	Co-Chair
1994–2017	Joint Russia-U.S. Working Group on Space Biomedicine, Life Support Systems, and Microgravity Science	Co-Chair
1991–2017	Joint Working Group of European Space Agency/IBMP on Life Sciences	Co-Chair
1989–1993	Section of Life Sciences, International Academy of Astronautics	Chair
1992–2007	Commission on Gravitational Physiology, International Union of Physiological Sciences	Member
1991	Space Biology and Physiology of the Space Sciences	Chair
1993	Space Medicine Division of Biomedical Sciences, Medical Sciences	Chair
1993	Scientific Council on Space Medicine of Medical Sciences	Chair
1988–2008	Main Medical Commission, Russia's Space Agency on Medical Certification of Candidates for Cosmonauts, Astronauts, and Cosmonauts' Instructors	Chair
1998	Coordinating Council of the Ministry of Science and Technology of Russia in the Priority Line "Technology of Living Systems"	Member
1999	"Organism and Environment" of the Scientific Council of RAS for Physiological Sciences	Chair
1995	Scientific-Technical Council of Rosaviakosmos and Sciences	Deputy Chairman
1997–2023	RAS	Full member
1993–2023	Russia Academy of Medical Sciences	Full member
1996 –2023	Russia Academy of Natural Sciences	Full member
1997–2023	Academy of Astronautics Tsiolkovsky	Full member
1985–2023	International Academy of Astronautics	Full member (Vice President – 1993–2003)
1991	Aerospace Medical Association	Member
1994	New York Academy of Sciences	Member
1995	International Academy of Sciences	Member
2004–2008	International Astronautical Federation	Vice President

anniversary meeting in Philadelphia. This demonstration linked Dr. Michael DeBakey, Dr. Sam Lee Pool, and colleagues in Houston, TX; Dr. Grigoriev, Dr. Oleg Orlov, and colleagues in Moscow, Russia; Drs. Earl Ferguson and Ashot Sargsyan in Krasnoyarsk-26 (a closed former Soviet city now known as Zheleznogorsk), Russia; and Dr. Nicogossian, Dr. Ronald Merrell, and Mr. Charles Doarn via a telemedicine link in Philadelphia, PA. This multi-international link demonstrated the utility of telemedicine on the internet. Telemedicine in Russia grew after these initial programs.[1]

Gore-Chernomrydin – space biomedical center. In the 1990s, under the Vice President Al Gore/Victor Chernomyrdin Commission, Dr. Grigoriev worked with officials at Lomonosov Moscow State University, NASA, and the U.S. Department of State to establish a western-style medical school at Moscow State University, where Grigoriev established and served as the chair of environmental and extreme medicine. This commission also established the Space Biomedical Center for Research and Training at this academic institution, which included a telemedicine curriculum. A key proponent of this medical training was Dr. Michael DeBakey, who lent his expertise in the education of medical students. Academician Grigoriev mentored over 30 candidates for Doctor of Science in space biology and medicine of extreme environments through this effort.

Mir/Shuttle program (ISS-Phase 1). In the early 1990s, Russia became part of the ISS program and, as part of that participation, the Space Shuttle docked with the Mir space station. This collaboration led to flights of cosmonauts on the shuttle and U.S. astronauts on Mir. Known as Phase 1, this entire program was designed to garner operational experience in preparation for the ISS program. Academician Grigoriev was key in the development of an international space medicine program to sustain the selection, training, and support of the multinational crews operating, working, and living in a space habitat designed and built by five different countries. Under his leadership, he and his colleagues were participatory collaborators on the Multilateral Medical Operations Working Group. This working group, which was based on earlier foundations of the JWG and Apollo-Soyuz Test Project, established the framework that ISS and its panels and boards would use in support of crew selection and certification and all operational aspects of crew health and safety.[3,5] Academician Grigoriev served as the chief medical officer and cochair of the Multilateral Medical Policy Board from its inception in 1998 until his retirement in 2020.

Joint publications on space biology and medicine. Two key book volumes were another outcome of the JWG. The first, *Foundations of Space Biology and Medicine*, was a deliverable from a NASA and USSR Academy of Sciences agreement between Hugh Dryden (NASA) and Anatoliy Blagonravov (USSR). This volume, edited by Drs. Melvin Galvin (NASA) and Oleg Gazenko (USSR), consisted of four books and was published in 1975. It covered a wide range of known materials based on the experiences of both the United States and USSR in spaceflight up to that point. This book series included a

Table III. Awards and Recognition.

YEAR	AWARD
1976	Badge of Honor Medal of USSR
1982	Red Banner of Labor Medal awarded by the USSR
1984	Sergei Pavlovich Korolev Medal of the USSR Cosmonautics Federation
1985	The Banner of Labor, awarded by the German Democratic Republic
1987	Yuri Gagarin Medal of the USSR Cosmonautics Federation
1988	Hubertus Strughold Award of the Aerospace Medical Association
1988	Jan Evangelista Purkyne Honorary Merit in the Biomedical Sciences awarded by the Czech Academy of Sciences
1989	Honorary Doctor of the University of Lyon (France)
1989	Laureate of the USSR State Prize
1993	Golden Decoration of Honor for Services to the Federal Republic of Austria
1993	NASA Public Service Medal
1995, 1999, 2001	Prize of the International Academy of Astronautics
1996	Title of the Honored Scientist of Russia
1996	Medal for the COSPAR International Cooperation
1996	Allan D. Emil Memorial Award of the International Astronautical Federation
1996	Melbourne W. Boynton Award from the American Astronautical Association
1996	Vasily Vasilievich Parin Award from the Russia Academy of Medical Sciences
1996, 2003	Russian Federation Government Prize
1996	Hermann Julius Oberth Award from *Internationaler Förderkreis Für Raumfahrt*
1999	François-Xavier Bagneux Award from the University of Michigan
2001	Louis H. Bauer Award of the Aerospace Medical Association
2001	Order of Dostyk (Friendship of the II Degree) – Kazakhstan
2002, 2013	Russian Federation State Prize in Science and Technology
2002	NASA Silver Snoopy Award
2003	Recipient of the Order "For Merit to the Fatherland," IV class, of the Russian Federation
2003	Vasily Vasilievich Parin Award from the Russian Academy of Medical Sciences
2003	Medal of the Ministry of Health of the Russian Federation for merit to Russian health care
2003	Badge of K.E. Tsiolkovsky of the Russian Space Agency
2003	Star of Icarus Medal of the Russian Space Agency
2003	N.V. Timofeev-Resovsky Medal
2004	Officer of the Legion of Honor Order (France)
2005	Medal of the University of Pierre and Marie Curie (France) for merits in science and medicine
2005	Mereny-Scholz Medal (Hungary) for merits in science
2005	Award of the Hungarian Society of Aerospace Medicine
2006	"Triumph" Award for outstanding achievements in the field of experimental and theoretical research
2007	Gold medal named after Academician V.F. Utkin
2007	Jubilee silver medal named after N.M. Sissakian of the RAS
2008	Recipient of the Order "For Merit to the Fatherland," III class, of the Russian Federation
2008	"A.I. Burnazyan" badge of the Russian Federal Medical-Biological Agency
2008	Demidov Prize for outstanding contribution to fundamental and applied research in space biology and medicine
2008	S.I. Vavilov Medal for great personal contribution to the development of the educational process in Russia
2008	N.I. Pirogov Medal of the Russian Academy of Medical Sciences
2009	A.A. Ukhtomsky Award of the RAS
2009	National Prize "Vocation"
2011	"50 Years of Yu.A. Gagarin" Medal
2011	Medal of the International Association of Space Flight Participants
2013	Recipient of the Order "For Merit to the Fatherland," II class, of the Russian Federation
2013	Leon Abgarovich Orbeli Award from the RAS
2013	Mikhail V. Lomonosov I Degree Medal awarded by Moscow State University
2014	Ivan Mikhaylovich Sechenov Gold Medal awarded by the RAS
2016	Commemorative medal "Academician O.G. Gazenko" of the Russian Federation of Cosmonautics
2018	Badge of the Golden Cross of the Russian Federal Medical-Biological Agency
2019	"Space Without Borders" medal of State Space Corporation "Roscosmos"
2021	Badge of K.E. Tsiolkovskiy of State Space Corporation "Roscosmos"

plethora of contributors from both nations, including Academician Grigoriev.

As the knowledge grew on both sides, a new agreement was established to develop a five-volume set (six books in total); Academician Grigoriev served as a contributor and editor along with others, including Academician Gazenko Grigoriev and Drs. Nicogossian and Stanley Mohler. This compendium was published by the American Institute of Aeronautics and Astronautics in the mid-1990s.

The knowledge and collaboration over Academician Grigoriev's career have been instrumental in not only understanding life's processes in the extreme environment of space and on Earth, but also protecting the international community of men and women who have flown in space.

Summary

Academician Grigoriev authored or coauthored over 400 scientific publications, including 7 monographs and 16 chapters in various books, and held 22 patents. He served as the editor-in-chief of the Russian journal *Aviakosmicheskaya i Ekologicheskaya Meditsina* (*Aerospace and Environmental Medicine*), was a member of the editorial board of the journal *Human Physiology*, was an adviser to the drafting committee of *Space Medicine and Technology* (China), was a coeditor of the joint Russo-American *Labor Fundamentals of Space Biology and Medicine*, and contributed to seminal papers in support of crew health. While a lifetime of scholarly work is too extensive to be listed here, some of Academician Grigoriev's work in physiology and its impact on the safety of the crew is especially worth noting, including research on protein expression endocrinology (Grigoriev et al.[4]) and work on electrolytes with Dr. Carolyn Huntoon.[10]

It is with great sadness that we mourn the loss of our friend, colleague, and space medicine pioneer. His contributions to the field of space medicine, space physiology, telemedicine, and international collaboration are immeasurable. Academician Grigoriev leaves the future of Russian space medicine efforts in the able hands of a new generation of leaders. His impact on the international community, especially in the United States, transcends politics and culture. Many of those in the United States can attribute their career paths to Academician Grigoriev because of his guidance, knowledge, and, simply, his friendship. His legacy will endure and influence those who come after him both in Russia and around the world as human spaceflight continues to grow.

ACKNOWLEDGEMENTS

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

Authors and Affiliations: Arnauld E. Nicogossian, M.D., Adjunct Faculty, George Mason University, Fairfax, VA, and Faculty, American Public University and former NASA Associate Administrator for Life and Microgravity Sciences, Washington, DC; and Charles R. Doarn, M.B.A., FATA, FAsMA, Research Professor, Department of Environmental and Public Health Sciences, University of Cincinnati, College of Medicine, Cincinnati, OH.

REFERENCES

1. Doarn CR, Lavrentyev VA, Orlov OI, Nicogossian AE, Grigoriev AI, et al. Evolution of telemedicine in Russia: the influence of the space program on modern telemedicine programs. Telemed J E Health. 2003; 9(1): 103–109.
2. Doarn CR, Nicogossian AE, Grigoriev AI, Tverskaya G, Orlov OI, et al. A summary of activities of the U.S./Soviet-Russian joint working group on space biology and medicine. Acta Astronaut. 2010; 67(7–8):649–658.
3. Doarn CR, Polk JD, Grigoriev A, Comtois JM, Shimada K, et al. A framework for multinational medical support for the International Space Station: a model for exploration. Aerosp Med Hum Perform. 2021; 92(2): 129–134.
4. Grigoriev AI, Huntoon CL, Morukov BV, Lane HW, Larina IM, Smith SM. Endocrine, renal, and circulatory influences on fluid and electrolyte homeostasis during weightlessness: a joint Russian-U.S. project. J Gravit Physiol. 1996; 3(2):83–86.
5. Grigoriev AI, Williams RS, Comtois JM, Damann V, Tachibana S, et al. Space medicine policy development for the International Space Station. Acta Astronaut. 2009; 65(5-6):603–612.
6. Houtchens BA, Clemmer TP, Holloway HC, Kiselev AA, Logan JS, et al. Telemedicine and international disaster response. Medical consultation to Armenia and Russia via a Telemedicine Spacebridge. Prehosp Disaster Med. 1993; 8(1):57–66.
7. Kazakova AE, Abrashkin VI, Stratilatov NV, Smirnov NN. Bion-M satellite – the unique special-purpose laboratory. 57th International Astronautical Congress; October 2–6, 2006; Valencia, Spain. Paper No. IAC-06-A2.P3.
8. Kozlovskaya IB, Grigoriev AI. Russian system of countermeasures on board of the International Space Station (ISS): the first results. Acta Astronaut. 2004; 55(3–9):233–237.
9. Larina IM, Percy AJ, Yang J, Borchers CH, Nosovsky AM, et al. Protein expression changes caused by spaceflight as measured for 18 Russian cosmonauts. Sci Rep. 2017; 7(1):8142. Erratum in: Sci Rep. 2019; 9:8570.
10. Leach Huntoon CS, Grigoriev AI, Natochin YV. Fluid and electrolyte regulation in spaceflight. San Diego (CA): American Astronautical Society; 1998.
11. Nicogossian AE. compiler. The Apollo-Soyuz test project: medical report. Washington (DC): National Aeronautics and Space Administration; 1977. [Accessed June 15, 2023]. Available from https://ntrs.nasa.gov/api/citations/19770023791/downloads/19770023791.pdf. Report No. NASA-SP-411.

Aerospace Medicine Clinic

This article was prepared by Syed Shozab Ahmed, M.Sc., M.D., and Adam Sirek, M.D., M.Sc.

You're the flight surgeon in a small Canadian community, where you also serve as a Civil Aviation Medical Examiner (CAME). Today's exam is for a 36-yr-old civilian aviator presenting for medical recertification following a recent COVID-19 infection.

1. Which of the following are the most important questions to ask regarding the course of illness?

   A. Length of symptoms.
   B. Vaccination status.
   C. Presence of COVID-19 sequelae.
   D. Complicated course of illness with hospitalization.
   E. C and D.
   F. All of the above.

ANSWER/DISCUSSION

1. **E.** As a CAME, it is typically your discretion to renew a Medical Certificate (MC) for a pilot post-COVID-19 infection, unless the course of illness was complicated (e.g., hospitalization) and/or there is presence of COVID-19 sequelae. In those cases, you must defer the decision to Transport Canada's Civil Aviation Medicine Branch (CAM). Hospital records must also be submitted to CAM for review. For those seeking recertification with a history of asymptomatic infection, or symptomatic infection with no complications or sequelae, medical certification can be renewed by a CAME.

The presence of Post-Acute Sequelae of COVID-19 (PASC) has been seen as a function of severity of an acute COVID-19 infection. One study examined 181,384 U.S. veterans who survived the first 30 d of COVID-19 infection, categorizing patients by disease severity: non-hospitalized (*N* = 155,987), hospitalized (*N* = 19,359), and those requiring intensive care unit (ICU) treatment (*N* = 6038).[19] Results were compared to a control population of 4,397,509 noninfected veterans. It was found that the rate of having at least one sequela in the 6-mo period following acute infection dramatically increased depending on the severity of the acute illness. Those who were non-hospitalized had a rate of 44.51 per 1000 persons. The hospitalized rate of PASC was 217.08 per 1000 persons, and the ICU rate was 360.16 ICU per 1000 persons. Overall, the study found that the burden of PASC beyond the first 30 d of infection was 4.4% in non-hospitalized, 21.7% in hospitalized, and 36.5% in those who required ICU admission.

Two separate longitudinal studies found a high rate of sequelae in COVID-19 patients requiring hospitalization both 3 mo[20] and 6 mo[10] post-discharge from hospital. Of 538 survivors in one study, 49.6% reported general symptoms 3 mo post-discharge, including 28.3% reporting physical decline and fatigue.[20] 39% reported respiratory symptoms, 13% reported cardiovascular symptoms, and 22.7% reported psychosocial symptoms—with the most common being somnipathy (17.7%).[20] Similarly, a cohort study of 1733 patients 6 mo post-discharge found that 63% reported ongoing fatigue or muscle weakness, and 23% reported sleep difficulties.[10] Disease severity was stratified based on patients not requiring supplemental oxygen, patients requiring supplemental oxygen noninvasively, and patients requiring invasive ventilation.[10] Patients with more severe illness had significantly more impaired diffusing capacity of the lungs for carbon monoxide on 6 mo post-infection pulmonary function tests, as well as more abnormal findings on chest CT as compared to patients with less severe acute illness.[10]

The correlation between PASC and severity of illness, as well as the high rate of sequelae in those previously hospitalized for COVID-19, defines the rationale behind a more detailed review of these pilots prior to recertification. Further, many of the sequelae seen in previously hospitalized patients can be particularly dangerous for pilots, including: fatigue, cardiovascular symptoms, respiratory symptoms, weakness, and somnipathy. Impaired pulmonary functioning (as demonstrated with reduced diffusing capacity of the lungs for carbon monoxide) and abnormal imaging findings could represent grounds for disqualification from recertification, depending on the impact to the ability to safely operate in the aerospace environment.

DOI: https://doi.org/10.3357/AMHP.6202.2023.

2. The pilot describes mild COVID-19 symptoms with an uncomplicated course of illness. What are some examples of COVID-19 sequelae that they may report?

   A. Fatigue.
   B. Muscle weakness.
   C. Exercise intolerance.
   D. Somnipathy.
   E. Presyncope/syncope.
   F. Arthralgia.
   G. Depression, anxiety, dysphoria.
   H. Cardiovascular dysfunction.
   I. All of the above.

ANSWER/DISCUSSION

2. **I.** PASC have been reported in almost all bodily systems. Examples of cardiac PASC include chest pain, palpitations, and myocarditis.[13,14,17] Some respiratory PASC include pleurisy, pulmonary fibrosis, and dyspnea.[14,15] Neural deficits including anosmia and sensorineural hearing loss have also been reported.[3,8,11] With regards to the musculoskeletal system, previous studies report patients experiencing symptoms such as myalgias, arthralgias, and weakness.[12,14,15] Mental health PASC include depression, anxiety, and cognitive impairment, among others.[6,7,16] Renal injury, erectile dysfunction, and urinary dysfunction are all examples of genitourinary PASC.[5,7,15] Lastly, numerous gastrointestinal PASC have been reported such as diarrhea, nausea, and abdominal pain.[4,5,14] A summary of PASC (grouped by body system) is presented in **Table I**. Potential findings that may be uncovered during review of systems and examination procedures, as outlined in the CAME handbook, are also listed.[18]

Although some sequelae may have more pertinence to pilot medical recertification than others, current regulations state that the presence of any sequelae warrants deferral to CAM for review and decision. It should be noted that Table I is not an exhaustive list of all possible PASC. In the event that other explanations for the presence of PASC are likely, further investigations may be warranted prior to decision. However, the presence of these symptoms must still be communicated to CAM with decision for recertification being deferred at the time of examination.

3. Which PASC may result in a decision to deem the pilot unfit for recertification, according to the CAME handbook?

   A. Myalgia.
   B. Guillain-Barré syndrome.
   C. Severe migraines.
   D. Irritable bowel syndrome.

Table I. PASC with Potential Examination/Testing Findings.

SYSTEM	SEQUELAE	POTENTIAL FINDINGS ON REVIEW OF SYSTEMS	POTENTIAL EXAMINATION/ TESTING FINDINGS
Cardiopulmonary[7,14,15,17,20]	Myocarditis; pericarditis; myopericarditis; right ventricular dysfunction; myocardial infarction; vasculitis; venous thrombosis; postural tachycardia syndrome; arrythmias; Pulmonary fibrosis; pneumonitis; pleurisy; secondary bacterial infection; pulmonary emboli	Chest pain; palpitations; dyspnea; cough; fever; sore throat; pre- syncope/syncope; dizziness	Tachycardia; dyspnea; poor perfusion; hypertension; labile heart rate and blood pressure with orthostatic and activity changes; ECG abnormalities*; murmurs; extra heart sounds; unilateral leg swelling; carotid bruit; focal neurological deficits; crackles, decreased breath sounds, and/or adventitious sounds on lung auscultation.
ENT[3,7,8,14,15]	Sensorineural hearing loss; anosmia	Loss of smell/taste; difficulty hearing	Failed whisper test; audiology abnormalities†
MSK[7,12,14]	Sarcopenia; myopathy; myositis; arthritis	Post-exertional malaise; joint pain; weakness; disturbed balance/gait	Muscle weakness; muscle/joint stiffness; abnormal balance/gait
Nervous[6,7,11,14-16]	Encephalitis; ischemic stroke; cerebral hemorrhage; Guillain- Barré syndrome; anxiety, depression, PTSD; cognitive impairment; migraines; seizures; somnipathy	Profound fatigue; problems concentrating; brain fog; low mood; anxiety; dysthymia; headaches; seizure-like symptoms	Mental status changes; focal neurological deficits; abnormal gait; abnormal reflex test
Genitourinary[5,7,14,15]	Urinary dysfunction; post-inflammatory glomerulonephritis; orchitis; epididymitis; embolic renal infarction	Involuntary voids; difficulty voiding; testicular pain; hematuria; oliguria; erectile dysfunction	Hematuria and/or proteinuria on urine dipstick‡
Gastrointestinal[4,5,7,14,15]	Pancreatitis; hepatitis; gastroenteritis; irritable bowel syndrome; ischemic colitis	Diarrhea; nausea; overall changes in bowel habits; hematochezia; abdominal pain; bloating; anorexia	Pruritis; jaundice; hepatomegaly; tenderness; guarding

*ECG only required at first examinations for class 1 and 2 medical categories, and then incrementally depending on age. For those seeking class 3 or 4 medical categories, ECG requirement is dependent on age.
†Audiogram only required for first examinations for class 1 and 2 medical categories and then at 55 yr old. For classes 3 and 4, it is only required if clinically indicated.
‡Generally, urine dipstick is performed to examine for presence of glucose; however, the presence of proteinuria/hematuria can also be examined using most dipsticks.

ANSWER/DISCUSSION

3. **C.** Widely, any condition which may compromise a pilot's ability to safely operate an aircraft can be determined to be grounds for disqualification for medical certification. Within the CAME handbook,[18] migraines are classified into 'without aura' and 'with aura'. Pilots who experience migraines without aura can generally be considered fit. Migraines with aura are further categorized into three groups: 1) migraines with aura which do not interfere with flight safety and for which the same aura has been consistent over several years; 2) migraines with auras which are slow onset, occur infrequently, are not associated with any cognitive impairment and/or cause only minor sensory difficulties which do not impair performance, and for which the same aura has been consistent over several years; and 3) migraines with significant auras that could affect flight safety and do not fit into Group 2 with regards to onset, frequency and effect on cognition. Most pilots who suffer from migraines and fall into the first two categories can be considered fit for certification. Due to the safety risk associated with those who fall into Group 3, such pilots are considered unfit; however, they may be considered for restricted medical certification if they fall into Group 2 after a 3-yr period of stability.[18] Other COVID-19 sequelae that can deem a pilot unfit for certification are demonstrated in **Fig. 1**.

Although not explicitly outlined in the CAME handbook,[18] many other PASC would likely impact the determination of fitness of a pilot for medical certification. For example, fatigue and cognitive impairment are some of the most commonly experienced sequelae as reported in contemporary literature.[6,14,15] The degree of severity of these sequelae and their potential impact on one's ability to safely operate an aircraft have not been well examined and can likely vary notably from pilot to pilot. Nevertheless, the potential dangers of granting medical certification to pilots experiencing any PASC are significant. It is therefore important for CAM to review these pilots on a case-by-case basis to best determine fitness for aircraft operation.

4. How would your approach change for a pilot serving in the Canadian Armed Forces (CAF)?

   A. They would be disqualified from aircrew selection for life.
   B. The degree of severity of acute infection would not factor into my decision.
   C. They would require a brain MRI to look for evidence of ischemic damage.
   D. The approach is the same as for civil aviation.
   E. They would require exertional testing either by 6-min walk test and/or 1-min sit-to-stand test.

ANSWER/DISCUSSION

4. **E.** CAF has released a Flight Surgeon guideline outlining procedures to determine aircrew medical fitness post-COVID-19.[2] Similar to CAM, military post-COVID-19 fitness certification procedure is stratified based on infection severity and the presence of complications. For mild symptoms with an uncomplicated course of illness (e.g., no hospitalization) as well as full resolution of symptoms, CAF has outlined mandatory history, physical examination, and testing to be completed.[2]

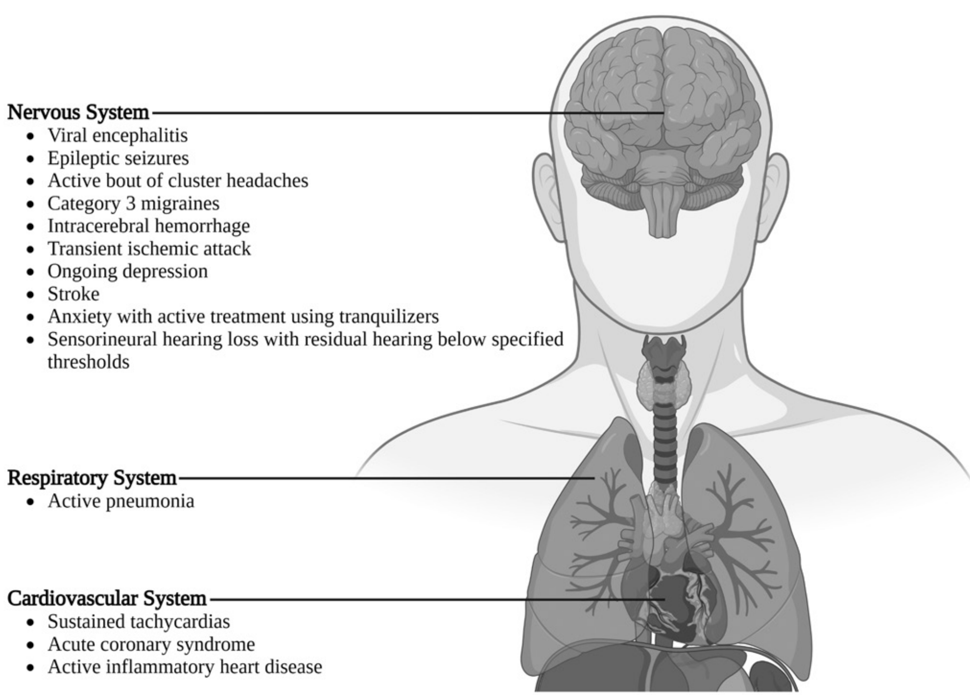

Fig. 1. Pathologies and symptoms which are post-acute COVID-19 sequelae and can make a pilot unfit for medical certification according to the Transport Canada CAME Handbook. Created with BioRender.com.

Additionally, a history of COVID-19 infection within the past 3 mo is automatically disqualifying for aircrew selection, and a remote history can be considered only on a case-by-case basis.[1] Current aircrew members are deemed temporarily unfit with a confirmed diagnosis and must undergo the same testing as new pilots in order to return to service.[1] Another key difference between military and civilian guidelines is unto whom discretion to issue medical certification falls. Largely, discretion falls to CAME's within civil aviation.[18] Only in the cases of hospitalization or with evidence of sequelae must decisions be deferred to CAM. Within CAF, multiple regulatory bodies review each complex case.[2] Unsurprisingly, military guidelines call for more specific and extensive examination of pilots as compared to those for civil aviation.[1,2,18] The higher demands and increased danger of military aircraft operation necessitate more comprehensive review of pilots after an acute COVID-19 infection, in order to determine medical fitness. The Federal Aviation Administration (FAA) has also amended their own guidelines for aviation medical examiners to include guidance for examination of pilots with previous COVID-19 infection.[9] These guidelines are similar to their CAM counterparts, with the main difference being that, according to the FAA, hospitalization does not necessitate deferral of decision to the regulatory body.[9] Only in cases where ICU care is required, and/or post-acute-COVID-19 sequelae are apparent, is deferral mandated.[9] A comparison between CAM, CAF, and FAA guidelines in illustrated in **Fig. 2**.

Much remains unknown with regards to the effects of COVID-19 infection on a pilot's ability to safely operate an aircraft. Potential sequelae of the disease are numerous and varied. It is therefore important for aviation medicine practitioners to carefully examine cases of pilots seeking recertification following acute infection. Aviation regulatory bodies have differing procedures and requirements for recertification, depending on disease severity and the presence of sequelae. In Canadian civil aviation, there should be a low threshold for deferral of decision to the CAM if doubts arise. Furthermore, the process and requirements for recertification following COVID-19 infection are likely to evolve as the disease process and post-disease state is further understood. It is the responsibility of the aviation practitioner to remain up to date with these changes to best serve their aircrew. As the aviation industry re-emerges in the post-pandemic world, aviation medicine serves a critical role in maintaining flight safety.

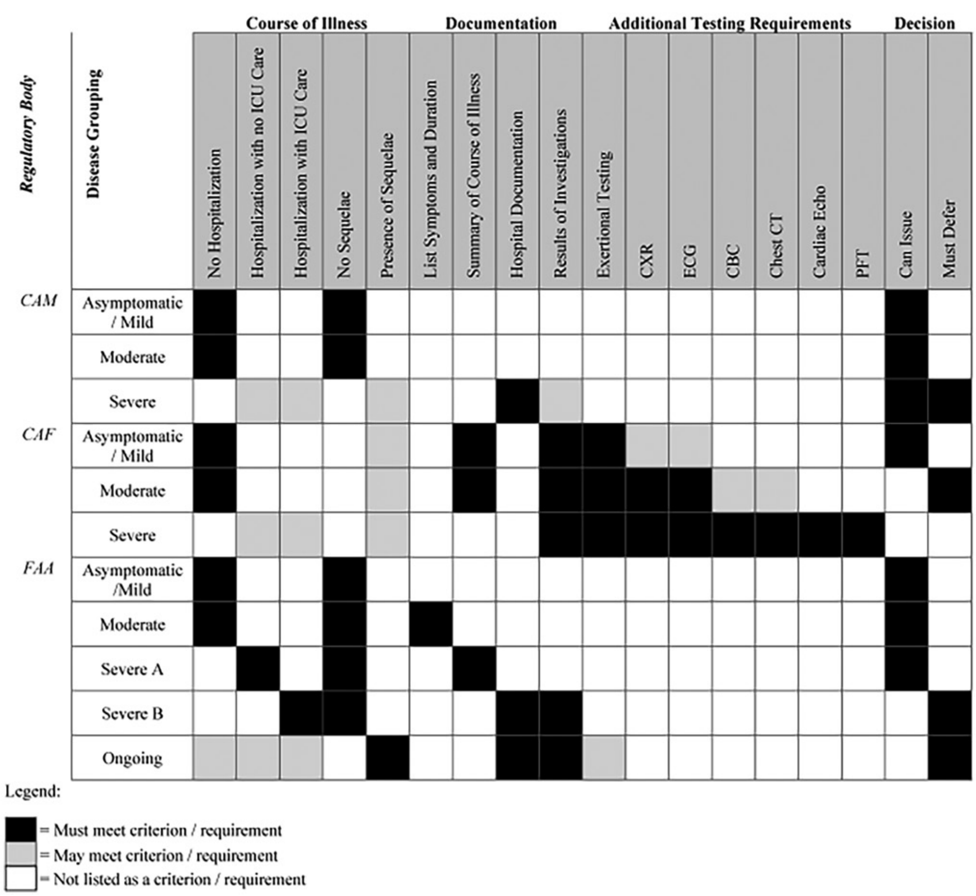

Fig. 2. CAM vs. CAF vs. FAA post-acute COVID-19 Medical Certification comparison chart. CAM = Transport Canada's Civil Aviation Medicine Branch; FAA = Federal Aviation Administration; and CAME = Civil Aviation Medical Examiner.

Ahmed SS, Sirek A. *Aerospace medicine clinic: COVID-19 infection in a pilot.* Aerosp Med Hum Perform. 2023; 94(9):728–732.

REFERENCES

1. AMA directive 100-01: medical standards for CAF aircrew. Canadian Air Division. 2021.
2. FSG 100-05: aircrew medical fitness post COVID-19. Canadian Air Division. 2022.
3. Araújo L, Arata V, Figueiredo RG. Olfactory disorders in post-acute COVID-19 syndrome. Sinusitis. 2021; 5(2):116–122.
4. Bogariu AM, Dumitrascu DL. Digestive involvement in the long-COVID syndrome. Med Pharm Rep. 2021; 95(1):5–10.
5. Buoite Stella A, Furlanis G, Frezza NA, Valentinotti R, Ajcevic M, Manganotti P. Autonomic dysfunction in post-COVID patients with and without neurological symptoms: a prospective multidomain observational study. J Neurol. 2022; 269(2):587–596.
6. Ceban F, Ling S, Lui LM, Lee Y, Hartej G et al. Fatigue and cognitive impairment in post-COVID-19 syndrome: a systematic review and meta-analysis. Brain Behav Immun. 2022; 101:93–135.
7. Crook H, Raza S, Nowell J, Young M, Edison P. Long-COVID mechanisms, risk factors, and management. BMJ. 2021; 374:n1648. Erratum in: BMJ. 2021; 374:n1944.
8. Fancello V, Fancello G, Hatzopoulos S, Bianchini C, Stomeo F et al. Sensorineural hearing loss post-COVID-19 infection: an update. Audiol Res. 2022; 12(3):307–315.
9. 2022 guide for aviation medical examiners. Federal Aviation Administration. 2022.
10. Huang C, Huang L, Wang Y, Li X, Ren L et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021; 397(10270):220–232. Expression of concern in: Lancet. 2023; 401(10371):90.
11. Ludwig S, Schell A, Berkemann M, Jungbauer F, Zaubitzer L et al. Post-COVID-19 impairment of the senses of smell, taste, hearing, and balance. Viruses. 2022; 14(5):849.
12. Malik AM. Musculoskeletal symptoms in patients recovering from COVID-19. Muscles Ligaments Tendons J. 2022; 12(1):9–16.
13. Ramadan MS, Bertolino L, Zampino R, Durante-Mangoni E. Cardiac sequelae after coronavirus disease 2019 recovery: a systematic review. Clin Microbiol Infect. 2021; 27(9):1250–1261.
14. Raman B, Bluemke DA, Luscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. Eur Heart J. 2022; 43(11):1157–1172.
15. Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: an overview. Diabetes Metab Syndr. 2021; 15(3):869–875. Erratum in: Diabetes Metab Syndr. 2022; 16(5):102504. Erratum in: Diabetes Metab Syndr. 2022; 16(12):102660.
16. Renaud-Charest O, Lui LM, Eskander S, Ceban F, Ho R et al. Onset and frequency of depression in post-COVID-19 syndrome: a systematic review. J Psychiatr Res. 2021; 144:129–137.
17. Satterfield BA, Bhatt DL, Gersh BJ. Publisher Correction: Cardiac involvement in the long-term implications of COVID-19. Nat Rev Cardiol. 2022; 19(5):342.
18. TP 13312: handbook for Civil Aviation Medical Examiners. Government of Canada. 2019.
19. Xie Y, Bowe B, Al-Aly Z. Burdens of post-acute sequelae of COVID-19 by severity of acute infection, demographics and health status. Nat Commun. 2021; 12(1):6571.
20. Xiong Q, Xu M, Li J, Yinghui L, Zhang J et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. Clin Microbiol Infect. 2021; 27(1):89–95.

Aerospace Medicine Clinic

This article was prepared by Matthew Hoyt, D.O., M.P.H.

You are the flight surgeon attached to a U.S. Air Force flying squadron. A healthy and experienced 32-yr-old male heavy-lift aircraft pilot presents to the Flight Medicine clinic with persistent headache, which he woke with 2 d prior. He described his headache as constant, rated 5/10 in the left frontotemporal area, and not responsive to his usual self-treatment with one dose of acetaminophen, hydration, and rest. In the clinic, the aviator denies any recent trauma, changes in exercise/activity, or changes in his diet/caffeine intake. He does admit to moderate increase in work stress recently but finds his stress level manageable overall. The aviator denies dizziness or vertigo, vision changes, hearing changes, motor changes, sensory changes, balance issues, nausea/vomiting, or cognitive difficulty. Although the pain has been distracting, he denies any difference from his usual headache. He also denies aura, photophobia, and phonophobia.

The aviator states this is not the worst headache of his life, and the headache was not described as "thunderclap" or sudden onset. He denies any significant past medical, surgical, or family history. He admits to drinking moderately but denies any tobacco use. The aviator is actively flying in a multiseat, non-ejection aircraft, but feels current symptoms would prevent him from performing flying duties safely. His physical examination and vitals are unremarkable with no neurological deficits, vision changes, weakness, or balance concerns. He was treated initially with battlefield acupuncture, with improvement in his symptoms to 2/10. The aviator was advised to increase his acetaminophen dose and follow up in 24–48 h if symptoms had not completely resolved.

The next day, he returned to clinic with unchanged symptoms but now endorsing a sensation of "being outside my body," which was causing increased concern. Exam remained unchanged during this visit. Labs were ordered, including a complete blood count and comprehensive metabolic panel, and computed tomography (CT) imaging of the head without contrast was scheduled. That evening while calling with normal results of labs, you discover the member is being transported by ambulance to a local hospital due to symptoms of sudden left-sided paresthesia and slurred speech. Upon arrival at the emergency room, the aviator's symptoms of paresthesia and slurred speech have resolved. Vital signs and exam are normal. A CT of the head is obtained, revealing a 3-cm hemorrhagic lesion with surrounding vasogenic edema and midline shift. Additional imaging, including brain CT angiography and brain magnetic resonance imaging (MRI), further defines the mass. Imaging of chest, abdomen, pelvis, and scrotum rules out an extracranial primary tumor.

Neurosurgery is consulted, and the aviator is taken to the operating room where craniotomy with surgical resection of the mass is performed. A final diagnosis of multiple cerebral cavernous malformations (CCMs) is given. Post-surgery, the aviator recovers well and, on follow-up, has neither residual deficits nor abnormal findings on exam. The cause of the cavernous malformations is determined to be genetic. He is coming to you seeking a waiver to return to flying duties.

1. When evaluating an aviator who presents with headache in the clinic, what should be the first step in your evaluation?
   A. Ask for aviator's mental health history.
   B. Ask about family history of cancer.
   C. Evaluate for headache red flags.
   D. Ask about recent immunizations.

ANSWER/DISCUSSION

1. C. Initial headache evaluation should always begin with a careful history and assessment to rule out red flags and other secondary causes. A helpful mnemonic for headache red flags is SNNOOP10:

- Systemic symptoms including fever.
- Neoplasm history.
- Neurological deficit (including decreased consciousness).
- Onset is sudden or abrupt.
- Older age (onset after 50 yr of age).
- Pattern change or recent onset of new headache.

DOI: https://doi.org/10.3357/AMHP.6270.2023

- Positional headache.
- Precipitated by sneezing, coughing, or exercise.
- Papilledema.
- Progressive headache and atypical presentations.
- Pregnancy or puerperium.
- Painful eye with autonomic features.
- Post-traumatic onset of headache.
- Pathology of the immune system such as human immunodeficiency virus.
- Painkiller (analgesic) overuse (e.g., medication overuse headache) or new drug at onset of headache.

In the absence of any of the above red flags, conservative management is the evidence-based practice of choice.

2. True or false? Imaging is usually warranted for patients presenting with migraine headache.
   A. True.
   B. False.

ANSWER/DISCUSSION

2. B. According to an article by Walling,[11] serious conditions should be ruled out using patient history, the SNNOOP10 screening tool, a physical exam including neurological evaluation, and targeted imaging as indicated by findings from the history and physical. This article reaffirms that imaging is not recommended in the absence of red flags, or suspected trigeminal autonomic cephalgia, or other atypical headache. If an underlying disorder is suspected, specific imaging may be necessary to rule in/out this disorder. Personal and family history may be particularly helpful in identifying familial or other disorders that may be causing the patient's headache presentation.

Other more conservative assessments should be pursued prior to imaging in the absence of indicators. These assessments may include medication use evaluation to assess for any chronic medication overuse that could be triggering the patient's headache. Additionally, headache diaries can be helpful in identifying temporality and causation. Headache effects and impacts on quality of life are also helpful insights potentially gained from a headache diary.

3. In the nonemergent setting when both CT and MRI are available, what is the imaging modality of choice when evaluating a patient for headache with no allergies?
   A. CT with or without contrast.
   B. MRI of the brain.
   C. Both MRI and CT.
   D. Imaging of choice is dependent upon clinical presentation and clinical setting.

ANSWER/DISCUSSION

3. B. In the Choosing Wisely® campaign, several neurological recommendations have been made, including the American College of Radiology recommendation to not perform imaging for uncomplicated headache.[2] The American Headache Society recommends not performing neuroimaging studies in patients with stable headaches that meet criteria for migraine and not performing CT for headache when MRI is available, except in emergency settings.[3] The American Academy of Neurology recommends not performing electroencephalography for headaches.[1]

Where available, MRI would be the nonemergent imaging modality of choice for evaluation of a headache that meets criteria.[10] If timely MRI is not available, or in an emergent evaluation setting, CT of the head can exclude intracranial hemorrhage or mass effects.

4. What is the 5-yr recurrence rate for seizures associated with CCMs?
   A. 10%.
   B. 25%.
   C. 60%.
   D. 90%.

ANSWER/DISCUSSION

4. D. Based on evidential data, patients with CCMs who present with hemorrhage have a 5-yr hemorrhage risk of at least 18%, higher initially, and potentially diminishing to about 5% annual risk at the 5-yr point. Risk of hemorrhage in incidentally identified solitary nonbrainstem CCMs is about 0.6% annually. However, this risk is increased with the presence of multiple lesions. The aviator's temporal lobe hemorrhage and surgery incur an increased risk for seizures, as do the presence of multiple subcortical cavernous malformations. It was not definitively concluded that the aviator's transient neurological episodes were seizures, but this is an additional potential aeromedical concern, as seizures associated with cerebral cavernous malformations carry a 5-yr recurrence rate of over 90%. Familial CCM patients also have a risk of developing future additional lesions, making serial clinical and radiological follow-up paramount.[5,6]

AEROMEDICAL DISPOSITION

Your aviator was taken off flying status and his case was sent to the Aeromedical Consultation Service for review of multiple CCMs due to genetic predisposition and history of acute hemorrhage of one of the CCMs that required craniotomy for resection. Aeromedical concerns in this interesting case include effects of any baseline symptoms on flight safety, impact of any treatment regimens on flight safety, and the risk of future symptom development, with potential for operational distraction or incapacitation.

In this case, the aviator presented with subacute new-onset headaches. No concerning clinical findings were seen, but due to persistence and member concerns, cranial imaging was obtained showing a large left temporal hemorrhage and multiple additional abnormalities that were eventually identified as cavernous malformations. These were located primarily supratentorially and in the cerebellar hemispheres, with no definitive brainstem involvement. The aviator had at least two episodes of transient neurological symptoms, one initially and the second 4 mo later with accompanying headache, which were suspicious for seizures. He underwent craniotomy for evacuation of the left temporal hemorrhage and did well post-surgically, except for persistent intermittent left-sided headaches that were managed with nonprescription medications.

The current frequency and intensity of headaches were not listed in the aviator's medical record. His father had a history of CCM with hemorrhage and the aviator tested positive for one familial CCM genetic marker. Follow-up cranial imaging showed no new abnormalities. Neuropsychological testing showed unremarkable findings. Current examination findings were noted as normal.

Unfortunately, the aviator's potential aeromedical risks associated with familial CCM[5,6] are deemed unacceptable for both U.S. Air Force flying class II and ground-based operator waiver[8] consideration. Therefore, for the familial CCM diagnosis, neither a flying class II nor a ground-based operator waiver is recommended. The Federal Aviation Administration,[4] Army,[9] and Navy standards[7] for intracranial lesions and vascular abnormalities have similar outcomes for this aviator. A sleep-deprived electroencephalogram study will be obtained locally and, if epileptiform changes are seen, reinstitution of antiepileptic medication will be strongly considered. The aviator will continue clinical and radiological follow-up as advised by his specialty consultants. He is advised to avoid activities that could potentially trigger seizures, such as prolonged sleep deprivation, binge ethanol intake, excessive stimulant intake, prolonged fasting or dehydration, and medications that list seizure as a significant adverse side effect.

Hoyt MG. *Aerospace medicine clinic: familial cerebral cavernous malformation*. Aerosp Med Hum Perform. 2023; 94(9):733–735.

ACKNOWLEDGMENTS

The author would like to thank Dr. Aven Ford, neurology consultant at the Aeromedical Consultation Service, Wright-Patterson AFB, OH, for his valuable time and expertise. The views expressed are those of the authors and do not reflect the official guidance or position of the U.S. Government, the Department of Defense (DoD), or the U.S. Air Force. The appearance of external hyperlinks does not constitute endorsement by the DoD of the linked websites, or the information, products, or services contained therein. The DoD does not exercise any editorial, security, or other control over the information you may find at these locations.

REFERENCES

1. Choosing Wisely. American Academy of Neurology. 2013. [Accessed March 20, 2023]. Available from https://www.choosingwisely.org/clinician-lists/american-academy-neurology-electroencephalography-for-headaches/?highlight=headaches.
2. Choosing Wisely. American College of Radiology. 2017. [Accessed March 20, 2023]. Available from https://www.choosingwisely.org/clinician-lists/american-college-radiology-imaging-for-uncomplicated-headache/?highlight=uncomplicated%20headache.
3. Choosing Wisely. As part of Choosing Wisely® campaign American Headache Society releases list of commonly used tests and treatments to question. 2013. [Accessed March 20, 2023]. Available from https://www.choosingwisely.org/as-part-of-choosing-wisely-campaign-american-headache-society-releases-list-of-commonly-used-tests-and-treatments-to-question/?highlight=neuroimaging%20studies%20in%20patients%20with%20stable%20headaches.
4. Federal Aviation Administration. Arteriovenous malformation (AVM). Brain aneurysm. In: Guide for aviation medical examiners. Washington (DC): Federal Aviation Administration; 2023:161–163. [Accessed March 23, 2023]. Available from https://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/.
5. Flemming KD, Lanzino G. Cerebral cavernous malformation: what a practicing clinician should know. Mayo Clin Proc. 2020; 95(9):2005–2020.
6. Jagathesan T, O'Brien M. Aeromedical implications of cerebral cavernomas. Aerosp Med Hum Perform. 2021; 92(2):120–123.
7. Naval Aerospace Medical Institute. 10.17. Traumatic brain injury – permanently disqualified. In: U.S. Navy aeromedical reference and waiver guide. Pensacola (FL): Naval Aerospace Medical Institute; 2023. [Accessed March 23, 2023]. Available from https://www.med.navy.mil/Navy-Medicine-Operational-Training-Command/Naval-Aerospace-Medical-Institute/Aeromedical-Reference-and-Waiver-Guide/.
8. U.S. Air Force. Section L: neurologic USAF medical standards, L39. In: Medical standards directory; 2021:49. [Accessed March 23, 2023]. Available from https://afspecialwarfare.com/files/MSD%2019%20Mar%202021.pdf.
9. U.S. Army Aeromedical Activity. Subarachnoid hemorrhage. In: Flight surgeon's aeromedical checklists. Aeromedical policy letters. Ft. Rucker (AL): U.S. Army Aeromedical Activity; 2014. [Accessed March 23, 2023]. Available from https://docplayer.net/5184761-Aeromedical-checklist.html.
10. Viera AJ, Antono B. Acute headache in adults: a diagnostic approach. Am Fam Physician. 2022; 106(3):260–268.
11. Walling A. Frequent headaches: evaluation and management. Am Fam Physician. 2020; 101(7):419–428.

SEPTEMBER 1998

Mountaineering pharmaceuticals (University of Maryland Medical Systems, Baltimore, MD): "In a double-blind study, we compared the efficacy of a combination of sustained-release acetazolamide and low-dose dexamethasone and acetazolamide alone for prophylaxis against acute mountain sickness (AMS) caused by rapid ascent to high altitude. Before ascent, 13 subjects were randomly assigned to receive a combination of one sustained-release acetazolamide capsule (500 rag) in the afternoon and 4 mg dexamethasone every 12 h, or a combination of the same dose of acetazolamide once daily and a placebo every 12 h. Days 1 and 2 were spent at 3698 m (La Paz, Bolivia), while days 3 and 4 were spent at 5334 m (Mount Chaclataya, Bolivia). Ascent was by 2 h motor vehicle ride. Heart rates, peripheral oxygen saturations and a modified score derived from the Environmental Symptom Questionnaire (modified-ESQ) were measured on each day. In addition, weighted averages of the cerebral (AMS-C) and respiratory (AMS-R) symptoms were calculated for days 3 and 4. … Heart rate and modified-ESQ scores increased on days 3 and 4 compared with the other days in the acetazolamide/placebo group only ($p<0.05$). Oxygen saturations decreased in both groups on days 3 and 4 ($p<0.05$), but the decrease was greater in the acetazolamide/placebo group ($p<0.05$). AMS-C and AMS-R scores rose above the suggested thresholds for indication of AMS on days 3 and 4 in the acetazolamide/placebo group only ($p<0.05$). … We conclude that this combination of sustained-release acetazolamide once daily and low-dose dexamethasone twice daily is more effective in ameliorating the symptoms of AMS than acetazolamide alone at the ascent that was studied."[1]

SEPTEMBER 1973

Hyperbaric air and memory (York University, Downsview, Ontario, Canada): "Three experiments are reported which investigated the effects of hyperbaric air on STM and LTM (short- and long-term memory). In the first experiment the dichotic stimulation technique was used to examine STM at 1, 4 and 7 ata. The second experiment was similar to the first except that an increased pressure (10 ata) was used. A decrement in performance was found in both experiments but this was attributed to a deficit in auditory perception and it was concluded that STM is not affected by hyperbaric air. In the third experiment a free-recall learning task was used to examine input to, and retrieval from, LTM. A decreased rate of learning was found at 10 ata breathing air. After switching to an 80/20 helium-oxygen mixture midway through the learning task the rate of learning returned to that found at the surface although the relative difference in recall that was established breathing air remained. It was concluded that these results indicate a loss of ability to store information in LTM and may explain the amnesia that has sometimes been observed after breathing hyperbaric air."[2]

Barotrauma mishaps (Air Force Inspection and Safety Center, Norton AFB, CA): "Barotrauma has been implicated in several USAF accidents and incidents. In order to determine the significance of this disease entity in USAF operational flying, all accidents and incidents reported to the Air Force Inspection and Safety Center on AF Form 711gA, 'Life Sciences Report of an Individual Involved in an AF Accident/Incident,' for the period 1968 through 1972 were reviewed. Barotitis media with possible medical vertigo resulted in a fatal accident. Barosinusitis was the cause of several incidents which could well have ended in fatal accidents. Barotrauma continues to occur and can be a problem particularly in high performance, single-seat aircraft. Continued educational efforts are required to prevent aircrews from flying with conditions which predispose them to barotrauma."[3]

SEPTEMBER 1948

Say what? (Royal Netherlands Army Air Force, Ypenburg, Holland): "It is a well-known fact that many pilots develop a certain amount of deafness, which becomes more serious as their number of hours flown increases.

"This form of deafness may present itself in different ways. Sometimes this deafness is slight and transient, e.g., in those cases in which the ossicular chain does not operate properly because of a temporary lower or higher pressure in the middle ear as a result of descending and climbing in the atmosphere. This often results in a slight edema with a swelling of the submucous tissue. After some years this may result in an increased production of fibrous tissue in the middle ear which condition may be the reason of a permanent conduction deafness. …

"Far more importance has to be given to the permanent type of deafness caused by noise of the engines and of the radio equipment. This deafness is traumatic in origin; it is a deafness of the inner ear, demonstrating itself in the beginning of its development by a diminished perception of the C-5 tuning fork (4096 c.p.s.). As the process continues then eventually the hearing acuity of the C-4 (2048 c.p.s.) and the C-3 (1024 c.p.s.) tuning forks will deteriorate also. …

"The recruitment factor is responsible for the fact that experienced flyers with a considerable hearing loss do not have the slightest difficulty in their flying duties, although their hearing acuity does not come up to the present hearing standards. …

"Flying deafness can largely be prevented. Some methods are indicated."[4]

REFERENCES

1. Bernhard WN, Schalick LM, Delaney PA, Bernhard TM, Barnas GM. Acetazolamide plus low-dose dexamethasone is better than acetazolamide alone to ameliorate symptoms of acute mountain sickness. Aviat Space Environ Med. 1998; 69(9):883–886.
2. Fowler B. Effect of hyperbaric air on short-term and long-term memory. Aerosp Med. 1973; 44(9):1017–1022.
3. Lewis ST. Barotrauma in United States Air Force accidents-incidents. Aerosp Med. 1973; 44(9):1059–1061.
4. Pothoven WJ, Schuringa A. Aviation noise deafness, hearing standards and recruitment. J Aviat Med. 1948; 19(5):380–388.

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 and other articles are available for download from Mira LibrarySmart via https://submissions.miracd.com/asmaarchive/Login.aspx.

DOI: https://doi.org/10.3357/AMHP.6310.2023

Aerospace Medicine and Human Performance

INFORMATION FOR AUTHORS

http: //editorialmanager.com/AMHP

Now Accepting Open Access Articles!

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 web site. 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 submissions 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 layed out below, an exception may be granted. Please contact the Editoiral 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.

Review Articles are scholarly reviews of the literature on important subjects within the scope of the journal. Authors considering preparation of a review should contact the Editor to ascertain the suitability of the topic. Reviews generally may not exceed 6000 words with up to 150 references, but longer reviews of exceptional quality will be considered.

Case Reports and ***Case Series*** describe interesting or unusual clinical cases or aeromedical events. They should include a short Introduction 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.

Commentaries are brief essays that set forth opinion or perspective on relevant topics. Such manuscripts may not exceed 1000 words with approximately 10 references without tables or figures.

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.

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.

PREPARATION OF TABLES AND FIGURES

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.

REFERENCE STYLE

The style for references is the National Library of Medicine (NLM) format, using name-sequence, i.e. alphabetical by author.

SELECTION AND FORMATTING OF REFERENCES

The Corresponding Author is responsible for providing complete, accurate references so that a reader can locate the original material. References must be formatted in a modified Vancouver style, and listed alphabetically, numbered, then cited by number. An extensive set of examples of different types of references can be found on the web site under Documents to Download. If electronic references are used, they should be readily available to the reader.

MANUSCRIPT SUBMISSION (see details online)

Items for keystroke input:

1) Title; 2) Authors; 3) Keywords; 4) Classifications.

Files for uploading:

1) Cover Letter/Explanation; 2) Manuscript; 3) Figures.

Items requiring signature to be sent by fax or e-mail:

1) Cover letter with original signature; 2) Copyright release form; 3) Agreement to pay charges for figures (if more than four), color, excessive tables and supplemental materials; 4) Permissions (if applicable); **FOR OPEN ACCESS ONLY:** Licensing agreement and agreement to pay Open Access Fee.

PUBLICATION PROCEDURES

Once the Editor has accepted a manuscript, the electronic source files for text and figures (TIFF or EPS preferred) are forwarded to the publisher, the Aerospace Medical Association, for conversion to printable format and final copy-editing. Correspondence related to publication should be directed to the Managing Editor at the Association Home Office: (703) 739-2240, X101; rtrigg@asma.org.

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" (Qs).

EDITORIAL OFFICE

Frederick Bonato, Ph.D., Editor-in-Chief
c/o Aerospace Medical Association
320 South Henry Street
Alexandria, VA 22314-3579
Phone: (703)739-2240, x103 **Fax:** (703) 739-9652
E-mail: AMHPJournal@asma.org

Corporate and Sustaining Members of the Aerospace Medical Association

Now in Our 94th Year!

The financial resources of individual members alone cannot sustain the Association's pursuit of its broad international goals and objectives. Our 94-year history is documented by innumerable medical contributions toward flying health and safety that have become daily expectations by the world's entire flying population—commercial, military, and private aviation. Support from private and industrial sources is essential. AsMA has implemented a tiered Corporate Membership structure to better serve our corporate members. Those tiers are shown below for the following organizations, who share the Association's objectives or have benefited from its past or current activities, and have affirmed their support of the Association through Corporate Membership. As always, AsMA deeply appreciates your membership, sponsorship, and support.

For information on becoming a Corporate Member, please check out our website: https://www.asma.org/for-corporations, or contact our Membership Department at 703-739-2240, x107.

Platinum
Leidos
Mayo Clinic
Medaire, Inc.

Silver
InoMedic Health Applications, Inc.
Institutes for Behavior Resources, Inc.

Bronze
ADDMAN Group
Environmental Tectonics Corporation

Standard
Adams Advanced Aero Technology
Aerospace Medical, PLC
Aerospace Medicine Residency Program, UTMB
Air Line Pilots Association
Aircraft Owners and Pilots Association
Airdocs Aeromedical Support Services
Aviation Medicine Advisory Service
David Clark Company, Inc.
Education Enterprises, Inc.
Environics, Inc.
GO2 Altitude (Biomedtech Australia)
Harvey W. Watt & Company
International Federation of Air Line Pilots Association
Jet Companion Canada Ltd
KBR
Konan Medical USA
Martin-Baker Aircraft Company, Ltd.
Pilot Medical Solutions, Inc.

Aerospace Medicine and Human Performance
Published by the Aerospace Medical Association
320 South Henry Street
Alexandria, VA 22314-3579

Periodicals Postage
Paid at Alexandria, VA
and at Additional
Mailing Offices

Attention Members!

Turn over for important announcements!

CPC IPM# 0551775

Call for Papers

94th AsMA Annual Scientific Meeting
"Honoring the Past ...
Preparing for the Future"

Hyatt Regency Chicago,
Chicago, IL, USA
May 5–9, 2024

Photo by Rick Lobes from Pixabay.

Link to the abstract submission website
will be posted on the AsMA home page:
www.asma.org

The site will open on or about **September 1, 2023.**
The Deadline is November 1, 2023—NO EXCEPTIONS!

Aerospace Medicine and Human Performance • VOL. 94, NO. 8, PAGES 665–736
SEPTEMBER 2023