HIGH SCHOOL EDITION
Journal of Student Research
Volume 12 Issue 3 (2023)

Effects of Microgravity on Astronaut Physiology in Long-Term Space Missions and Proposed Countermeasures

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ABSTRACT

The interest in long-term space travel (>6 months) has gained popularity in the space community after multiple short-term missions exploring the Moon and Mars since the 1970s, to understand true habitability and early developments of long-term space settlements. With new missions being proposed by major pioneers in aerospace, such as NASA, SpaceX, and JAXA, scientists are concerned with human health, especially the long-term effects on health. Long-term settlements have been hypothesized to have major short-term and long-term detriments to multiple physiological systems, most notably musculoskeletal, cardiovascular, and neurophysiological. This is because of microgravity (negligible gravity); however, more experimentation must be conducted to understand these effects sufficiently. So far, scientists have linked microgravity to decreased osteoblastic differentiation, rapid bone loss, and increased risk of kidney stone formation in the musculoskeletal system. Additionally, the cardiovascular system is impacted by space anemia, which is hypothesized to be reversible but may induce detrimental effects. Finally, microgravity affects the vestibular system significantly, especially spatial recognition. Countermeasures have been proposed to reduce these effects like inducing artificial gravity, administrating bisphosphonates and other drugs/therapies, and utilizing tactile aids. The long-term effect of microgravity is still an emerging topic of space research, and much more research must be conducted through various programs like AGBRESA to fully understand long-term results better.

Introduction

With the focus of space travel set on Moon and Mars travel and long-term settlements, an important question is posed: what are the effects of space and space travel on astronauts? Specifically, astronauts undergo *microgravity*, which is near negligible gravity (<0.1g) due to the large distance from nearby planets (high radii decrease the force determined by Newton's universal law of gravitation $F_g = \frac{Gm_1m_2}{r^2}$ due to the inverse relationship.) Due to the shortage of previous long-term settlements and missions and research conducted during such missions, little is known about microgravity's effects on humans, specifically their physiology. However, it is now essential to understand adverse health effects as scientists propose missions longer than 6 months. Previous research has studied humans and other vertebrate subjects on the International Space Station (ISS) and artificial gravity simulations. Other papers have attempted in vivo ("research done with or within an entire, living organism") and in vitro ("work that's performed outside of a living organism") simulations to collect accurate results on different physiological systems. This paper discusses the effects of microgravity on astronauts' musculoskeletal, cardiovascular, and neurophysiological systems, as well as current proposed countermeasures such as centrifugal gravity simulations, clinical medicine such as bisphosphonates, and tactile aids.

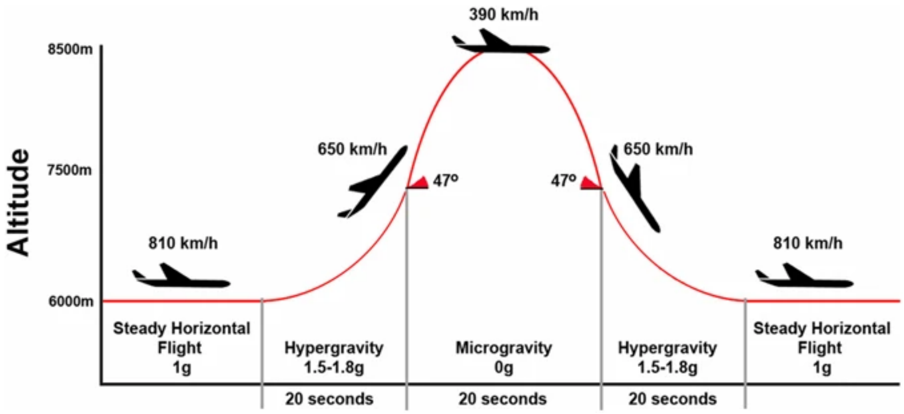

Figure 1. Flight trajectory during the parabolic manoeuvre at varying levels of gravity. (Van Ombergen et al., Scientific Reports, 2017)

Effects on systems

Musculoskeletal System

Research links the connection between decreased bone density and microgravity. As Jeffrey Sutton, the director of the National Space Biomedical Research Institute, and Nitza Cintrn, chief of NASA's Space Medicine and Health Care Systems Office, note, "Space is a harsh environment that affects the body in many ways. In microgravity, bone loss occurs at a rate of 1 to 1.5 percent a month, leading to an acceleration of age-related changes similar to osteoporosis." (Sutton, 2005) Additionally, it has been proven that the rate at which this change occurs is faster than what is typically found in aging. (Juhl IV et al., 2021) This is especially important for astronauts, who may spend months or even years in space. While astronauts may undergo exercise programs and other interventions to help counteract the effects of microgravity on their bones, the risk of bone loss remains a significant concern for long-duration space missions. It is worth noting that bone loss may be restored after returning to baseline levels.

However, these connections were only hypothesized and researched in 2005, which led to a recent update in 2021 regarding scientific experimentation using in vivo and in vitro simulations due to the spike in interest in long-term missions. (Seladi-Schulman, 2019) Overall, research concludes that microgravity decreases bone mineral density, increases fracture risk, and increases the prevalence of a premature osteoporotic phenotype. (Juhl IV et al., 2021) This study provides a different perspective compared to previous studies concerning the musculoskeletal systems as it studies bone and skeletal muscles with regards to each other to truly understand microgravity's and gravity's effects on the musculoskeletal system, even though the bones and skeletal muscles are usually studied separately.

Bone marrow stem cells (BMSC) aid the formation of healthy bones by differentiating into cells that make up bone tissue. These include osteogenic lineage cells, which differentiate into osteoblasts that deposit minerals to repair bone tissue, and myogenic lineage cells, which differentiate into skeletal muscle cells responsible for generating movement and maintaining posture. BMSCs could also differentiate into adipogenic lineage cells that differentiate into adipocytes (fat-storing cells.) An excess accumulation of adipogenic cells can lead to increased health problems, usually resulting from aging and sedentary adults, including diabetes and cardiovascular disease. It has been proven that exposure to microgravity "leads BMSCs to preferentially differentiate to adipogenic lineage cells as opposed to the osteogenic or myogenic lineage cells." (Juhl IV et al., 2021) This makes it more difficult for the body to adapt to the changes and stresses induced by microgravity. Damaged bones also are harder to repair due to the lack of osteogenic lineage cells.

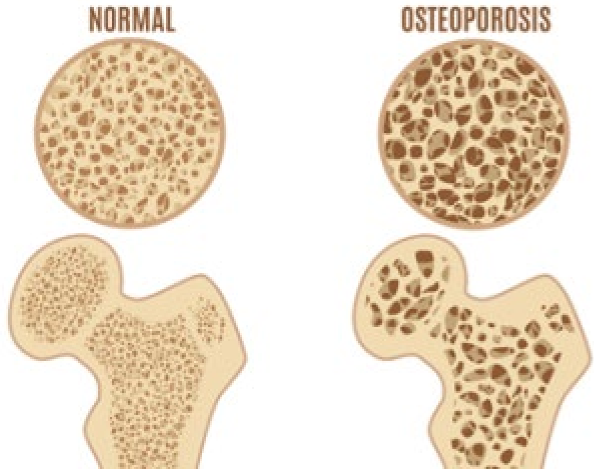

Figure 2. Normal bone vs. osteoporosis bone affected structure. (National Institute on Aging, n.d.)

The in vitro section of the study involves analysis of the effects of microgravity on cells "in and on constructs." (Juhl IV et al., 2021) These commonly used methods such as rotary cell structure systems (slow-rotating liquid-filled containers approved by NASA as artificial gravity simulators), Clinostats (tube-like structures that spin rapidly to simulate artificial gravity exposure), and random positioning machines ("two motor-driven frames that allow cells and constructs to be freely rotated.") Simulated microgravity generated by the in vitro studies prove that microgravity can decrease cell nucleus size and reduce expression of cytoskeletal and musculoskeletal proteins. Progression of the cell is also disrupted, leading to a "decreased osteoblastic differentiation seen in microgravity." These changes seem to be long-term as the negative impacts are not restored post-flight. It is clear that the gene expression associated with bone formation is decreased (*Alpl, Col1a1, Runx2,* and *Sparc*) and gene expression associated with adipogenesis is increased (*Ppar-γ, Cfd, Lep,* and *Glut-4*.) (Juhl IV, 2021)

Furthermore, a decrease in calcium concentration has been linked to microgravity generated bone loss that rapidly occurs in space. (Whitson, n.d.) Calcium (Ca^{2+}), which assists in bone health, is passed in urine in high concentrations, leading to an increased risk of kidney stones. If developed and left untreated, these kidney stones have the power to negatively impact mission success due to severe health consequences that cannot easily be treated in flight compared to on the ground.

As demonstrated by these studies, the musculoskeletal system is extremely impacted by the effects of microgravity, and these may reflect on other symptoms such as the formation of kidney stones.

Cardiovascular System

The cardiovascular system is mainly affected due to the lower rate and force at which the heart pumps blood. Unlike on Earth, where the heart must counteract gravitational forces, the heart in space pumps less often, resulting in reduced blood flow. According to NASA, due to the lack of gravity pulling blood and other bodily fluids down, less blood stays near the heart. It reaches as far as an astronaut's head in much higher quantities compared to that of Earth, resulting in major swelling. (Johnson, 2020) However, when astronauts return to Earth, especially after long periods of space travel, the heart is not used to this lower threshold and regularity, making it hard for astronauts to stand up without fainting. Gravity once again "pulls" these fluids back down, making it difficult to regulate this drop in blood pressure due to the loss of blood volume and the atrophy of the heart and blood vessels in space. This is commonly referred to as orthostatic intolerance: "this condition results from insufficient blood being pumped to the brain and reflects the adaptation of the cardiovascular system to micro-gravity." (Washington Aerospace Scholars, n.d.)

Orthostatic intolerance affects the autonomic nervous system reflexes that control the balance between heart rate and blood pressure, resulting in an abnormal situation for astronauts returning to Earth.

This phenomenon results in space anemia: the loss of blood cells. On Earth, humans normally create and destroy about 2 million red blood cells per second; however, in space, humans destroy more than 3 million red blood cells per second—a 54% increase. (Strickland, 2022) Space anemia has been recognized by researchers ever since the first space missions; however, the condition was initially perplexing. Like anemia, the lack of blood cells results in a condition where the body does not have enough red blood cells to carry oxygen to the body's tissues. To follow up with the study, recently, in 2022, researchers studied the breath and blood samples of 14 astronauts on a 6-month stay on the International Space Station, collecting samples four times during the flight. After careful analysis, scientists have concluded that there is increased blood pressure in the brain and eyes, causing a loss of 10% of the liquid in blood vessels. The liquid in blood vessels is called plasma, and it contains essential components such as water, proteins, electrolytes, and other substances that are necessary for maintaining blood volume and blood pressure. The loss of plasma may lead to hypovolemia, with symptoms including dizziness, lightheadedness, fainting, and even shock. Losing liquid in blood vessels can also affect the delivery of oxygen and nutrients to the body's tissues, leading to tissue damage and dysfunction.

After conducting another follow-up study measuring whether space anemia is reversible, scientists have concluded that “long-duration space missions could result in structural changes that impact red blood cells.” (Strickland, 2022) This poses a major problem when discussing long-term missions on the Moon and Mars. Although the loss of blood cells occurs and may be reversible in temporary missions, long-term structural missions may hinder the ability to restore health after returning to Earth. Better diets have been proposed to combat the effects of space anemia and structural change. Still, ultimately, more research must be conducted to identify the root cause of cardiovascular/blood changes and if structural restoration can be developed through preventative measures such as drugs and therapies.

Neurophysiological System

Microgravity affects the neurophysiological systems, most notably the vestibular system, which controls balance and spatial orientation. To perform properly, it senses the head’s position and movement concerning gravity and other external forces. Gravity is a vital constant and consistent force that aids in determining linear and rotational motion and acceleration. However, introducing low gravitational situations removes the constant force ingrained in external non-consistent forces, which originally acted much like a reference point. This makes it much harder to distinguish between linear and rotational motion, manifesting itself “as postural illusions, tumbling sensations, dizziness, and space motion sickness.” (Washington Aerospace Scholars, n.d.) According to a study conducted by Gualtierotti and colleagues (1965), when a bullfrog was put in a simulation of low gravity for short periods of time (20 s), its vestibular system responded by “exhibiting an immediate increase in activity when the animal was introduced into weightlessness, and activity recovered to baseline levels on return to 1g.” This study was followed up by Cohen (2005), who attests to similar findings in alert monkeys in spaceflight. The evidence presented by Gualtierotti and colleagues (1965) and Cohen (2005) suggests that animals, specifically bullfrogs and alert monkeys and possibly humans, have the ability to adapt to short periods of low gravity exposure by altering their vestibular system activity. However, it is important to note that these findings do not necessarily indicate how other animals or humans would adapt to long-term exposure to low-gravity environments, such as those experienced during extended space missions.

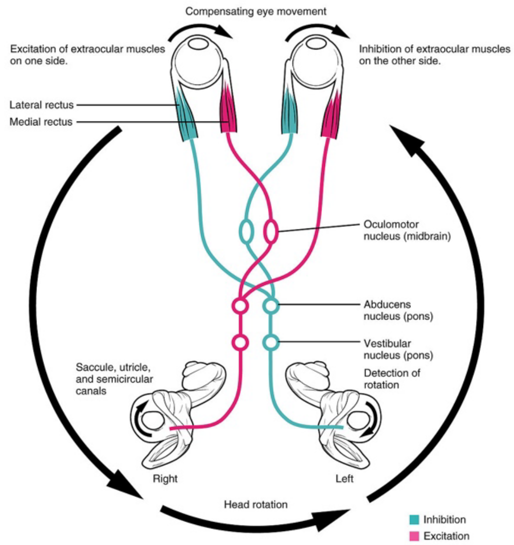

Figure 3. Vestibulo-Ocular Reflex. Eye compensation is closely tied to head rotation/motion. (Anatomy & Physiology, Connexions, 2013)

The abnormal vestibular response corresponds as the up-down directional concept does not apply to microgravity. Due to the lack of a reference point, there is no context as to how external forces and spatial markings relate as there is disorientation and conflict with the signals from the vestibular system: it is a “new spatial reality” controlled by only visual cues. (Washington Aerospace Scholars, n.d.) Astronauts must, therefore, learn to adapt to this "new spatial reality" and develop strategies to maintain their orientation and balance. One strategy astronauts use is relying on visual cues such as the position of the ceiling and floor to orient themselves. They may also use other visual cues like equipment, landmarks, and the position of other crew members to help them navigate and perform tasks.

In terms of spatial recognition, astronauts under microgravity can overestimate height and underestimate depth and distance. (Clément et al., 2020) This reduces the ability for hand-eye coordination, on top of being unbalanced physically. This can make it difficult for astronauts to judge distances when working with tools or equipment. Additionally, astronauts may struggle with tasks that require them to navigate in three dimensions, such as docking a spacecraft or performing a spacewalk. Eye-head coordination should also be equally considered. The vestibular-ocular reflex (VOR) is an essential component of eye and head coordination. It allows the eyes to maintain a stable image on the retina during head movements by producing an equal and opposite movement of the eyes in the opposite direction of the head movement. In terms of the long-term effect during flight, according to a 2017 study, “the mean time to visually acquire targets was 7-10% slower than mean preflight values,” describing the significant delay in eye coordination, impacting astronauts’ ability to perform tasks and maintain situational awareness. (Reschke et al., 2017) This is theorized to be “due to a decrease in velocity and amplitude of both the eye saccade and head movement toward the target.” However, these seem to be restored to baseline after 48 hours. (Reschke et al., 2017)

Proposed Countermeasures

For a long time, diet and exercise have been proposed as countermeasures, especially to combat a sedentary lifestyle in space. However, relying on simply these measures is not possible, especially since these changes in the physiological systems are often long-term. Three countermeasures have been identified: generating artificial gravity, consuming bisphosphonates and other drugs/therapies, and textile aids.

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Artificial Gravity

In 2016, The Japan Aerospace Exploration Agency attempted to use centrifugation to generate artificial gravity to counter weightlessness by subjecting a population of mice to continuous centripetal acceleration at the International Space System. (Clément et al., 2020) This has proven to provide some protection against adverse physiological effects, including "increases in apoptosis of retinal cells and changes in expression of proteins related to cellular structure, bone, and muscle mass, immune response, and metabolic function."

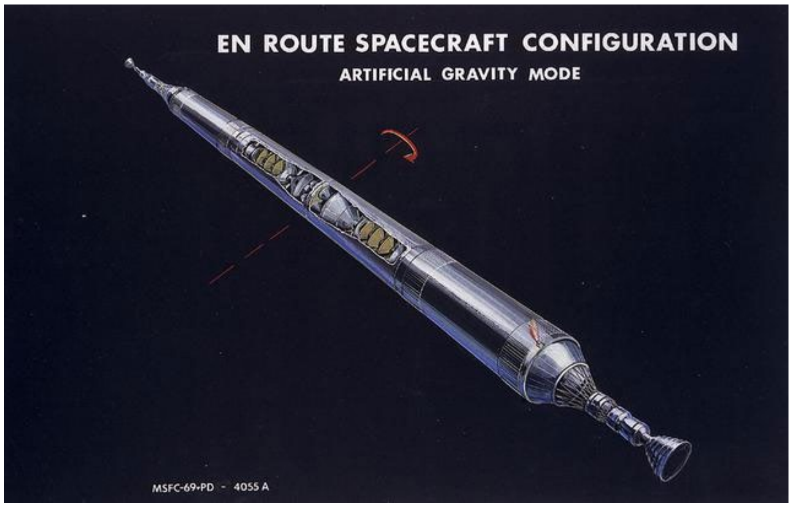

Figure 4. NASA's concept from 1969 for a manned Mars mission. Two planetary vehicles are joined together during the flight and rotated to provide artificial gravity for crew members. (NASA, 1969)

NASA has also been interested in this method of inducing artificial gravity. After conducting a bed rest study on Heather Archuletta (out of a series of bed rest studies), NASA scientists realized the effects of "space sickness." (Mars, 2019) Being tilted at -6 degrees with her head tilted, she mentioned any movement of her head induced nausea. This propelled them to partner with the DLR and the European Space Agency on a two-part study named the Artificial Gravity Bed Rest - European Space Agency (AGBRESA) that measured whether spinning was a counter to the body's physiological changes and whether it was better to spin continuously for 30 minutes a day or intermittently. Results have proved that the 30-minute exposure "to 1 Gz supine centrifugation mitigates bone loss in the femur and lumbar spine and lessens the effects of bed rest on aerobic capacity, biochemistry, and immunology." (Clément et al., 2022) With such recent studies highlighting the correlation between physiological health and induced artificial gravity, it is evident that this method will be used as a preventative measure in future long-term missions. However, using centrifugation in space comes with challenges and limitations. For example, the equipment required for centrifugation is heavy and bulky, posing challenges for launching and operating in space. Additionally, long-term exposure to centrifugation could have negative health effects, which would need to be carefully monitored and studied through similar studies. Despite these challenges, using centrifugation as a countermeasure to the negative effects of microgravity is an exciting area of research due to its promising efforts in significantly improving astronaut health and safety during long-duration spaceflight. Further research will be needed to understand the potential benefits and limitations of this approach fully and to determine the most effective methods for implementing centrifugation in space.

Bisphosphonates and other drugs/therapies

The Japan Aerospace Exploration Agency and NASA have also been involved in collaborative biomedical research to develop drugs that counter these adverse physiological effects. (Washington Aerospace Scholars, n.d.) As knowledge and research on osteoporosis increase, clinical treatments and drug development are becoming more relevant, especially bisphosphonate. Being relatively cost-effective, "bisphosphonates work directly on bone by limiting the formation and action of bone-resorbing osteoclasts." (Juhl IV et al., 2021) Generally, they have shown high efficacy in hindlimb unloading and spaceflight studies. Promising results were exhibited when astronauts were subjected to a study that recorded the results of "seven astronauts receiving weekly oral bisphosphonates (alendronate) and combined exercise treatments (treadmill, cycle ergometer, and a resistance exercise device (aRED))." Those who received the oral drug demonstrated no bone loss, whereas those who only relied on the intensive exercise program showed some bone loss. Anti-RANKL therapies work similarly, as proven by a study that measured the efficacy of the OPG-Fc antibody (RANKL inhibitor) on female mice. Those that were given the treatment resulted in reduced bone loss compared to those that weren't. Bisphosphonates and anti-RANKL therapies are promising; however, more research must be conducted in long-term spaceflight to determine true efficacy and safety results. (Juhl IV et al., 2021)

Potassium citrate has been identified as a method to combat the risk of developing kidney stones. Due to the higher concentration of Ca^{2+} in urine, NASA researchers analyzed the effect of potassium citrate in flight as it had previously been proven to "minimize calcium-containing renal stone development on Earth." (Whitson, n.d.) After examining astronauts in an International Space Station study for 30 days, it was clear that those who consumed potassium citrate showed decreased urinary calcium excretion and the risk of uric acid stones. NASA has also developed an efficient way to measure the urine production of crew members, which is vital due to the important bio-information gained about a person's health. This can allow dieticians/physicians to modify health plans or other routines (diet, exercise routine, water intake) based on their likelihood of developing a kidney stone. (NASA Human Research Program, 2021)

Tactile Aids

Visual or tactile aids have also been considered to assist with orientation. Since it is difficult to stabilize orientation after landing, scientists have proposed tactile spatial awareness systems, which "use small tactors attached to the torso that vibrate when the body tilts relative to gravity, alerting the subjects when their body is misaligned." (Clément et al., 2020) This method allows astronauts to regain proper alignment more easily post-flight as they don't have to rely purely on visual cues or references in flight to maintain proper alignment and balance. In fact, research provided that tactile feedback "has restored their early postflight performance to the level of their performance before the mission," making this an effective tool to combat postflight orientational problems. (Clément et al., 2018)

Conclusion

Microgravity has a significant effect on multiple physiological systems, including the musculoskeletal system (decreasing bone health and increasing risk of kidney stones), the cardiovascular system (increasing orthostatic intolerance and space anemia), and the neurophysiological system (negatively impacting the vestibular system and spatial recognition.) To combat these adverse effects to set the stage for long-term settlement missions on the Moon and Mars, many countermeasures have been thoroughly researched, including the induction of artificial gravity for bone health and immune response, bisphosphonates/anti-RANKL therapies for bone health and potassium citrate for reduction of kidney stone risk, and medical devices for misalignment complications post-flight. More research must continue to determine the long-term effects of said countermeasures to determine their safety and prolonged use.

Acknowledgements

I would like to express my sincere gratitude to Dr. Erik Hurlen from the University of Washington - Seattle, Department of Aeronautics and Astronautics, for providing valuable feedback, insight, and guidance on this review paper. Thank you to the Washington Aerospace Scholars' organizer Ms. Janice Crew for coordinating the program and curriculum.

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