

Acclimation during space flight: effects on human physiology

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∞ See related review by Thirsk and colleagues, page 1324

Patients on earth with illness can be described as people who live in a normal earth environment but who have abnormal physiology. In contrast, astronauts are people with normal physiology who live in an abnormal environment. It is this abnormal environment in space that, for the most part, causes unique alterations in astronauts' physiology that require the attention of clinicians and scientists. In this review, we build on the first article¹ in this series and provide an overview of the many complex physiologic changes that take place in short- and long-duration space flight, most often in response to microgravity.

The goal of sending people farther into space and extending the duration of missions from months to years will challenge the current capabilities of space medicine. The knowledge and experience in bioastronautics, associated with almost 50 years of human space flight, will be critical in developing countermeasures and clinical interventions to enable people to participate in these missions and return safely to earth.

Evidence

To complement our first-hand experiences from space (collectively over 2000 hours), we reviewed technical and special publications from the National Aeronautics and Space Administration (NASA) and peer-reviewed medical literature. Most of the literature in this field is made up of case series and descriptive studies. In this article, unreferenced statements reflect our opinions as physician-astronauts who have observed first-hand the physiologic acclimation to microgravity. Our clinical experiences as crew medical officers have also been incorporated where applicable.

Acclimation

Acute changes in normal physiology in response to abnormal environments are labelled acclimation for short-term exposure (hours to days) or acclimatization for longer-term exposure (days to months). In this review, we use the term acclimation to describe the physiologic and psychological responses to the space-flight environment. Table 1 provides a timeline of these responses from launch to the period after landing.

Microgravity has the largest effect of the space-flight environment on human physiology; all organ systems are affected

Key points

- Physiologic acclimation to space flight is a complex process involving multiple systems.
- Countermeasures before, during and after space flight are essential to reduce health risks.
- Although most physiologic effects resolve shortly after return to earth, bone demineralization may be a permanent consequence of long-duration space flight.
- The recovery period after a long-duration mission may be longer than the mission.
- Countermeasures to mitigate medical risk of long-duration space flight are being evaluated on the International Space Station.

to some degree. Isolation and confinement can also have important effects on the psychological well-being of astronauts. Table 2 outlines the key effects of the space-flight environment on humans and the countermeasures that are taken to address them.

Shift in body fluids

Acclimation of the cardiovascular system to weightlessness is complex and not completely understood. Control mechanisms involving the autonomic nervous system, cardiac functions and peripheral vasculature all play a role.^{20,21} However, the primary cause of these acclimations can be attributed to a redistribution of body fluids toward the head.²² The supine prelaunch position with the lower limbs raised above the thoracoabdominal coronal plane initiates a fluid shift, which continues during orbit, with blood and other fluids moving from the lower limbs to the torso and head. During space flight, the volume in the lower limbs decreases by about 10% (1–2 L of fluid from the legs' vascular and tissue space) compared with preflight.²³ The facial fullness and unique puffy appearance of the head coupled with reduced volume in the lower limbs associated with this fluid redistribution is referred to anecdotally as the "puffy face–bird leg" syndrome.

The difficulty acquiring data during the ascent and post-insertion (into orbit) phase of shuttle flight has resulted in the

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use of “6-degree head-down tilt” models to study cardiovascular changes in microgravity. The shift of fluid toward the head distends the baroreceptors of the central vasculature, which triggers suppression of the renin-angiotensin-aldosterone system, release of atrial natriuretic peptide leading to increased renal excretion of salt and water, and a net reduction in plasma volume.²⁴ The early cardiovascular changes associated with entry to microgravity differ from those observed in bedrest models,²⁵ suggesting a more complex process of acclimation.

The first 24 hours of space flight are characterized by a 17% reduction in plasma volume that results in transiently increased levels of hematocrit. This appears to cause a decrease in erythropoietin secretion,²⁵ leading to a reduction in the mass of red blood cells. The net effect is an overall reduction of about 10% in total blood volume.

Aerobic capacity can be maintained or improved in space, but it is decreased in the postflight phase largely because of reduced stroke volume and cardiac output in response to the orthostatic challenge of reacclimation to gravity.²⁶ Redistribution of body fluids with pooling of blood volume back in the vasculature of the lower body in association with reduced intravascular blood volume contributes to landing-day orthostatic stress. Typically, 1 out of 4 astronauts is unable to stand quietly for 10 continuous minutes within hours of landing because of light-headedness, heart palpitations and syncope.

Countermeasures during space flight focus on exercise to maintain aerobic capacity with a number of techniques and devices to redistribute body fluids before landing (Table 2).

Space motion sickness

Most astronauts experience symptoms of neurovestibular acclimation during the first 1–2 days after arriving in space. There is a similar period of reacclimation to gravity upon return to earth at the end of a mission. The predominant symptoms include facial pallor, cold sweating, stomach awareness, nausea and, in some cases, vomiting. The term space motion sickness has been used to describe this syndrome.²⁷ The broader syndrome of space acclimation includes space motion sickness, facial fullness, headache and lethargy.

Terrestrial motion sickness typically occurs when there is a mismatch between the visual and neurovestibular perception of motion. Many astronauts report alterations in perception while working in the unique weightless, 3-dimensional environment of space where there is no up or down; these aspects of space may contribute to space motion sickness.

The redistribution of body fluids that occurs on entry into microgravity is thought to account for some of the early symptoms, and it may produce transient benign intracranial hypertension.²⁸ The range of reported symptoms is most likely because of a complex interaction between the autonomic nervous system and the gastrointestinal system,²⁹ as well as neurovestibular³⁰ and cardiovascular changes.^{31,32}

Typically, space motion sickness is a short-lived phenomenon, with rapid improvement over the first 2–3 days of a mission. Occasionally, some astronauts take longer to overcome the symptoms. In very rare cases, a crew member has been incapacitated by motion sickness for the duration of a shuttle mission.

Table 1: Timeline of physiologic acclimation and acclimatization experienced by astronauts from launch to after return to earth

Physiologic effects	Launch	Duration of flight				Landing	Postflight period			
		24 h	48 h	2 wk	> 1 mo		24–48 h	1–2 mo	> 1 yr	
Fluid redistribution	<ul style="list-style-type: none"> • Redistribution of fluid to the torso and head • 10% decreased fluid volume in the legs 	<ul style="list-style-type: none"> • 17% reduction in plasma volume 	<ul style="list-style-type: none"> • Gradual decrease in erythropoietin secretion, leading to a 10% decrease in total blood volume 		<ul style="list-style-type: none"> • Orthostatic hypotension from pooling of fluids in the legs 	<ul style="list-style-type: none"> • Return of normal fluid distribution 				
Neurovestibular effects	<ul style="list-style-type: none"> • Space motion sickness 				<ul style="list-style-type: none"> • Space motion sickness 					
Muscle changes		<ul style="list-style-type: none"> • Gradual decrease in muscle mass by 20% 	<ul style="list-style-type: none"> • Gradual decrease in muscle strength (up to 50% loss observed) 		<ul style="list-style-type: none"> • Gradual decrease in muscle mass by 30% 	<ul style="list-style-type: none"> • Muscle soreness and tightness 	<ul style="list-style-type: none"> • Full recovery of muscle mass and strength 			
Bone demineralization		<ul style="list-style-type: none"> • 60%–70% increase in calcium loss (urinary, fecal). Reduced parathyroid hormone and vitamin D production. • Gradual loss of bone density (1%–2% per month) 						<ul style="list-style-type: none"> • Complete or almost complete restoration of bone density 		
Psychosocial effects	<ul style="list-style-type: none"> • Fatigue, sleep debt, isolation, emotional effects, stress to the astronaut’s family, multicultural crew environment 									
Immune dysregulation		<ul style="list-style-type: none"> • Possible reactivation of latent herpes viruses and impairment of cell-mediated immunity 			<ul style="list-style-type: none"> • Numerous cellular and other changes leading to impaired immunity 		<ul style="list-style-type: none"> • Gradual improvement in immunity (days to weeks) 			

Similar neurovestibular acclimations are noted after landing and persist for the first 1–2 days in a gravitational environment. Orthostatic intolerance may contribute to a multifactorial syndrome after landing, which includes light-headedness, vertigo, gait disturbance and motion sickness. This condition has, in some cases, required intravenous drug and fluid administration. This constellation of symptoms after landing is of particular concern for astronauts on long-duration missions, for whom the magnitude of the symptoms is greater than for those on shorter missions. Neurovestibular changes are important because they affect crew performance in the final minutes of the mission during the critical landing phase and impair the ability of the crew to leave the space vehicle in an emergency situation after landing. The measures to mitigate space motion sickness are described in Table 2.

In the coming decades, humans will return to the moon and will ultimately begin to explore Mars. To prepare for these missions, it is critical that we develop countermeasures to prevent or reduce motion sickness associated with adapting to space and gravitational environments. Future missions will expose astronauts to 3 days of microgravity while in transit to the moon. Once on the lunar surface, they will adapt to the lunar gravitational force, which is 16% of that of earth. Some of the *Apollo* crew members experienced space motion sickness during acclimation to microgravity, but no symptoms of space motion sickness were reported during acclimation to lunar gravity.¹⁶ Neurovestibular countermeasures will be developed to optimize astronaut performance while adapting to lunar gravity and the 38% gravitational field of Mars.

Muscle atrophy

Muscles lose both mass and strength during space flight. The muscles most affected are the postural muscles that maintain our bodies upright in a gravitational environment. After a 2-week space flight, muscle mass is diminished by up to 20%.⁶ On longer missions (3–6 months), a 30% loss is noted.⁷

The fundamental cause of this muscle atrophy is the absence of gravitational loading on bones and muscles during space flight. Muscle unloading results in biochemical and structural changes. Additional factors that contribute to muscle loss may be suboptimal nutrition and stress.⁸

Gross muscle atrophy is paired with a reduction in the size, not the number, of muscle fibres. Protein synthesis in muscle fibres is decreased, and protein degradation is increased. In the new in-flight equilibrium state, protein synthesis is decreased by 15% compared with preflight, and fibre cross-sectional areas are reduced by 20%–50%.^{6,9} Type 2 fibres of the postural muscle groups seem to experience greater losses than type 1 fibres. Muscle biopsies after landing also indicate a phenotypic shift from type 1 to type 2 fibres, allowing the muscles to contract faster but resulting in more fatigue.^{6–8}

In concert with atrophy, muscles also lose strength. Following short flights, a 12% loss of peak knee extension torque was measured, and a 31% loss was noted after a long flight.⁷ The loss of volume and the loss of strength do not always correlate. After a 6-month mission, one astronaut lost 20% of calf muscle volume, while the explosive force of these muscles was decreased by 50%.⁹ The discrepancy between lost mass and de-



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Expedition 13 Flight engineer Jeff Williams exercises on a treadmill aboard the International Space Station.

creased force may be due to alterations of motor unit recruitment, the contractile apparatus, electromechanical efficiency or muscle damage. After 4 months in space, muscle mass and strength seem to reach a new steady state, although the elevated level of nitrogen excretion in the urine persists.^{6,8}

Following return to earth, astronauts' deconditioned muscles are once again loaded by gravitational forces. Astronauts then report muscle soreness, tight hamstrings and calves and, in some cases, symptoms of plantar fasciitis.^{6,7}

Preflight physical conditioning is used to optimize muscle strength and endurance, aerobic capacity and bone density before long-duration flights. The primary countermeasures against microgravity induced muscular changes are exercise during space flight and rehabilitation after landing (Table 1). Exercise during space flight is helpful, but it does not fully prevent muscle loss.^{8,9} Additional countermeasures must be developed for future flights because a required 2-hour daily exercise program consumes valuable resources on the International Space Station including oxygen, water, food and crew-time.⁸ Each astronaut returning from the space station

participates in an aggressive muscle conditioning and rehabilitation program. In most cases, muscle mass and strength are fully recovered after 1–2 months back on earth.⁷

Bone demineralization

Microgravity induces a loss of bone density. In the microgravity environment of space, astronauts are no longer stati-

Table 2: Countermeasures to minimize risks to astronauts before, during and after spaceflight

Physiologic effects; duration of flight	Before flight	During flight	After flight
Shift in body fluids (cardiovascular effects) Long and short duration	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Exercise • Negative pressure suits for the lower body (to mechanically induce an earth-equivalent body fluid distribution while in space) • On re-entry: isotonic fluid taken orally,² use of a pressurized anti-gravity suit to minimize fluid pooling in the legs, use of a liquid cooling garment, recumbent position for astronauts on long-duration missions³ 	<ul style="list-style-type: none"> • The use of midodrine (to counter postflight orthostatic intolerance) is being considered
Space motion sickness (neurovestibular effects) Long and short duration	<ul style="list-style-type: none"> • Neurovestibular conditioning (virtual reality, parabolic or aerobatic flights) • Antinauseant medications 	<ul style="list-style-type: none"> • Antinauseant medications⁴ (promethazine, scopolamine⁵) often given with dextroamphetamine to counter sedation 	<ul style="list-style-type: none"> • Intravenous antinauseant and fluid administration for severe postlanding syndrome
Muscle atrophy Long and short duration	<ul style="list-style-type: none"> • Resistance exercise program • Aerobic exercise program 	<ul style="list-style-type: none"> • Exercise (aerobic and strength) monitored and modified by on-ground medical support team^{6,7,8} • Others measures under consideration: electrical muscle stimulation, dietary supplementation with amino acids, artificial gravity (e.g., rotating spaceship)^{6,7,8,9} 	<ul style="list-style-type: none"> • Muscle conditioning and rehabilitation program, including a combination of adapted exercises, massages, icing and nonsteroidal anti-inflammatory agents
Bone demineralization Long and short duration	<ul style="list-style-type: none"> • 3 DXA scans per year 		
Long duration	<ul style="list-style-type: none"> • 2 DXA scans within 6 months after flight 	<ul style="list-style-type: none"> • Resistance exercises^{10,11,12} • Diet supplemented with calcium and vitamins D and K^{10,13} • Others measures under consideration: bisphosphonates; potassium citrate; parathyroid hormone; low magnitude, high frequency vibrations^{10,11,14} 	<ul style="list-style-type: none"> • 4 DXA scans over 3 years • Temporary restriction of some activities (e.g., flying high-performance jets)^{14,15}
Psychosocial effects Long and short duration	<ul style="list-style-type: none"> • Specific criteria for recruitment^{16,17} and specific behavioural competencies for assignment to missions • Didactic training, including teamwork in multicultural settings, and field-based training in leadership and followership skills 	<ul style="list-style-type: none"> • Individualized work schedules monitored by ground support crew, with 8 hours rest per day • Short-acting hypnotics (to prevent sleep loss and cumulative sleep deficit) and modafanil (to enhance performance after periods of reduced sleep) 	
Long duration			<ul style="list-style-type: none"> • Psychological debriefing sessions
Immune dysregulation Long and short duration	<ul style="list-style-type: none"> • Quarantine program • Restricted contact with general public for 1 week before flight 	<ul style="list-style-type: none"> • Daily exposure to artificial gravity¹⁸ and nutritional supplementation with nucleotides¹⁹ are being considered 	<ul style="list-style-type: none"> • Collection of biological samples to assess immune function

Note: DXA = dual energy x-ray absorptiometry.

cally loaded by gravity. Skeletal impact loads typically associated with running and walking on earth are greatly reduced or absent. Because skeletal remodelling is dependent on the level of strain within the bone, this absence of loading is significant.^{10,11,17} Other factors that may contribute to bone loss in space include low levels of light, resulting in decreased vitamin D3, and higher ambient levels of carbon dioxide, leading to respiratory acidosis.¹⁰

Bone demineralization begins immediately on arrival in space. During the first days of a mission, a 60%–70% increase in urinary and fecal calcium is noted,^{10,14} which continues throughout the mission. Bone resorption markers are increased in urine¹⁰ and the blood levels of parathyroid hormone and 1,25-dihydroxyvitamin D production are reduced.¹⁷

The loss of bone density is about 1%–2% per month in weight-bearing bones such as the lumbar vertebrae, pelvis, femoral neck, trochanter, tibia and calcaneus.^{10,12,14,15,33} In these regions, the loss of bone density after a 6-month stay on the space station is typically 8%–12%.¹¹ There are large differences in the loss of bone density between individuals, as well as between bone sites in a given individual. A voyage to Mars (a 2.5-year round-trip) would deteriorate bone to osteoporotic levels if no countermeasures were used. The loss of trabecular bone could be so great that osteoblasts would be unable to rebuild the bone architecture upon return to earth.^{10,11,14,17}

Preflight assessments of bone mineral density using dual energy x-ray absorptiometry and quantitative computed tomography have been used to evaluate changes in bone mineral density associated with long-duration missions aboard the International Space Station and to monitor the efficacy of rehabilitation after landing with resistance exercise and, in some cases, bisphosphonate therapy.

Following return to earth, the loss of bone density may continue. The recovery process is typically lengthy³³ and is frequently much longer than the time spent in space. Similar to patients on bedrest or with incomplete spinal cord injuries, bone recovery may not be complete for several years. Patients on long-duration bedrest experience similar patterns of bone loss and calcium balance (–180 mg/day) as astronauts, who experience elevated resorption markers, unchanged formation markers, decreased 1,25 vitamin D and calcium absorption, and increased serum ionized calcium.¹²

After returning to earth, astronauts are temporarily restricted from participation in some activities, such as flying high-performance jets because of the axial skeletal loading associated with high G forces.^{14,15} Most astronauts on long-duration missions to the International Space Station will fully recover their bone density within 3 years after flight. However, some astronauts will never regain preflight



NASA/courtesy of nasaimages.org

An astronaut is tethered to the Canadarm2 outside the International Space Station during mission STS-114.

levels,¹⁴ and the recovered bone may have different structure and mineralization.³⁴

There is concern that astronauts may become osteoporotic at an earlier age and that the risk of bone fracture may be increased.¹⁴ Fractures could theoretically occur during strenuous spacewalks or upon return to earth.¹¹ Furthermore, elevated calcium excretion increases the risk of kidney stone formation. Kidney stones have been reported following shuttle flights.^{10,11} Because it takes such a long time to regain lost bone mass after flight, the focus of countermeasures is on the prevention of bone loss during flight (Table 1)

Psychosocial effects

Astronauts possess a wide range of technical skills related to the objectives of the space mission and a repertoire of behavioural competencies that enable them to function in a multicultural crew setting. These competencies play a critical role in the psychosocial acclimation of an astronaut to space, where faults cannot be tolerated.³⁵ The operational setting in which time-critical decisions with major consequences are required may contribute unique stressors to crew interactions throughout the mission, particularly during long-duration space flight.^{9,36} A number of these elements are presented in training for space-flight resource management. The same principles are directly applicable to medical practice, both to reduce errors and create peak-performing clinical teams.

Selection criteria for the recruitment of astronauts from the general population (“select-out”) and assignment of astronauts to specific missions (“select-in”) are used to prevent mission-critical behavioural issues.^{37,38} Extensive preflight training is used to develop “expeditionary behaviour,” a complement of space-related psychosocial skills that are typically associated with the success of missions. The ground-based

medical support team also works to maintain the performance of the on-orbit crew by providing behavioural support via video teleconferences with family, private psychological conferences and provision of recreational material such as DVDs, books and musical instruments.

The unique space-flight environment (e.g., temperature extremes, circadian dyssynchrony, acoustic noise) and operational requirements of long-duration space flight can contribute to fatigue and sleep debt. Scheduled uninterrupted sleep periods, noise-attenuated sleep stations and the intermittent use of short-acting sleeping medications or modafinil can reduce the amount of fatigue experienced by the crew and the deleterious effects on performance.

Although the emotional effects of space flight are mostly positive, they are profound.³⁹ These effects can be negative and may last long after a flight if a performance-related issue affects an astronaut during the mission. Fatigue, for example, increases an astronaut's probability of making an error and decreases the capacity of each crewmember to deal with adversity, frustration and interpersonal challenges.

Long-duration expeditions aboard the International Space Station are a major undertaking for the astronaut's family. The prolonged training phase and the international travel requirements add to the challenges experienced by the family. The prolonged stress of having a spouse or parent exposed to the time demands and risks associated with training and long-duration space flight can be deleterious to the well-being of the family. The astronaut's spouse must cope with all of the family and household responsibilities.

Support is provided after landing to astronauts and their families by behaviour health and performance teams. A multinational behaviour and performance working group has made a number of important recommendations to the International Space Station program to enhance crew performance.^{40,41} Many international partners have implemented family-support programs to help with the myriad issues faced by astronauts and their families.

The importance of developing the appropriate criteria for select-out and select-in decisions, as well as the training required to develop the necessary behavioural competencies for long-duration space exploration, will play a critical role in the future as we prepare to send people back to the moon and on to Mars.⁴²

Immune dysregulation

Immune dysregulation was first observed in astronauts following missions in the 1960s and 1970s. Half of the *Apollo* astronauts reported bacterial or viral infections that occurred during flight or soon after return to earth.⁴³ Blood samples drawn from 9 astronauts after flight from the Skylab Space Station showed that lymphocyte activation by mitogens was significantly reduced compared with that of preflight samples and samples from control people.⁴⁴

Much is known about astronauts' immune status immediately following space flight, but less is known about immunity during space flight. The few in-flight studies that have been performed indicate that space flight may be specifically associated with reactivation of latent herpes viruses⁴⁵⁻⁴⁷ and impairment of cell-mediated immunity.⁴⁸

Observations of astronauts' immune status after landing have shown numerous changes, including altered distribution of circulating leukocytes, altered production of cytokines, decreased activity of natural killer cells, decreased function of granulocytes, decreased activation of T cells, altered levels of immunoglobulins, latent viral reactivation, altered virus-specific immunity, expression of Epstein-Barr virus immediate-early/late genes, and altered neuroendocrine responses.⁴⁹

Immediate immune impairment before and after space flight probably reflects the very high levels of physical and psychological stress endured by astronauts at these times. Causal effects for impairment during flight likely include physiologic stress, isolation, confinement, disrupted circadian rhythms or other flight-associated factors. Increased circulating levels of glucocorticoids and catecholamines, a common occurrence during space flight,⁴⁶ may mediate changes in the immune system. The role of ionizing radiation on immune dysfunction is not yet certain. Weightlessness may also contribute to flight-associated immune dysregulation. In-flight and ground-based studies have shown that the lack of gravity impedes signalling pathways essential for early T-cell activation⁵⁰ and leads to alterations in the organization of the cytoskeleton and microtubule organizing centres.^{51,52}

Potential adverse clinical events that may be related to prolonged dysregulation of the immune system include hypersensitivities, autoimmunity, allergies, infectious diseases, latent viral reactivation and even malignant diseases. Bacteria that were recently cultured in-flight were found to have significantly increased pathogenicity.⁵³ We need to determine the clinical risk related to immunity and space flight before initiating missions to the moon and Mars.⁵⁴

Most of our knowledge is limited to low earth orbital flights of short duration. Very few of the incidents of infectious disease during space flight⁴⁹ have jeopardized a mission. Nevertheless, countermeasures for before takeoff have been developed, including verification that astronauts' hematological and immunological function are within normal ranges for healthy people, as well as a quarantine program to reduce exposure of the crew to communicable diseases (Table 1).

Future considerations include exposing astronauts to earth-like gravitational forces while onboard a spacecraft. Daily exposure to artificial gravity by use of short-radius centrifugation has been shown to be protective against immune dysfunction and other adverse physiologic changes (musculoskeletal, cardiovascular) associated with weightlessness.¹⁸

Conclusion

Space physiology and medicine is a young discipline that has made great strides in the first half century of human space flight. We have a good understanding of the medical problems associated with short-duration space flight, and have successfully developed countermeasures. The new challenge is long-duration space flight. Clinicians are currently refining the delivery of medical care for astronauts who live for longer periods aboard the International Space Station. They also seek to better understand the medical issues that future astronauts will face when we venture back to the moon and eventually on to Mars.

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