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Astronaut Health & Performance in Space: A Review

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Abstract

Since the dawn of time, humans have looked up to the skies for answers. Over the centuries, many have come up with ideologies that have helped move civilizations forward. We now live in an era with increased scientific breakthroughs that are shaping our understanding of the cosmos. Our innate curiosity distinguishes us from all other beings on Earth, and it is the main driver pushing us to explore the universe beyond what our physical bodies are capable of. The challenges of human spaceflight remain of great concern, and need to be managed before being able to venture beyond Earth's magnetosphere. The effects of microgravity on the cardiovascular system, central nervous system, bone mechanics, myology, and the vestibular system are not yet completely understood. Current available countermeasures are not sufficient to assure astronauts' ability to adequately perform the necessary tasks upon landing on Mars, after a prolonged exposure to microgravity. Even extended exposures to 1/6th G on the Moon are of concern. Other important factors to consider are the effects of exposure to solar radiation, including heavy ions, that are present in galactic cosmic rays. Determining the time course and magnitude of harmful, and potentially life-threatening, effects is of utmost importance to inform and prioritize countermeasure development. A foundational understanding of the human requirements for future deep space and planetary exploration is necessary. This study will present an overview of our current understanding of the physiological effects of long duration spaceflight, and project the impact for deep space missions if we employ only current countermeasures. We will begin with an analysis of the epidemiological approach currently used to predict the impacts of spaceflight, and discuss the value of precision medicine approaches that will allow for prevention and targeted countermeasures. The outcome of this study is to define research questions in each of these areas, in order to effectively develop solutions for future deep space missions. This study is performed by the Deep Space Initiative (DSI). DSI is a non-profit entity for which the goal is to increase accessibility and opportunity to space research, and its main focus is to help enable deep space exploration for the benefit of all humankind.

Keywords: aerospace medicine; space flight medicine; emergency medicine in microgravity; Mars; deep space; radiation

Acronyms/Abbreviations

Deep Space Initiative (DSI)
Cardiovascular system (CVS)
Central Nervous System (CNS)
Low Earth orbit (LEO)
National Aerospace Agency (NASA)
Solar particle events (SPEs)
Galactic cosmic rays (GCRs)
Vestibular ocular reflex (VOR)
Ocular counter roll (OCR)
Spaceflight Associated Neuro-Ocular Syndrome (SANS)
International Space Station (ISS)
European Space Agency (ESA)
Space Motion Sickness(SMS)
Intranasal scopolamine (IN SCOP)
Device for orientation and motion environments (DOME)
Sensorimotor adaptability (SA)
Bone mineral density (BMD)
Bone mineral content (BMC)
Compensatory reserve measurement (CRM)
Artificial intelligence (AI)
Platelet rich plasma (PRP)
Obstructive sleep apnoea (OSA)
Cytochrome P450 (CYP450)

1. Introduction

The challenges of human spaceflight to the human body remain of great concern. In the last few years, there has been tremendous progress in space accessibility, in the public, commercial, and not-for-profit domains. Risk prediction to the health of spaceflight participants are based on limited literature, with only several longitudinal studies available. As humankind looks to travel outside of Low Earth Orbit (LEO), go back to the moon with the Artemis missions within this decade, and plan for trips to Mars soon thereafter, it has never been more important to characterize the changes and adaptations that the human body undergoes in space travel.

This study presents an overview of our current understanding of the physiological effects of long duration spaceflight. These include the Cardiovascular System (CVS), the Central Nervous System (CNS), the Musculoskeletal System, Radiation, and Precision Medicine. The outcome of this study is to define research questions in each of these areas, in order to effectively develop solutions for future deep space missions.

2. Methods

PubMed and Google Scholar were used to search the literature, in English, pertaining to human spaceflight and deep space exploration. The searches were conducted with the terms “physiology” or “spaceflight” and keywords relevant to the respective organ systems and countermeasures. In order to specify the search to deep-space and long-duration flights, we excluded studies on suborbital and parabolic studies. Inclusion of terrestrial analogue and animal studies was dependent on its appropriateness according to each organ system. Studies concerning human physiological changes within the time-frame of weeks to months or longer were selected to ensure relevance. Radiation has been included as a discrete section due to its multitude of unique effects on the human body.

3. The Cardiovascular System (CVS)

NASA’s Longitudinal Study of Astronaut Health conducted between 1959 and 2010 showed no significant risk of increased cardiovascular disease incidence when compared to age, sex, and BMI-matched controls[1]. It is crucial to note that the cohort included in this study, besides Apollo astronauts, have all participated in missions within LEO, most of which are relatively short-duration spaceflight.
Aspects of re-entry are excluded in our analysis, as it is unclear whether changes in the CVS experienced by astronauts on return to Earth would be similar to those experienced while landing on the Moon or Mars. Ground-base analogs, such as bedrest and water immersion studies, are excluded as these introduce artificial pressure gradients, complicating their interpretation and extrapolation.

3.1 The Heart

After leaving the 1G environment on Earth, there is a cephalad fluid shift from the lower extremities and the interstitium to the head, with a reduction in the total blood volume by 11%. The resultant haemoconcentration has been observed to remain present for at least 6 months[2] . For longer-term space travel, this will likely lead to increased destruction of newly formed red cells as a mechanism of homeostasis [3]. The adaptations of the CVS in Space is governed by this fluid redistribution, coupled with regulatory mechanisms such as the Frank-Starling law, the endocrine and autonomic nervous systems. The expansion of the thoracic cage and lungs also contribute to creating a negative pressure to increase the cardiac preload[4].

In a study of 8 male astronauts that have spent 3-6 months on the International Space Station (ISS), Norsk and colleagues found stroke volume (SV) and cardiac output (CO) increased by 35-41%[5]. CO was measured using pulmonary capillary blood flow as a surrogate, although this assumes no significant physiological pulmonary blood shunting being present. Similar trends were noted by Hughson and colleagues[6] using the same foreign gas rebreathing technique and reference posture, in contrast to earlier Mir missions that showed unchanged SV and CO, using a technique involving arterial pulse contour analysis. This technique has been deemed unreliable due to the change in compliance of the arterial tree during spaceflight, and does not account for the regional differences in capacitance. The recently published NASA twin study[7] corroborated the finding of increased CO and reported that after nearly 1 year in space, CO increased by 10% in a caucasian male astronaut.

Twenty-four hour ambulatory brachial blood pressure (BP) measured at 3 and 6 months on the ISS was observed to be reduced by 8–10 mmHg, with a decrease in systemic vascular resistance (SVR) of 39%, and preserved trend of the nightly dip in space. This was not associated with suppression of sympathetic nervous activity, as catecholamine concentrations between pre-, in- and post-flight plasma were unchanged[5]. One contributor leading to this BP finding may be the baroreflex response to the cephalad fluid shift.

3.2 The vascular network

Conditions in space pose several risks to the efficiency of flow and vessel integrity. Endothelial dysfunction can arise from triggers such as space radiation, altered shear stress, and chronic inflammatory states from deranged metabolic pathways. Risk of death due to cardiovascular disease (CVD) has been noted to be 4-fold higher in Apollo astronauts compared to those who flew only in LEO[8], despite comparable total mission time. This difference has been suggested to be due to increased radiation exposure on the vascular endothelium beyond Earth's magnetosphere.

Increased vascular stiffness and intima-media thickness (IMT) was seen in the carotid artery after 6 months of ISS stay in astronauts without pre-flight cardiovascular risk factors, although intake of food and liquid, and exercise regimen were not controlled for. This change correlates with higher risk of cardiovascular disease in patients, and with increasing age[9]. The increase of 12% in carotid IMT can be approximated to 20-30 years of aging[10], [11]. These changes have also been linked to inflammation and increased insulin resistance[12]. Exploring whether the insulin resistance could potentiate the development of diabetes mellitus in long-term spaceflight is required, as it is a well-established risk factor for the development of microvascular and macrovascular complications. The changes in the vascular network could also potentiate the development of diseases such as atherosclerosis and hypertension, with later effects on the cardiac structure and function.

Venous stasis, sevenfold increase of the mean internal jugular vein area on ultrasound imaging, and reverse flow have been documented in a 100-day mission, in 6 out of 11 crew members. One astronaut was found to have complete internal jugular vein occlusion[13]. This not only raises the need for regular monitoring during longer exploratory missions, but also the importance in countermeasures to prevent venous thromboembolism, due to the risk of bleeding from anticoagulant treatment. Moreover, what is yet to be characterized, is how oral contraceptives, taken by most female astronauts for menstrual cycle suppression, can affect the vascular risks in deep space travel, as it is known to increase the risk of deep vein thrombosis on Earth[14].

Calf volume was reduced in concert with increased lower extremity venous compliance and decreased resistance in the first 3 months of an ISS mission. With time, these changes became more pronounced[15]. One area of investigation could be the impact on valve integrity, and whether it could potentiate the development of chronic venous insufficiency.

3.3 Countermeasures

Pharmaceutical countermeasures to prevent and mitigate cardiovascular risk in space have been studied and can be broadly divided according to the time of onset of the adaptations. After overcoming the initial adjustment stage to the space environment, late cardiovascular adaptations, such as cardiovascular remodeling, may be indications for antihypertensives and antiarrhythmics. Drugs that reduce cardiovascular risk, such as lipid-lowering agents, may be considered prior to the mission itself. Antioxidants and dietary supplements may be of interest as prophylaxis against space-induced oxidative stress, despite having controversial clinical utility on Earth[16].

To combat risks associated with inactivity, resistive exercise, such as with advanced resistive exercise device (ARED)[17] and whole-body vibration exercises, are frequently used by astronauts during space missions as exercise countermeasures (Maggioni 2018). Recent research has demonstrated that high intensity interval training (HIIT) significantly raises blood pressure, endothelium and left ventricular function, vasomotor function, and aerobic capacity during long duration bed-res, and may therefore be of potential benefit for astronauts on deep space missions[18].
It is currently unknown whether long duration space missions lead to an amplification of previously known reversible changes, or the emergence of previously unknown irreversible alterations in cardiovascular function. Long-term cardiovascular deconditioning, and the safety and ability to carry out mission-critical tasks upon landing on a celestial body will need to be accounted for.

4. Central Nervous System (CNS)

4.1 Space Environment and Risk Factors

Altered gravity fields, high radiation levels, and absence of normal day/night cycles, changing astronauts' circadian rhythms, have been described to lead to both behavioral and cognitive decline[19]. This is further worsened by isolation, and the stress of living in a hostile environment[20]

4.2 CNS and Microgravity

At the CNS level, the most notable changes relate to vestibular deconditioning and sensorimotor adaptation[21]. Along with alterations in cephalic fluid shifts[22] , ocular structures[23], and cell morphology, migration, proliferation, and apoptosis[24], these changes suggest an overall altered neuroplasticity.

Microgravity is also known to exacerbate the risk of developing neurodegenerative diseases and aging-associated manifestations, such as dysfunction of the glymphatic pathways, leading to reduced metabolic waste removal and neuroinflammation[25]

4.3 CNS and Radiation Exposure

Neuronal damage and neuroinflammation are consistently reported, along with a reduction in the production of new neurons, lasting months after exposure[26]. This corresponds to the radiation-induced augmentation of oxidative stress[27]. Observations during the Apollo and Skylab missions also highlighted accelerated cataract formation and retinal effects due to heavy ions exposure by crew members. From animal models, it is thought that the extent of behavioral impairments and cognitive alterations in learning and memory[28] are correlated to the dose and type/composition of the radiation [29]. However, because of the complexity of the radiation environment and the lack of models replicating all the space variables (cosmic rays/particles in addition to the combined effect of the vehicle/suit shield influence), the exact consequences remain challenging to describe.

4.4 CNS Structures and Functions in Space: Neuronal Connectivity

Ground-based studies with simulated microgravity and ionizing radiation consistently reported that neuronal structure and connectivity remain deeply impacted by the spaceflight experience with blood-brain barrier integrity implications [30]. Neuroinflammatory responses such as proinflammatory cytokine elevation [31] and microglia activation[32] are constated in human analogs and animal models exposed at doses relevant to Mars missions, indicating the processes of regulation and homeostasis. Experiments using space radiation simulations in rodents, notably with Galactic Cosmic Rays (GCRs) and high charge Z and high energy E particles, highlighted changes at the cell level These changes include decreases in dendritic branches and spines complexity[33], impaired synaptic plasticity [34], and inhibition of proliferation and differentiation of hippocampal neuronal precursor cells, inducing reduced neurogenesis[27]. These structural manifestations ultimately result in cognitive deficits in learning and memory, as well as in novel object recognition and spatial memory[35].

4.5 Vestibular System

Vestibular inputs are particularly affected with symptoms ranging from nausea and fatigue, to cognitive performance decrement that impact the internal representation of visual space[36]. Spatial disorientation and alterations in voluntary movements, with a decline in mobility and balance are also commonly reported by astronauts[37]. These changes are likely to increase the levels of anxiety, and influence decision-making and strategy control behaviors, which will be problematic if unaddressed in deep space missions.

4.6 Vestibulo-Ocular Changes (VOR)

The VOR is responsible for maintaining gaze while rotating the head by generating an opposite, compensatory movement of the eye; it maintains the gaze during head rotation, the ocular counter roll (OCR) reflex stabilizes the gaze during static head tilt. After 4-9 months of ISS flight, the OCR amplitude was reduced relative to preflight values for four days. Hallgren et al. also found a statistically significant decrease in OCR in their study of 13 astronauts returning from a 6-month stay in the ISS [38]. The measured OCR response was seen to normalize 9-10 days after reentry compared to preflight, however it remains to be determined if this reversibility persists in longer missions.

4.6.1 Cephalic fluid shifts and ocular structure

Microgravity and simulated microgravity are known to induce headward shifts in body fluids and severe alterations in cerebral fluid pressures. Neuroimaging studies have consistently reported decreases in frontal and temporal gray matter volumes[39], an upward displacement of the brain within the skull, and cerebrospinal fluid volume changes, including ventricular volume expansion[40].

It has been shown in postflight follow-up studies that the ventricles are the last structures showing significant changes between the preflight and postflight measurements 7 months after returning to the Earth[41]. This persistent expansion has been notably correlated to decreased visual acuity[42].

Fluid shifts and upward brain displacement are indeed thought to influence neuro-ophthalmic impairments. Between 40% and 60% of astronauts returning from ISS long-duration missions, and 23% from short-duration missions, report near sight vision reduction[43].The concept of Spaceflight Associated Neuro-ocular Syndrome (SANS) is characterized by optic disk edema, posterior globe flattening, choroidal folds, and hyperopic shifts in refraction. Its etiology is possibly due to how microgravity-induced cephalic fluid shifts affect the eye vasculature by reducing arterial blood supply and slowing the venous flow[44]. Interestingly, astronauts who developed SANS-related problems showed a low B vitamin status and higher risk alleles,

suggesting that the genotype is implicated in the development of anatomical damages[45]. Moreover, the majority of these changes were associated with prolonged exposure, at least 12 months, to the space environment[46], highlighting the role of mission duration in health outcomes and the need to develop countermeasures for Mars missions. By exerting static and inertial forces that simulate Earth's gravitational forces, lower body negative pressure (LBNP) devices could offer interesting insights to prevent cephalad fluid shifts and, by extension, SANS effects. However, their potential for long-term spaceflights requires further research, and the difficulty of application of LBNP led to it falling out of use on the American and European astronauts' sides; only the Russian cosmonauts continue to use a version of LBNP on the ISS.

4.7 ***Countermeasures***

4.7.1 ***Inflight Medication***

Astronauts have been using pharmaceuticals for space motion sickness prophylactically and in inflight since the 1960's. Many different drugs have been tested against this problem, but with variable and individual effectiveness, and none can completely prevent the occurrence of signs and symptoms of space motion sickness. Scopolamine and promethazine are two of the most evaluated drugs that exhibit more favorable results as a prophylactic treatment[47].

4.7.2 ***Training and Rehabilitation***

Two training devices are currently used to provide a variety of stimulus rearrangements and train sensorimotor reflexes: device for orientation and motion environments (DOME) that acquires graviceptor stabilization, and the tilt-translation device (TTD) that produces graviceptor-visual rearrangement. These preflight training devices have been used to minimize the symptoms of space motion sickness. The theory is that by exposing the astronauts to similar conflicting sensory inputs as in microgravity, they will either adapt through sensory compensation, reinterpret and rearrange the sensory stimuli, or learn and store appropriate responses to different sensory stimuli conditions.

5**. Musculoskeletal System: Inflight**

5.1 ***Muscle***

In microgravity, atrophy of the muscle is primarily caused by the reduction of gravitational forces on the body. Without the need to support the body upright against gravity, postural (trunk) muscles and leg muscles degrade most rapidly. Astronauts that were on the ISS for 4-6 months showed an average loss of 4.7% of overall trunk cross-sectional area between pre-flight and post-flight, and a 3.2% decrease in trunk muscle quality accompanied by an increase of intermuscular fat [48]. This combination of decreased lean muscle mass and increased fat deposition is also related to a reduction in overall strength [49]. Significant strength losses in the core and lower body may significantly impact the ability of the astronaut to conduct necessary missions, including exploration or facilitation of repairs during spaceflight. Additionally, muscle loss in the core may have a particular impact on postural stability upon return to gravity.

The rate of loss of both core and appendicular muscle mass appears to be directly related to overall weight bearing of the particular muscle [50]. Upper body and core muscular endurance, and strength measures have been shown to remain relatively stable during a 4-6 month mission, while lower body flexibility, agility, and strength significantly decreased despite partaking in exercise interventions aboard the ISS [51]. In lower leg muscles, the soleus and gastrocnemius, significant loss of both Type I and Type II fibers occurred during a 6-month mission aboard the ISS. Type I fibers were found to atrophy faster than Type II with more significant degradation seen in the muscle fiber diameter due to a shrinkage in myofibrils. Post-flight declines in absolute peak isometric muscular force were found to be correlated with fiber atrophy as relative fiber force capabilities remained the same [52].

High levels of treadmill exercise were found to decrease loss of muscle in the lower body compared to low treadmill exercise, but it must be considered that running places particular stresses on these muscles[52]. This may suggest, that similar to other findings, high-intensity exercise stress must be particular to the individual muscles in order to reduce atrophy. However, a resistance exercise regimen that does not adequately use all muscle groups will inevitably result in muscular imbalances both in-flight and post-flight, leading to impairment of functional performance[48], [53]. Significant strength losses in the core and lower body may impact the ability of the astronaut to conduct necessary tasks, including exploration or facilitation of repairs during spaceflight.

5.2 ***Bone***

Significant loss of bone mineral density (BMD) occurs in the axial skeleton for every month that individuals are exposed to microgravity, specifically impacting the spine (1.06%/month), neck (1.15%/month), pelvis (1.35%/month), and trochanter (1.56%/month). Rate of BMD loss in the appendicular skeleton appears to be

based on the amount of weight that the bone and joint bears. For example, BMD loss in the arms occurs at a significantly lower rate than the bones of the leg [50]. Changes in BMD and bone mineral content (BMC) as a response to spaceflight does not appear to differ between men and women. However, those with greater pre-flight BMC have been shown to lose a larger percentage of their bone at a faster rate than those with lower pre-flight levels [54]. This finding suggests that it is the reduction of gravity-induced loading on the skeleton that is the primary cause in bone mass loss and that those who have more skeletal mass on Earth seem to lose it more quickly when exposed to microgravity.. When following these guidelines, it was found that after 6 months on the ISS, risk of fractures did not appear to increase in the lumbar spine or bones of the lower body. It is important to note that astronauts are required to have pre-flight BMD levels that are associated with low fracture risks and facilitate a low-risk prediction despite anticipated BMD losses [55].

Despite this evident impact of skeletal unloading in microgravity, progress has been made to reduce overall bone loss in spaceflight. Astronauts on long-duration missions that have access to sufficient resistance training while maintaining adequate energy intake and vitamin D status appear to experience little to no changes in whole body BMD, but may still experience significant loss of BMD in the lumbar spine and hip complex if exercise does not specifically target these regions. In astronauts exposed to long duration spaceflight and followed strict nutrition and exercise regimens, serum levels of calcium were shown to remain unchanged, while bone turnover and formation biomarkers (osteocalcin, alkaline phosphatase, and bone specific alkaline phosphatase) increased[56]. Urinary excretion of biomarkers of bone tissue resorption (breakdown) (creatinine, C-telopeptide, pyridinium crosslinks, N-telopeptide, deoxypyridinoline) and calcium remained significantly elevated during spaceflight, regardless of intervention. These results seem to suggest that continued loss of total bone mass, although at minimal rates, still occurred, while resistance training and proper nutrition seem to be sufficient to support bone remodeling and maintenance of bone strength throughout spaceflight. Even if overall skeletal BMD and BMC appear to be able to remain relatively stable, some studies suggest that recovery of bone density, strength, and trabecular thickness may be incomplete, particularly in weight-bearing bones, even up to 12-months post-long duration flight[57] .

5.3 Combined Impact of Musculoskeletal Changes on Postural Health

The combination of postural muscle atrophy, elongation of the spine, and decreased spinal BMD associated with microgravity are the likely causes of in-flight back pain [48], [58]. In-flight back pain is highly prevalent in both short and long-duration space flight (~70%) and is more common in those with a prior history of low back pain [59]. Additionally, NASA crewmembers are 4.3x more likely to develop herniated intervertebral disks, particularly in the cervical spine, than their civilian and military aviator counterparts[58], [60]. Low back pain during spaceflight may also be exacerbated by the shortening of the musculature in the hamstrings and lower back. Due to postural changes, this reduces overall flexibility and favors the fetal positions in the microgravity environment[51]. These conditions present a constant and potentially debilitating state, which may further increase following spaceflight as crew are re-exposed to gravity.

5.4 Countermeasures to Preserve Muscle and Bone Mass

5.4.1 Medical Screening/ Standards

Pre-flight fitness, muscle mass, and BMD are significant predictors of muscle and bone loss during long duration space exposure. These metrics are currently monitored before flight, however, the standards used are generally based on Earth health standards and may not properly translate to long duration deep space missions [51], [55].

5.4.2 Exercise

Recent research has found that resistive exercise in astronauts and bisphosphonate therapy can mitigate bone loss that happens in space[61], [62]. While it appears that those who exercise more frequently, and for longer periods of time, during long duration spaceflight have better preservation of both core and peripheral muscle mass, these countermeasures do not appear sufficient to maintain preflight mass, structure, or functionality. Furthermore, it is clear that the exercise devices available on the ISS are able to cater to only certain muscle groups and that the equipment required to facilitate a well-balanced exercise regimen does not exist in space yet [52], [53]. It has been suggested that the focus should shift from self-selected, light to moderate exercise, to a more structured, high intensity resistance program such as HIIT, which has the potential to reduce the time investment required to preserve muscle and bone mass[52].

The use of the ARED resulted in improved maintenance of BMD, lean mass, and levels of biomarkers associated with bone turnover during

spaceflight exposures ranging from 1.5 to 7 months [56]. LBNP application could be added to training regimens in future space missions and analogue studies to see if this reduces post-spaceflight orthostatic intolerance and enhances overall astronaut health, including muscle and cardiovascular health[63].

5.4.3 Diet and Nutritional Supplements

Adequate energy intake is vital for optimal preservation of muscle and bone mass during spaceflight. Higher intakes of energy or protein have specifically shown to be correlated with maintenance of overall body weight and pelvic bone mineral content. Supplementing astronauts with vitamin D has been a standard for decades. However, the initial prescribed intake of 400 IU per day proved to be insufficient in preventing a diminished vitamin D status in astronauts. Since doubling the prescription, a dosage of 800 IU per day appears to adequately maintain serum levels of vitamin D [56].

5. Radiation

5.1 Current paradigms

Mitigating the effects of radiation has been a major focus of human spaceflight for more than fifty years. From the Mercury-era missions to the early 2000's, approaches to mitigation strategies shifted from limiting exposure – IE by avoiding certain orbital trajectories, such as the South Atlantic magnetic anomaly, or by limiting time in space – to passive shielding, detailed exposure surveillance, and defining ideal occupational exposure limits [64], [65]. As the aerospace community plans for long-term, deep-space exploration and habitation, strategies for complex medical risk modeling, personalized medicine, real-time space weather monitoring and prediction, pharmacologic and even nutritional intervention, have risen to dominate the radiation risk mitigation effort.

Current radiation risk mitigation strategies for deep space exploration are pinned by two main forces: design considerations inherent to deep space exploration and the nature of the radiation itself. Predicting and planning for acute, high-dose radiation exposure from solar particle events (SPEs) drives medical risk modeling and mission planning. Both strategies are aimed at protecting explorers from whole-body effects by rare, but potentially serious, influxes of high-energy protons. Many of the models related to SPE effects and countermeasures derive from radiation-rich accidents and events that have occurred here on Earth. Meanwhile, mitigating risks due to GCRs – a constant, substantially more predictable source of lower-energy radiation exposure – relies on experimentation, typically in vitro or in animal models. In contrast to SPEs, what is known about the medium- and long-term effects of GCRs is largely extrapolated from non-human or in vitro studies in laboratory environments. As a result, optimal mitigation techniques for and countermeasures strategies against GCRs may not be well understood before human deep space missions are well underway.

Though our current capacity to completely model GCR radiation effects on human physiology and function is limited, efforts to characterize the radiation environment during deep space missions are ongoing. In 2020, Sobel and Duncan estimated that during a three year mission to Mars, explorers may receive an average dose-equivalent rate of 45 μSv/h[66]. Against this radiation onslaught, which is over ten times what was observed during the Space Shuttle era, current shielding modalities are known to be of limited effectiveness[67], [68] (Wilson, 2001 and 2004). As we continue to pursue deep-space exploration and habitation, there is no escaping relentless radiation. Fortunately, numerous reviews, studies, and models addressing the state of knowledge regarding the physiological radiation effects, the potential impacts of those effects, and the potential countermeasures to those effects have been published within the last few years. Our efforts in this section are designed to assist the reader in developing a general understanding of the most up-to-date information relating to radiation and human exploration of deep space, which remains, to date, one of the most difficult risks to manage.

5.2 Main Effects of Concern: CNS Alterations, Immunologic Dysfunction, and Cancer Risk

Background GCR, while representing radiation exposures at levels lower than those of SPEs, is sufficient to induce deficits and alterations in CNS function [69]. This may be due, at least in part, to tracks from single, heavy nuclei, such as ^{28}Si. Numerous controlled rodent-based studies, including some by Blackwell and colleagues [70], [71], have demonstrated neurocognitive performance decrements analogous to decreased sensorimotor function, motivation, and concentration after simulated exposures. Projected effects on the human CNS due to prolonged, unshielded GCR exposure include decreased spatial and complex learning as well as behavioral implications and increased anxiety[72]. When cell membrane disruption (e.g. oxidation, leakage, inflammation), occurs at the level of the immune system, the vascular system, or the eye, the risk profile shifts from psychomotor and mood effects to B Cell and T Cell down-regulation [73], increases in the inflammation and formation of reactive oxygen species[74], and cataract formation[75], respectively.

Cancer risk is a related and also significant issue, largely due to high-energy proton and cosmic ray exposure. Extended exposure to space radiation has been found to produce persistent DNA damage in long duration spaceflight cohorts similar to that found in cancer patients undergoing radiation therapy[76]. Furthermore, the long term cancer risks associated with consistent exposure to GCRs are challenging to predict. This may be due to the fact that DNA damage from GCR is stochastic, and chronic, and because there are a few sources on chronic GCR's effects on earthly organic material available to study. By contrast, the literature treats cancer induction secondary to acute SPE exposure as somewhat analogous to acute radiation exposure on Earth [77]. A notable caveat, Earth-based exposures are generally more continuous and of a lower energy than what would be expected in space. Modeling of all-cause cancer risk in middle-aged astronauts indicates that even at a solar minimum, there is a significant increase in the post-mission risk of exposure-induced leukemia as well as cancers affecting the colon, lungs, esophagus, stomach, and ovaries[78].

5.3 Countermeasures

Radiation effects are tough to model and tougher to manage. In response, the aeromedical community is expending significant energy to study exposure prevention. Mission planning around radiation countermeasures has expanded to include elements of active and passive vehicle shielding [79], crew selection based on potential radiation resistance [76], nutritional countermeasures [80], hibernation[81] and genetic alterations to improve crews' physiologic robustness.

As critical as it is to improve protection against radiation, is it equally important to bear in mind the nearly inescapable tradeoffs. Traditional spacecraft shielding can lower exposures to charged particles, but may also elevate neutron radiation levels [69]. The effects of trading one type of irradiation for another, varying durations and doses of chronic exposure, supplementing diets, and changing our genetic makeup are as unknown and challenging to predict in advance as the direct, and indirect effects of deep space radiation. Shortening the exposure duration with more efficient, interplanetary propulsion stands out as one of the few radiation countermeasures that might not carry with it significant unknown side effects [66]. Looking forward, deep space, radiation-minded mission planning will likely feature a trifecta of decreased transit time, improved SPE shielding, and medical GCR countermeasures.

6. Precision Medicine

Precision medicine has been defined by National Institute of Health as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person"[82]. In this section we explore its potential in addressing the risks posed to human health by spaceflight.

6.1 ***Prevention***

Presently, personalized medicine in astronauts is limited. Areas of opportunity for the adaptation of precision medicine in astronaut health have been proposed as countermeasures targeted to protecting astronauts from harmful effects of space flight, which include: radiation exposure mitigation, resistive exercises for bone health improvement, and pharmacogenetic screenings. Prior to embarking on space flight, astronauts undergo pre-mission screenings to assess performance and immunological function, allowing for limited mitigation of possible adverse effects[83].

In understanding how an individual adapts to change, traditionally accounted for measures are genomics, transcriptomics, proteomics, and metabolomics. Recent advances in the field have introduced other components such as epigenomics and microbiomics, and has allowed for the construction of a more comprehensive picture of a biological being. Targeted countermeasures and risk/susceptibility calculations using comprehensive molecular profiling is the future of spaceflight, as it is becoming increasingly recognised in clinical medicine, moving away from a dated and normative 'one-size-fits-all' approach.

6.1.1 Wearable Devices: targeting individualized physiological compensatory states

Wearable technology for individualized monitoring of an astronaut's physiological condition has been proposed as a means to assess real-time status and help guide clinical decision making. The compensatory reserve measurement (CRM), a portable technology that utilizes machine learning to create algorithms based on arterial waveforms, assesses parameters such as blood pressure, tissue oxygenation, and systemic blood flow. The CRM has been studied across trauma and military populations, with proposed translatability to space exploration[84], [85].

Furthermore, personalized nutrition through the use of artificial intelligence (AI) technology in the form of hand-held devices and other wearable technology has been proven to assess metabolism and nutritional status. Although these commercially available devices have not

been assessed for spaceflight applications, they can obtain data by using body waste products and respiratory gas sensors, further aiding in the identification of enterotype and metabolotype of each astronaut. These urine, stool, sweat, and respiratory gas samples help in identifying individualized dietary needs, hydration and electrolyte status amongst other metabolic parameters[86]–[89]. Such technologies will need further validation prior to its implementation on spaceflight crew.

Additionally, space flight-promoted insulin resistance has been discussed as a possible disruptor of wound healing, leading to wound chronicity and defective repair processes [90]. Accurate monitoring of individual insulin resistance status, by wearable devices sampling the interstitial tissue glucose concentration, currently in development for insulin-dependent diabetic patients, could mitigate susceptibility to problematic wound healing and can thus be used as a preventative countermeasure

6.1.2 Polygenic risk models for prognostic screening

There are various known conditions that are extensively screened for in the process of identifying optimal candidate profiles to undertake careers in spaceflight. These medical selection standards and qualifications have evolved over the years, and presently include "medically disqualified but surgically correctable" selections[91]. Given that the future gears towards deep space initiatives, it is imperative to refine screening methods. With the use of whole-genome sequencing techniques and polygenic risk models, there have been several pathologies identified for prognostication screening purposes. For example, obstructive sleep apnea (OSA), a condition that has significantly increased in prevalence in military members, is associated with disturbed sleep quality, inappropriate somnolence, leading to elevated risk of fatal aircraft accidents [92]. Recent studies have allured to the presence of strong genetic predisposition for OSA, which will enable early detection and personalized treatment, through increased polysomnography testing and surveillance for individuals with prone to developing OSA[92], [93].Other genetic predispositions to conditions relevant to spaceflight, such as ophthalmologic and cardiovascular diseases, are currently assessed in order to increase medical readiness[93].

6.2 ***Treatment***

6.2.1 Pharmacogenomics

Cytochrome P450 (CYP450) enzymes are responsible for a large proportion of drug metabolism in humans. It is widely accepted that variation in the polymorphic expression of these enzymes can account for reactions such as side-effects, and their efficacy in a particular drug in treating disease. In the space environment, it is crucial that the risk of adverse reactions and treatment failure are minimized, as higher-level medical capabilities may not be immediately available, particularly in deep space exploration. One example of the CYP450 family is CYP2D6, which is responsible for the metabolism of approximately 25% of all commonly used drugs, such as codeine, which is converted to morphine, a more potent opioid. In the likelihood that someone is an ultra-rapid metabolizer, they would be at risk to opioid toxicity, which can potentially lead to life-threatening respiratory compromise necessitating airway support. Another example is CYP3A4, which is the most abundantly expressed subtype of the enzyme family in humans, and is highly sensitive to enzyme induction, for instance through drug-drug interactions[94]. This can lead to reduced efficacy of the substrate drug due to the increased breakdown. In spaceflight, it would be essential to consider packing required medications based on the crew's CYP450 profiles to minimize the aforementioned risks.

Metabolism of many drugs also require a phase II biotransformation whereby a small molecule is bound to the drug to increase its solubility and its aid excretion[95]. As well as profiling the enzymes involved in these reactions, the levels of conjugation agents could be assessed pre-flight. It would be ideal to have in-flight, point-of-care testing capabilities, as it is possible that the spaceflight environment can change enzymatic expression, or deplete conjugate molecule stores. In such cases, replenishment of the conjugate molecules may be possible, and allow optimal function of the drug-metabolizing enzymes.

6.2.2 Autologous blood products

Microgravity has been demonstrated to delay wound healing and tissue repair. Platelet rich plasma (PRP), extracted from the one's own peripheral blood sample, has been shown to prevent these changes[96]. Since the production of these blood products to be used will be from the astronaut's own body, therefore eliminating the risk of rejection reactions. Technologies to allow this capability could be a useful tool for future long-duration deep space missions, by allowing these therapeutic strategies to become available on demand.

7. Limitations and future considerations

We appreciate that in our review, many included studies are from ISS stays of >6 months, and that there are

distinctive differences between the environmental conditions experienced during deep space and ISS missions. The existing partial gravity on the moon or beyond could potentially offset some of the described changes seen in microgravity in the aforementioned studies.
Through our search, we have noted methodological differences that have led to conflicting conclusions on physiological adaptations. For instance, the choice in ground reference position as pointed out by Norsk and colleagues can lead to a discrepancy in the measured difference in cardiac workload, since the supine position increases the baseline CO by 15%–29% compared to the upright or seated position[5]. This highlights the importance of a consensus in experimental protocols of spaceflight physiology studies.

Moreover, definitions need to be universally agreed on by research groups in order to produce data amenable for comparison. Laughlin and colleagues reported that despite significant decrements found in the functional fitness of the lower body after 4-6 months in space, these decrements did not prevent crewmembers from successfully performing activities of daily life (Laughlin 2015); crucially, the definition of activities of daily life and measured success were not defined by the authors.

The inability to control ambient conditions during data recording can also introduce confounding factors. It has been recognised that there are fluctuations in ambient CO_2 levels on the ISS. This can influence the measurements of physiological variables which have a dynamic relationship with CO_2, as Kiely and colleagues pointed out, 30 minutes of acute hypercapnia (EtCO2 of 7 kPa) can increase HR, SV, CO, BP and also QTc[97]. Mitigation measures may include ambulatory ECG monitoring incorporated wearable technology, and atmospheric composition sensors to correlate with the recorded data.

Ultrasonography is the preferred imaging modality in space due to its relative ease and cost-effectiveness of transport and operation. However, in evaluating the utility of its findings in existing studies, one must recognise the added difficulty of performing ultrasonographic imaging studies in microgravity, since the images obtained are extremely operator-dependent.

Gallo and colleagues have recommended the use of computational modeling to circumvent the issue of inconclusive data on human physiology in space[98] . Utilizing data from existing studies, they reported that long-term spaceflight (>5 months) can lead to a degree of cardiovascular deconditioning such that one's exercise tolerance could be similar to an untrained person with a sedentary lifestyle. Of course, computational modeling of the heart and arterial hemodynamics is limited by the exclusion of the influences from other reactive regulatory mechanisms in the body, such as the endocrine system, and interstitial fluid shift. When designing future studies, a combination of computational modeling with clinical experiments is likely the best strategy moving forward to understand the physiological adaptations, and planning for exploration of the deep space environment.

For future studies on effects of space on human physiology, we would recommend taking an holistic approach rather than the one adopted by most existing studies, focusing on one discrete body system. Since all physiologic systems are interdependent, i.e. a primary change in one system can impact the physiological status of another as a secondary effect, and it is their interaction that gives rise to function and adaptation, an integrated approach would allow for more accurate translation to astronaut health and performance. This highlights the importance of longitudinal studies, as facilitated by deep Space missions to understand the consequence of long-term space travel.

8. Conclusion

Compared to other areas of research, the demographic of those that have traveled to space, let alone for what we now consider "long-duration" is quite small. In addition, individuals are exposed to slightly different conditions, making the assessment of the physiological mechanisms that occur during spaceflight quite difficult. This is further complicated by unknown interactions between individual genetic profiles and environmental risk factors.

This paper provides a snapshot of the physiological impacts of spaceflight that require specific consideration for extended duration to the Moon or Mars. As a result, we propose the following research topic recommendations:

1. Identification of the extent of cardiovascular deconditioning during long-term exposures to microgravity and radiation, with emphasis on:
    a. Cardiovascular disease risk and implications for long-term survival,
    b. Operational impacts of a compromised cardiovascular system on EVA's and stress of re-entry
    c. Long-term implications of decreased venous return and applicable countermeasures
    d. Nutrition programming and pharmacological solutions that taper

excess cardiovascular stress and manifest upon return to partial or full gravity following long-duration missions

2. Investigation of the risk of developing concurrent disease paradigms, due to factors including but not limited to space-flight promoted insulin resistance, increased intramuscular fat deposition, and vascular stiffness
3. Implementation of multiple risk factor models to better understand impacts on neuromotor signaling and function, sensation, perception, coordination, and ocular function
4. Assessments of populations with neurodegenerative diseases that mimic those seen in space to understand the operational impacts and mitigation procedures related to cognitive deficits in learning, memory, and novel object recognition and spatial memory
5. Exploration of the biomechanical stress on the body while performing functional and operationally relevant movement patterns under variable gravitational stress
    a. Identification of muscle and bone mass, strength, power required for said movement patterns
6. Development of improved exercise regimens and equipment to prevent inevitable muscular imbalances
7. Diversification of the current screening battery to include comprehensive genetic and molecular profiling to develop targeted countermeasures and risk/susceptibility calculations
8. Validation of portable medical tools and techniques that can provide real-time, individualized assessment and treatment for various conditions

In conclusion, there is much more to be understood about the human body in space. Continuing to advance our knowledge of extraterrestrial physiological changes, in concert with the development of adequate screening standards and countermeasures will be fundamental to humanity's inexorable spacefaring goals.

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