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Human Health in Space

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1.1 Introduction

The human is capable of surviving in ordinary and extreme environments on every continent on Earth. This robustness indicates that humans adapt to various diverse environments and use resources to endure conditions that challenge our survival. The most extreme and austere environments that humans have inhabited are low-Earth orbit, lunar orbit, and the lunar surface otherwise known as spaceflight. Being prepared to enable survival and performance during spaceflight requires an understanding and assessment of the natural course of human health as we age and are exposed to environmental and biological stressors, specifically spaceflight stressors such as microgravity, isolation and confinement, closed loop environmental systems, and space radiation.

Human health and performance form a continuum and data used to quantify and describe each requires context to be adequately interpreted for risk assessment to provide a rational foundation for space exploration medical and countermeasure systems [1–4]. This concept is especially important in the extreme environment of spaceflight where small or unanticipated changes may have critical impacts to the individual and the mission. Loss of crew (LOC) and loss of mission (LOM) are common endpoints that are used to assess the severity of acute and off-nominal events. All mission planning and space vehicle development from the time of conception are designed to avoid or mitigate LOC or LOM events and parallels the occupational health model (engineer out the exposure, provide personal protective equipment for unavoidable exposures, and perform surveillance for untoward effects for early intervention) used to manage the human system risk. This is challenging given the independent and intersecting components of the spaceflight environment, vehicle design, and missions requirements. This challenge is compounded during human spaceflight due to the human changing over time in response to the natural course of their biology (aging?) and exposure to the spaceflight environment that includes novel stressors such as microgravity, extreme isolation and confinement, and space radiation (chronic galactic cosmic rays and acute solar particle events).

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Establishing a comprehensive understanding and record of an individual's baseline health is extremely important to risk assessment and risk acceptance processes of human spaceflight. Each human spaceflight participant represents a unique combination of genetics and environmental exposures including lifestyle factors (diet, smoking, alcohol consumption, exercise training, etc.) that contribute to the risk of disease and impaired function that might affect the mission, LOC, or LOM. However, requirements that drive decisions about vehicle design, inclusion of large countermeasure equipment (treadmill, cycle ergometer, resistive exercise, lower body negative pressure (LBNP), etc.), and mission objectives are determined long before specific participants are identified. This temporal chasm between knowing an individual's risk and needs versus locking-in a vehicle design and capability has been addressed by using an epidemiological approach to human spaceflight requirements. This approach has been refined over time and adjusted for healthier populations based on updates to terrestrial medical and public health standards and practices. It allows the development of requirements based on a generic representation of humans as an average and standard deviation with occasional allowance for accommodations of ranges such as that associated with anthropometrics, and a risk management approach that uses current evidence for both the likelihood and consequence of a medical event. In addition, historical human spaceflight and dedicated research data are used to assess the effect of exposure to spaceflight specific stressors on the risk of a medical event or a performance decrement. The implication of this process is that participants that do not fall into an acceptable risk posture based on the requirements that were used to generate design and capability of the vehicle may not be permitted to fly on a mission. Since we are entering the era of commercial spaceflight and opening access to spaceflight to a broader population, this undesirable and restrictive potential outcome can be mitigated by actions on the human, the vehicle, and the mission. The human risk can be affected by aggressive risk factor and disease management that may shift the risk benefit assessment in favor of prophylactic surgery or use of additional pharmaceuticals, but each action must have a thorough assessment to understand the inadvertent introduction of risk. The vehicle and mission can mitigate risk by accommodating specific medical and countermeasure hardware, custom protocols for existing hardware, providing personalized pharmaceuticals in custom kits, and adjusting mission duration so that pre-flight screening and treatment can effectively mitigate the medical risk during the mission. This approach is human system integration (HSI) and requires significant communication, evaluation of data, and integration by many specialists from the medical, engineering, and risk management communities.

1.2 Preflight Determination of Health and Performance Risk

The approach to assess health and medical risk is rooted in preventive medicine's clinical standard of care and focuses on gathering multi-system quality evidence, characterization of health risk factors and presence of disease, comparison to relevant populations (terrestrial and previous spaceflight) to assess probability of medical event, and quantification of the health and medical risk for the mission. Assessing performance begins with understanding the health of the individual and collecting fitness metrics, aerobic capacity, power output, endurance, etc. that can be used to characterize and benchmark functional performance and provide a comparison for in-mission assessment to detect decrements and develop an action plan if an unacceptable threshold is reached. Actual evaluation of mission-relevant performance that includes physical capabilities and executive function is done by the flight operations community during mission training and includes intra-vehicular activity (IVA; telerobotic, vehicle maintenance and repair, emergency procedures, medical officer functions, etc.) and extra-vehicular activity (EVA; microgravity and planetary) objectives to establish fitness for duty and a baseline for comparison during the mission. Establishing the pre-flight health and performance baseline provides evidence to calculate risk and also the ability to estimate the impact of changes over the course of the mission. The duration of a mission plays crucial role in estimating risk since many medical conditions have a limited window of prediction based on current screening techniques. This principle is illustrated by the terrestrial medical guidance for annual exams and regular screening tests such as blood work to assess high-density lipids (HDL) and low-density lipids (LDL), prostate specific antigen, fasting blood glucose, mammography, colonoscopy, and pap smears. Screening in-line with these recommendations allows for early and pre-symptomatic disease identification and treatment often remediating the pathological process and reducing the risk of a medical outcome to an acceptable baseline level. Most human spaceflight missions have not exceeded the recommended terrestrial screening durations and coupled with intensive preventive medicine the spaceflight community has been confident that most critical medical events of a natural origin are very unlikely to occur during the mission. [1, 2].

Exploration class missions require mission durations, three years or more, that are outside the prediction window of current medical screening and will require additional screening tools such as precision medicine 31 or more robust in-mission diagnostic and interventional capability to manage medical risk [32]. Missions that do not require extreme durations but have high tempo EVAs, such as lunar exploration, represent additional medical risk due to injuries associated with repetitive activities in the suit, use of heavy equipment, and lunar dust exposure. Therefore, pre-flight the overall health and performance risk for a mission is a complex matrix of medical event probability for each crewmember based on pre-existing risk factors and health risks induced by the operational environment. The element of human spaceflight that has been very challenging to include in the quantitative health and performance risk assessment is how the hazards of spaceflight (altered gravity, closed environment, isolation and confinement, and space radiation) influence how the human changes overtime in response to those unique exposures and how those changes alter the probability of a health and performance risk ultimately influencing LOC and LOM. [3, 4].

1.3 Physiologic Responses to Spaceflight

Human response to these hazards ranges from adaptive to maladaptive and has been documented through evaluation of data from medical operations and dedicated research performed during spaceflight and terrestrial analog missions. The interpretation and application of the data varies depending on the mission duration, time to effect of the adaptive or maladaptive process, and the ability of the individual and mission to tolerate the effect.

The following sections describe the known human responses to the spaceflight hazards and will provide context for the relevance to risk assessment [4]. The most challenging aspect to this section is that the human experiences spaceflight in its totality and begins adapting immediately. The hazard exposures are overlapping and influence each other leading to additive or synergistic effects that continue to be elucidated. Acute responses manifest over minutes and hours and depending on the sustained presence of the exposure may lead to a more chronic response process that includes compensatory mechanisms that may delay or mask overt symptoms and performance impacts [5] (Figure 1.1). The chronic responses to spaceflight hazards have more significant implications for late in-mission and long-term, post-mission health and performance consequences.

It can be very challenging to identify the first response to spaceflight because of intrinsic dependencies and continuous interaction between molecular and physiologic systems. Given this challenge, it seems logical to describe the human response to spaceflight based on the order in which they appear at a phenotypic level, i.e. cause symptoms or behaviors making the manifestation obvious. The issues are described in summary with in-mission and post-flight implications provided for context and relevancy.

1.4 Vestibular and Sensorimotor Disruption and Adaptation

One of the first issues that humans may experience when exposed to novel and new motion is motion sickness. Motion sickness is commonly associated with air travel and sailing, and spaceflight, a combination of aviation and sailing, is no exception. During the first 2–3 days of spaceflight 60–80% [6] of crewmembers experience symptoms that vary from mild nausea to severe vomiting requiring medication to reduce the risk of dehydration and allow crewmembers to adapt. Motion sickness may pose a significant risk within the first few days of the mission when severe but even mild cases of motion sickness may be accompanied by spatial disorientation, difficulty acquiring and tracking visual targets, and alterations of proprioception [7]. While overt motion sickness was not deemed a serious issue during the Apollo missions due to mitigating circumstances such as the small capsule and quick transit times, the spatial disorientation and tracking of visual targets was recognized as a potential issue by Apollo lunar module (LM) pilots compounded by visual illusions created by the angle of view from the LM windows and sunlight.

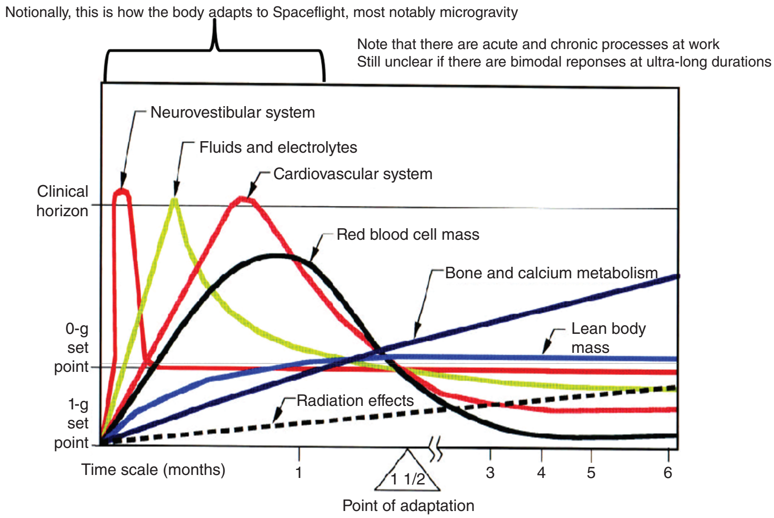

Figure 1.1 Time Course of Physiological Changes During Weightlessness. Source: Adapted from Ref. [5].

[8] To mitigate operational risk, EVAs are not scheduled within the first three days of a mission given the seriousness of the disruption to the performance capability of most crewmembers from the motion sickness and the medications used to treat it. This operational approach began with the Space Shuttle era and continues today for arriving crew on the International Space Station (ISS).

Once crewmembers adapt to the constant acceleration and lack of gravity during spaceflight, their symptoms abate, they function and navigate the environment well. While films from Apollo surface operations often captured astronauts falling, it is challenging to identify the role of contributing factors such as sensorimotor deficit, EVA suit configuration (high center of gravity), and EVA tool function to determine the most responsible contributor. Experience during microgravity operations on the Space Shuttle and ISS indicates that crewmembers adapt well within the first few weeks to the new environment and successfully accomplish tasks that require fine motor (e.g. cell culture and dissections experiments, telerobotics) and gross motor (e.g. EVA, unloading cargo) activities. The current countermeasures consist of medications to manage symptoms early in-mission and physical exercise such as walking and running on a treadmill and resistive training to engage sensorimotor and proprioceptive organs that lack stimulus in microgravity. While hard to quantify, the role of physical exercise is imperative to maintain physical, physiological, and psychological balance throughout the mission including landing and immediately postlanding which can be some of the most physically demanding aspects of the mission. This will be especially true during exploration class missions with landings on a distant planet such as Mars after a long transit in microgravity.

The process of re-entering Earth's atmosphere is a challenging event for the vehicle and the occupants. While the vehicle grapples with re-entering Earth's atmosphere, the occupants are experiencing g-forces in excess of 1 g depending on the configuration of the seating and angle of re-entry. The occupants are in suits designed for re-entry as protection from a rapid decompression, restrained by harnesses, and in various seated configurations (recumbent, conformal, upright, etc.). The neuro-vestibular and sensorimotor systems (NV/SM) experience the return to gravity in many ways based on the re-entry scenario and landing site, land or ocean, make the immediate postlanding period challenging to evaluate given the variety of provocative stimuli. Immediate postlanding evaluations of crewmembers from US and Russian space vehicles have included basic clinical neurological evaluations and structured multisystem research protocols. The postlanding evaluations have enabled the operational and research community to understand the timeline and challenges associated with the re-adaptation phase. While there is significant inter-individual variability, crewmembers experience both NV/SM symptoms (dizziness, nausea, vomiting, unstable gate, nystagmus, diminished visual target acquisition, reduced fine motor and gross motor function: [9–12]) postlanding that can be disabling for the first 24 to 48 hours with an asymptotic recovery (Figure 1.2e). It is important to know that recovery is facilitated by regular yet limited provocative movements in the new environment. Therefore, it is important for crewmembers to experience movement in 1g in a variety of axes, but it is equally important to accommodate rest and recovery to allow re-adaptation of the sensitive sensory organs of the inner ear [13, 14]. The postlanding data are crucial information to understand what the vehicle and the human are capable of during Earth landings with assistance and what they will need to be capable of when humans land on Mars for the first time completely unaided. The immediate postflight decrements in performance are informing current operations and research with respect to pre-flight conditioning, in-flight countermeasures, and postflight aides to enable a safe landing environment and an operational approach that is reasonable given the expected change in human capability during the transit portion of the mission to Mars.

The occupational health model for spaceflight indicates that the best course is to remove the exposure that causes the undesirable outcome and in the case of spaceflight associated neuro-vestibular and sensorimotor disruption that exposure is microgravity. One of the proposed solutions is the implementation of artificial gravity (AG) as a multi-system countermeasure [15]. The suggestions are for the whole vehicle to rotate (long-arm centrifugation) providing a living and working environment that has approximately a 1 g exposure or to have a module or portion of a module rotate (short-arm centrifugation) providing intermittent exposure to a gravity gradient for prescribed amounts of time. There have been research studies (e.g. Bedrest) of artificial gravity as a countermeasure, continuous (rotating room) or intermittent (short-arm radius), designed to describe and quantify the potential benefits and risks to humans [16, 17]. There have also been some preliminary engineering studies of AG estimating the cost and risk of implementing a rotating vehicle, module, or exercise hardware with a centripetal component. The low-fidelity nature of the engineering studies and human research of the physiological and functional benefit of AG have left the issue in a chronic state of discussion and speculation. A properly funded collaborative effort could provide a comprehensive set of objective data that would facilitate the ability to make a

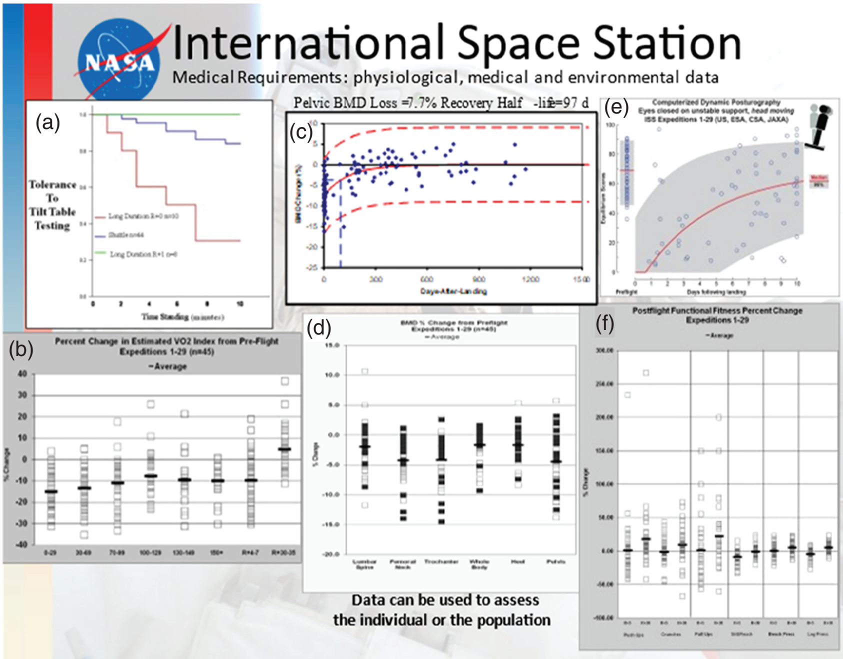

Figure 1.2 Pre- to Post-flight results from Multisystem Review of Inter-Individual Variability Among Astronauts, Fogarty 2016: https://ntrs.nasa.gov/citations/20160010832. Source: (a) NASA.

decision about the implementation of AG based on the risk mitigations benefits compared to risks it presents with respect to the engineering complexity and human experience.

1.5 Cardiovascular Adaptation

Much like the neurovestibular and sensorimotor systems, the cardiovascular system begins adjusting during launch as the body is exposed to an extended period in a recumbent seated position (crew on their back with legs up), various g-levels as the vehicle progresses through stages of flight, and the near absence of gravity within minutes of launch. The body begins adjusting the circulating amount of blood, plasma volume, due to sensors located in the upper chest perceiving an increased volume as a result of the headward (cephalad) shift of blood volume. Most of us have experienced this acutely when hanging upside down and even to a lesser degree when experiencing neutral buoyancy while swimming or diving. Without gravity, blood volume shifts toward the head, less volume is sequestered in the lower body and more easily returns to the heart while blood volume in the head experiences outflow resistance due to venous congestions on the way to the heart. This process leads to the puffy faces that you see in astronaut pictures since the additional volume causes an increase in pressure that exceeds the limits of the capillaries and plasma leaks into the tissue becoming trapped within and between cells creating swelling known as edema. Eventually some of that fluid will be removed by the lymphatics, a drainage system that parallels the venous system, and processed out by the kidneys with the residual remaining predominantly in the tissue of the upper torso and head. This fluid shift results in an absolute plasma volume loss of 10–20% over the first four to six weeks of spaceflight as crewmembers achieve a new normal plasma volume, normovolemia [19, 20]. This is possible because there is no gravity-induced hydrostatic gradient causing blood to collect in the lower body as it does on Earth and the cardiovascular system is capable of maintaining normal blood pressure accommodating metabolic needs of tissues at rest. However, this results in changes in vascular compartments and performance under stress like maximal exercise and exposure to gravity.

Components of the vascular system must adjust to the new plasma volume and the chronically reduced workload associated with living in the microgravity environment. Red blood cell (RBC) volume is acutely concentrated due to the rapid loss of plasma volume and RBCs are reduced to better match the spaceflight normovolemia maintaining proper viscosity. The venous system of the lower body begins a remodeling process that is associated with the lack of a hydrostatic gradient-induced column of blood in the lower limbs. This lower limb venous remodeling results in a reduction of sympathetic tone and loss of responsiveness to a blood volume [19]. So as with the absolute plasma volume loss, the relative RBC reduction and lower limb venous remodeling are not an issue during the microgravity portion of the mission unless there is a high aerobic capacity demand which has not occurred as a normal part of microgravity operations, but the demand is artificially created during exercise sessions to quantify a crewmember's aerobic capacity [25].

Aerobic capacity is the physiological metric of interest when assessing cardiovascular fitness that includes a role for metabolically active skeletal muscle. Changes to maximal aerobic capacity (VO2max; uptake of oxygen and production of carbon dioxide at a maximal workload) are often tracked to assess training, de-training, and fitness for duty. During long duration spaceflight estimated VO2max (based on heart rate versus workload as opposed to direct gas exchange) decreases 15–20% within the first month and recovers 5–10% during the mission, with plateau during months 2–6 [25]. This has not been an operationally relevant decrease since living and working in microgravity does not demand high workload, even microgravity EVAs are not a high total body workload, but it reflects the lost plasma volume and is very relevant for performance capability at landing especially in the scenario of self-egress and emergency evacuation of the vehicle. As expected in addition to neuro-vestibular disruption, aerobic capacity is significantly impacted immediately postlanding as the body struggles to adjust to gravity and plasma volume becomes sequestered in the lower body, both veins and tissues, and represents a state of dehydration. For long duration spaceflight, 80% of crewmembers experience orthostatic intolerance (OI) on landing day (Figure 1.2a), the inability to stand upright and maintain consciousness. Since dizziness, syncope, unsteady gate, nausea, and vomiting are symptoms of both NV/SM and OI, it is often difficult to identify the dominate cause of the postlanding inability to stand, walk, or run [30]. The current mitigation strategies, pre-landing fluid loading and lower body compression garment, have limited effectiveness and these symptoms significantly abate by 24 hours postlanding with OI having a quicker recovery than NV/SM.

Another critical cardiovascular component that remodels due to microgravity exposure is the heart. Without gravity exerting a force on the tissues of the body, blood flow to and from the heart is relatively unimpeded, and the heart does not have to produce the same contractile force as it does on Earth to maintain proper cardiac output. In addition, the heart is exposed to slightly lower intrathoracic pressures compared to that experienced on Earth [23]. Resistive and aerobic exercise can create an acute stimulus by redistributing blood volume to activated skeletal muscle and creating increased metabolic demand for oxygen supply and carbon dioxide removal. This exercise-induced demand may blunt the microgravity induced cardiac remodeling as indicated by spaceflight analog data but spaceflight missions have always included various forms and durations of exercise prescriptions so there is no spaceflight data to inform how extensive the remodeling could be. This cardiac remodeling is also central to another concern and that is the potential of arrhythmia or an abnormal heart rhythm.

Throughout spaceflight missions one of the main biomedical monitoring activities has been the electrocardiogram (ECG) to monitor the heart's electrical activity since it is a coordinated event necessary to elicit a proper cardiac contraction or heartbeat. Although crewmembers should be thoroughly screened upon selection and routinely monitored during their careers and training especially during the pre-launch period, abnormal heart rhythms can spontaneously develop with age or as a consequence of illness or even dehydration. Not all irregular heart rhythms are inherently dangerous and require context to understand their genesis as well as their potential to cause sudden cardiac death [21]. The concern has been that spaceflight as a unique physiological stressor may be a pro-arrhythmogenic environment. Although, irregular heart rhythms have been detected during early NASA missions there is no evidence that it has been caused by the complex environment of spaceflight but most likely by previously undetected presence of disease such as during the Apollo missions [24]. Subsequent missions have not demonstrated that crewmembers are more susceptible to arrhythmias during spaceflight compared to pre and postflight. The ongoing effort has been to establish a comprehensive baseline of ECG data for each crewmember at rest and during stress to compare over time to ECGs done during the mission for surveillance purposes. This process will provide context and allow interpretation of emerging cardiac rhythm issues, assessment of risk of a pathological process, and inform any treatment including something as straight forward as electrolyte replacement that is imperative before landing.

Immediately at landing the loss of plasma volume, changes to the vascular compartments, and (NV/SM) disruption in combination create an environment where the crewmember will have a measurable deficit compared to pre-flight in capabilities such as standing, walking, running, descending and ascending ladders, and operating vehicles. The magnitude and persistence of the deficit somewhat depends on the duration of the exposure to microgravity with longer spaceflights resulting in a greater degree of deficit and a longer persistence of the deficit (Figure 1.2a). While the effect is measurable at landing on Earth, there are questions about how this physiological adaptation will affect performance when crewmembers are exposed to partial gravity during planetary landings and EVAs. Of course we learned a great deal from the Apollo missions and have confidence that the short transit time will limit adaptation to microgravity and the exposure to lunar partial gravity will not be very provocative. Crewmembers will retain a significant amount of their pre-flight fitness and capability during short sortie-like missions. As lunar orbit and lunar surface missions increase in duration, as envisioned for the Artemis Program and the Moon to Mars initiative, it is unclear if partial gravity will have a mitigating effect on the adaptation to an extended duration microgravity exposure. Artemis missions, especially those later in the Program enabling long duration microgravity exposure followed by surface operations, will be invaluable to understanding the progression of adaptation and effectiveness of countermeasures for human system risks associated with exploration class missions like those proposed to Mars.

1.6 Musculoskeletal Adaptation a Tale of Disuse Atrophy and Remodeling

The human body is an amazingly energy efficient machine. Once a demand or stressor is removed the body will adjust supply. During spaceflight, the absence of gravity leads to biological processes that reduce the unnecessary muscle volume and bone density as it does in most Earth-relevant instances of disuse. The operational and research communities have been assessing changes in muscle volume and strength since the Apollo missions to understand the rate and persistence of the change to skeletal muscle and bone, but it has been challenging to relate any changes, particularly deficits, to a functional consequence. Astronauts and cosmonauts have been capable of completing mission objectives including EVAs, however, rarely are crewmembers required to self-egress upon landing and the off-nominal cases of self-egress in a crew of three have produced anecdotal evidence that only one of the three are capable of standing and often all three resort to crawling out of the vehicle and taking long periods of rest between activities until recovered. Therefore, the realistic concern is for future missions in which the disuse atrophy of both skeletal muscle and bone may progress given the extended duration of microgravity exposure and the workload demands on planetary surfaces may exceed the capability of the musculoskeletal system resulting in LOM or LOC.

While crewmembers' bodies adapt primarily to the absence of load in microgravity, new risks are created when the body is rapidly exposed to gravitational forces during landing and egress. Changes in muscle strength and volume have been studied during spaceflight for decades and not until recently have the changes been put into the context of the mission or expected tasks. The functional task test (FTT) has been a multi-disciplinary research effort to systematically assess and quantify changes in crewmember's performance starting immediately at landing and the recovery progression over several weeks [10, 11, 30]. The data analysis relates changes to the contribution of the various subsystems causing the pre to post deficits including NV/SM, cardiovascular, and musculoskeletal. Given the plasticity of the musculoskeletal system none of the changes appear permanent and crewmembers can recover both volume and strength with adequate training within weeks to months of return [27] (Figure 1.2f). This measurable change in muscle volume and strength can be mitigated with countermeasures such as resistance training and AG during the transit and at landing by having proper occupant protection to prevent landing injury and egress aids available to guide the crew. While skeletal muscle strength can be assessed and addressed in flight, it has been very challenging to get insight into bone density and only pre to post mission changes have been acquired to reflect back on how the mission has impacted that system.

Changes in bone mineral density (BMD) may put crewmembers at risk for fracture during deep space exploration missions but changes to BMD are monitored using pre and postflight dual-energy X-ray absorptiometry (DXA). Without insight into BMD loss during the mission it is difficult to know the true rate of loss. The current rate of bone loss is a simple calculation of the (Pre BMD – Post BMD)/duration of mission. This oversimplification has led many to believe that the loss rate is linear and would continue indefinitely for the duration of an exploration class mission of three years or more. This is not a reasonable assumption since we have observed crewmembers both female and male who have experienced varying mission durations such as extended ISS missions ranging from 8 to 12 months that have not demonstrated double the BMD loss as those who have had missions 4 to 6 months in duration. Unfortunately, this data has not been published due to the small "*n*" and inability to protect the identity of the subjects. It is more reasonable to hypothesize that the rate of BMD loss is asymptotic and does plateau at some point based on load exposure via countermeasures and genetics. It is still important to assess the projected loss of BMD and evaluate the mission objectives to understand the potential forces that will be encountered and the types of scenarios in which the forces might be applied to the skeleton (Figure 1.3).

To date regions across the entire skeleton are assessed and those with the most significant reductions in BMD are the trochanter, femoral head, and pelvis [26]

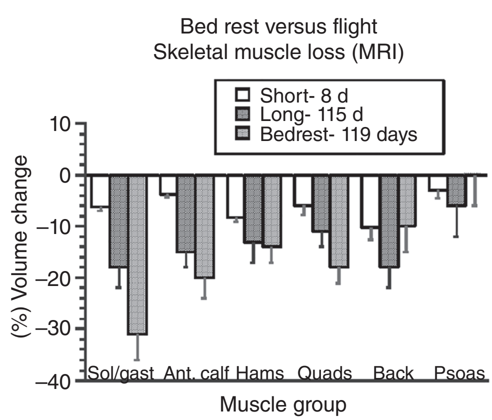

Figure 1.3 Percent change in selected muscle groups during short-duration (8 days; $n = 8$) and long-duration (115 days; $n = 3$) spaceflight (Mir 18) compared with long-duration bed rest (119 days). Data are from (LeBlanc et al. 1995; LeBlanc et al. 1992) and the Shuttle/Mir Final Report. [28].

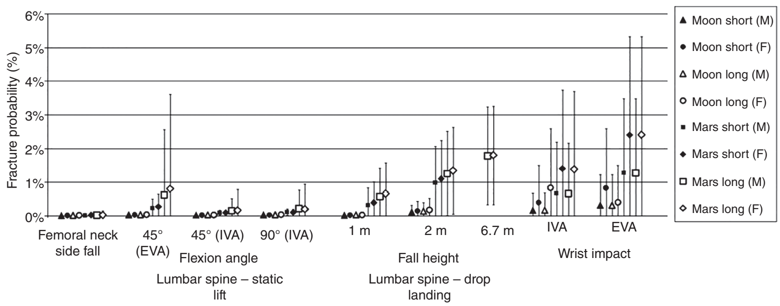

Figure 1.4 Fracture probability for astronauts during reference missions to the moon and Mars. Source: Nelson et al. [29], permission conveyed through Copyright Clearance Center, Inc. Republished with permission of Springer Nature.

(Figure 1.2c,d). Change in BMD for an individual overtime is a clinical surveillance tool and the results per bone region are compared to population norms for risk of fracture that include traumatic and atraumatic (or fragility) to be assessed. A complicating factor for crewmembers is that population norms for those younger than 65 are not robust and those comprising the population under 65 often have comorbidities. A unique effort sponsored by NASA [29] developed an astronaut fracture risk model and calculated the fracture risk for various missions (Figure 1.4). The results indicate that fracture risk varies by bone region based on the application of force and the mission duration aligning with greater BMD reductions.

One of the areas not specifically addressed by this model but still a significant area of research is the significance of the two different compartments of bone that are affected differentially by the BMD loss. Both the cortical and the trabecular compartments lose BMD, but the trabecular bone is disproportionately affected and also does not appear to fully recover [28]. Total BMD returns to pre-flight density due to the cortical bone exceeding its original volume to compensate for the loss of trabecular, however the trabecular bone plays a role in overall strength of the bone and the microarchitecture for the bone marrow. This differential response of the compartments has been challenging to assess due to applications of technologies that can elucidate these compartments and follow up over very long post mission time frames. Another complexity associated with the loss of BMD during spaceflight is the increased circulating calcium that increases the risk of renal stone formation [33]. If not prevented with hydration and potential manipulation of the urine pH, renal stones are a very serious and debilitating medical event that could be a contributor to LOM and, if left untreated due to an underprepared medical system, LOC [34]. Overall, in-mission countermeasures are necessary to maintain musculoskeletal health and fitness for duty given the expected rigors of planetary surface operations in addition to preventing unnecessary medical risks such as renal stone and fracture.

1.7 Multisystem Effects

Given that the human body is a system of systems, it is reasonable to treat all functions and outcomes as the product of multi-system interactions and with each action there will be opportunities and risks. While managing a complex endeavor like human spaceflight it is reasonable to articulate the known problems that drive requirements and factors of safety, the known unknowns that represent gaps in knowledge or technology and drive targeted research and development efforts, and the open space of the unknown unknowns that drive surveillance efforts and non-targeted research and data analysis. The first two categories drive formal programs that create bodies of work with budgets and schedules designed to culminate in quantifiable products that are delivered via requirements that can be debated and negotiated based on constraints such as time, money, launch mass capability, risk tolerance, etc. The third category is all about keeping your eyes and ears open and having some latitude to investigate or at least interrogate anomalies. It requires the ability to tolerate speculation and a rational approach to know if there is enough data available to constitute a real zero or a new gap. There are also many ways that unknown unknowns come to light and in the medical community they are often known as the sentinel case and often identified in hindsight.

Space Associated Neuro-Ocular Syndrome (SANS) is one of those non-targeted findings due to a sentinel case and now the most significant human finding of human spaceflight thus far this century. SANS represents how the body experiences the stressors of spaceflight and attempts to adapt using many compensatory mechanisms [35]. There is the pushing and pulling of fluid that drives conflict with organs and tissues that are very sensitive to pressure that attempt to autoregulate and at first succeed but overtime the mechanical forces prevail and the tissues succumb and remodel. The fluid shift that was mentioned earlier happens in all fluid compartments: blood volume (BV) and cerebral spinal fluid (CSF). The CSF and the brain shift up during flight, crowding the top of the skull where there are important veins to allow BV outflow. The CSF inundates the optic nerve stretching it and impacting the optic cup where it meets the eye and pressures in the tissues of the back of the eye are disrupted. The pressures exceed the tolerance of the tissues causing edema in the delicate choroid and retina. The choroid and retina begin to fold on themselves creating wrinkles that can affect vision but currently have not on orbit. The globe of the eye may flatten due to the CSF pressure in the optic nerve and/or the swelling of the choroid and retina. This flattening does affect vision to varying degrees and requires correction during the mission. One crewmember may have several prescriptions over the mission to address the evolving changes in eye shape. The venous outflow obstruction does not just exist at the top of the brain in the skull but is also functionally present in the neck and has been associated with blood clot-like formations found on ultrasound during a research study [36]. All of these findings have been unnerving at times and the community continues to find new ways to surveil for related changes as well understanding of the mechanisms. There has been extremely large inter-individual variability across the crewmembers and a large spectrum of presentations. Some aspects of the remodeling persist postflight and will forever be a scar on the individual who flew in space, and some aspects slowly return to the pre-flight state and show no long-term memory of the circumstances endured. There are also components of SANS that are still emerging given that the variety of case presentations has made understanding sensitivity and specificity challenging. A new emphasis has been placed on understanding the subtle anatomical brain changes in concert with functional outcomes. We are only now at the beginning of the long-term surveillance that is required to determine if spaceflight has forever changed the future of the health of crewmembers.

1.8 Vehicle-Induced Effects

The environmental control and life support system (ECLSS) is responsible for providing clean, breathable air at the appropriate temperature and pressure for human spaceflight. The provision of that environment and management of the air quality continues to evolve and be refined as new technologies are developed and tested. Selection and proper containment of materials used in the design of the vehicle and supplies are an important part of the process to prevent and control toxic exposures. Monitoring and surveillance are also present to alert the crew of a toxic release and indicate donning of proper protective gear while remediation occurs. Humans contribute carbon dioxide (CO_2) as a metabolic by product of respiration. The rate and quantity of production has challenged the current ECLSS system's capability to remove that CO_2 from the vehicle environment and that has challenged the human system with chronically elevated levels that contribute to physiological stressors of spaceflight. It has been difficult to quantify the contribution and studies using spaceflight analogs such as bed rest have not produced results that clearly identify the role CO_2 may be playing in spaceflight adaptation but there are several possible pathways that elevated CO_2 exposure may contribute that may worsen outcomes for crewmembers.

1.9 Conclusions

The abrupt g-transitions during and immediately following launch and landing induce some of the most provocative and short-lived disruptions to human health and performance and must be considered during the design of the vehicle and mission operations to enable not only survival but functionality during and after the transition is complete. As the duration of spaceflight has been extended such as that performed on the International Space Station, more substantial adaptations have been documented that persist after return to Earth and have various consequences as well recovery profiles.

Together the baseline health of the individual, the individual's response to spaceflight stressors, the ability to mitigate undesirable levels of adaptation, and the expected mission design and objectives are used to create a matrix of necessary information that can be used to assess the acceptable health status of the individual spaceflight participant. This chapter has provided the reader a limited overview of the human health findings in the context of vehicle and mission design from the historical short-duration spaceflight missions and the contemporary long duration missions as well as a perspective on the human health implications associated with the near future lunar orbit and surface missions. There are many more adaptations to discuss and elaborate upon including immunological, psychological, and psychosocial as well as more system level issues to debate such as food and nutrition, augmented and virtual reality, bioregenerative ECLSS with plants, and a well-informed crew medical system that can perform in-mission surveillance, diagnostics, crew medial decision support. Given the complexity of human exploration of space, the design and development transcends the concept of an enabling vehicle and approaches the concept of an exoplanet. To be successful, we must understand and respect the ecosystem required to support the most complex exploration endeavor attempted by humans.

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