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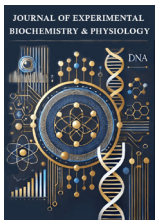

Effects of Spaceflight and Simulation on Hemoglobin Mass Regulation

Signe Berg*

[1]*Department of Health Sciences, University of Tromso, Tromso, Norway*

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Abstract

Spaceflight exposes the human body to unique environmental stressors, including microgravity, radiation, and altered atmospheric conditions, which can induce significant physiological adaptations. One well-documented consequence of spaceflight is a reduction in red blood cell mass, often referred to as "space anemia." Hemoglobin mass (Hb mass), a direct measure of the total amount of hemoglobin circulating in the blood and a key determinant of oxygen carrying capacity, is a critical parameter for assessing this adaptation. Studies utilizing techniques like Carbon Monoxide (CO) rebreathing have consistently demonstrated a decline in Hb mass during and after space missions, with the magnitude and duration of the reduction varying depending on mission length and individual factors. This decrease is primarily attributed to suppressed erythropoiesis (red blood cell production) and potentially increased red blood cell destruction early in flight. Ground-based analogs, particularly Head-Down Tilt Bed Rest (HDTBR), have been widely used to simulate the effects of microgravity and investigate the underlying mechanisms. HDTBR studies have largely replicated the spaceflight-induced decline in Hb mass, providing valuable insights into the roles of fluid shifts, reduced mechanical loading, and hormonal changes in regulating erythropoiesis. While significant progress was made in characterizing these changes and identifying questions remained regarding the precise time course of adaptation, the long-term consequences of reduced Hb mass for crew health and performance during extended missions, and the efficacy of potential countermeasures. Understanding the dynamics of Hb mass regulation in these unique environments is essential for ensuring crew health and mission success in future space exploration endeavors.

Introduction

Human space exploration presents a formidable challenge to physiological homeostasis. The transition from Earth's gravitational environment to the microgravity conditions of space triggers a cascade of adaptations across multiple physiological systems, including the cardiovascular, musculoskeletal, neurovestibular, and hematological systems [1,2]. Among these adaptations, changes in the red blood cell compartment have been a subject of scientific inquiry since the early days of spaceflight. The phenomenon of reduced red blood cell mass during spaceflight, often termed "space anemia," was initially observed in astronauts returning from even short-duration missions [3,4]. This reduction in circulating red blood cells directly impacts the blood's oxygen-carrying capacity, which is primarily determined by the total amount of hemoglobin (Hb) in the body the hemoglobin mass (Hb mass) [5]. Hemoglobin is the protein within red blood cells responsible for binding and transporting oxygen from the lungs to the tissues. Maintaining adequate oxygen delivery is critical for cellular function, tissue viability, and overall physiological performance, particularly during physically demanding tasks [5].

Understanding the changes in Hb mass during spaceflight is therefore paramount for assessing crew health, predicting performance capabilities, and developing effective countermeasures to mitigate potential risks, especially for longer-duration missions to the International Space Station (ISS) and future voyages beyond low Earth orbit [6]. Ground-based simulation models, particularly Head-Down Tilt Bed Rest (HDTBR), have played a crucial role in space physiology research [7]. HDTBR mimics some of the key physiological effects of microgravity, such as cephalad fluid shifts and reduced weight-bearing, making it a valuable analog for studying cardiovascular deconditioning, bone loss, muscle atrophy, and hematological changes in a controlled environment on Earth [7]. Studies utilizing HDTBR have provided significant insights into the mechanisms underlying spaceflight adaptations and have served as testbeds for potential countermeasures before their implementation in space. We will discuss the methods used to measure Hb mass, the characteristic changes observed in space and during simulation, the hypothesized mechanisms driving these changes, and the implications for crew health and countermeasures.

∗**Correspondingauthor:** Signe Berg, Department of Health Sciences, University of Tromso, Tromso, Norway; E-mail: signe.berg@uit.no

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Measurement of Hemoglobin Mass

Accurately quantifying total circulating hemoglobin mass is crucial for understanding changes in the red blood cell compartment. Unlike hematocrit or hemoglobin concentration, which are influenced by plasma volume shifts, Hb mass represents the absolute amount of hemoglobin in the body and is a more stable indicator of red blood cell volume [5]. The gold standard method for measuring Hb mass involves the rebreathing of a known amount of Carbon Monoxide (CO) [5]. CO has a high affinity for hemoglobin and binds to it to form carboxyhemoglobin (COHb). By measuring the increase in blood COHb concentration after rebreathing a known volume of CO, and accounting for the amount of CO remaining in the lungs and dissolved in plasma, the total amount of hemoglobin in the body can be calculated [5]. This method is considered safe when performed correctly with small, controlled doses of CO and has been widely applied in both ground-based studies and during spaceflight missions [4,8].Red blood cells, were historically used but are more invasive and involve handling radioactive isotopes, making the CO-rebreathing method generally preferred, especially in the context of spaceflight [9]. The CO-rebreathing method, while robust, requires careful execution and calibration. Factors such as pulmonary diffusion capacity for CO and the presence of endogenous CO production need to be considered for accurate measurements [5]. Despite these considerations, the CO-rebreathing technique has provided the most reliable data on changes in absolute Hb mass during spaceflight and its simulations.

Changes in Hemoglobin Mass During Spaceflight

Studies conducted across various space programs, including those involving short-duration missions on the Space Shuttle and longer stays on the Mir space station and the ISS, have consistently demonstrated a reduction in Hb mass in astronauts. Early spaceflights showed evidence of decreased red blood cell count and hematocrit [3]. With the advent of the CO-rebreathing technique, more precise measurements of Hb mass became possible. Studies on Space Shuttle missions, typically lasting 1-2 weeks, revealed a significant decrease in Hb mass, often ranging from 5% to 15% within the first few days of flight [4,8]. This rapid decline suggested an acute mechanism at play, potentially related to initial fluid shifts or increased red blood cell destruction. Longer-duration missions on Mir and the ISS confirmed that the reduction in Hb mass persists throughout the mission, although the rate of decline may slow down after the initial phase [11]. Studies on ISS crew members spending several months in space reported Hb mass reductions that could reach 10% to 20% or more compared to pre-flight baseline levels [11]. The magnitude of the decrease appeared to be somewhat variable among individuals. Upon return to Earth, Hb mass typically begins to recover, but the process can be slow [10,11]. Full recovery to pre-flight levels can take weeks to months, depending on the duration of the mission and individual factors [11]. This prolonged recovery period highlights the persistent impact of the spaceflight environment on erythropoiesis.

The observed reduction in Hb mass during spaceflight is a key component of “space anemia.” While the term “anemia” usually implies a clinical condition with symptoms, the reduction in space is often an adaptation to the reduced oxygen demand in microgravity and the initial plasma volume expansion. However, the decreased oxygen carrying capacity could potentially impact performance during re-adaptation to gravity or during physically demanding tasks in space [12].

Hemoglobin Mass During Ground-Based Simulations

Head-Down Tilt Bed Rest (HDTBR) has been the most widely used ground-based analog for simulating the effects of microgravity on the hematological system. Studies using HDTBR have largely replicated the changes in Hb mass observed during spaceflight and have been instrumental in investigating the underlying mechanisms and testing countermeasures.HDTBR, typically conducted at a -6° head-down tilt angle, induces a cephalad fluid shift similar to that experienced in microgravity. This fluid shift leads to an initial expansion of plasma volume, which can transiently decrease hematocrit and hemoglobin concentration, even if red blood cell mass remains unchanged initially. However, prolonged HDTBR consistently results in a decrease in absolute Hb mass, mirroring the spaceflight findings [13,14].

The time course and magnitude of Hb mass reduction during HDTBR are comparable to those observed in spaceflight [14]. Studies ranging from a few days to several weeks or months of HDTBR have shown a progressive decline in Hb mass, with the rate of decrease being more pronounced in the initial phase [15]. For example, studies involving 60 or 90 days of HDTBR reported significant reductions in Hb mass, often in the range of 5% to 15% [16].The mechanisms underlying the Hb mass reduction during HDTBR are thought to be similar to those in spaceflight. The initial fluid shift and subsequent plasma volume regulation play a role, but the primary driver of the persistent decline in Hb mass appears to be a suppression of erythropoiesis [17]. This suppression is likely mediated by a decrease in the production of Erythropoietin (EPO), a hormone produced primarily by the kidneys that stimulates red blood cell production [18]. Reduced tissue oxygen demand in the supine or head-down position, coupled with potential changes in renal blood flow, may contribute to the decreased EPO production [19].

HDTBR studies have also investigated the role of other factors, such as inflammation, oxidative stress, and nutritional status, in influencing Hb mass changes [14]. While the primary mechanism is likely related to EPO suppression, these factors might play modulating roles.The ability of HDTBR to reproduce the Hb mass changes seen in spaceflight makes it a valuable tool for studying the physiological responses to microgravity and for evaluating the effectiveness of potential countermeasures aimed at preserving red blood cell mass.

Mechanisms Underlying Hemoglobin Mass Changes

The primary mechanism responsible for the reduction in Hb mass during spaceflight and HDTBR is a suppression of erythropoiesis, the process of red blood cell production in the bone marrow [20]. This suppression is largely mediated by changes in the levels and activity of erythropoietin (EPO).In microgravity and during HDTBR, the initial cephalad fluid shift leads to an increase in central blood volume and cardiac filling [21]. This can be sensed by the kidneys, which are the primary producers of EPO. The resulting increase in renal blood flow and improved tissue oxygenation (due to reduced metabolic demand in microgravity and the supine position) are thought to decrease the stimulus for EPO production [22]. Reduced EPO levels, in turn, lead to decreased proliferation and differentiation of red blood cell precursors in the bone marrow, resulting in lower red blood cell production.

While suppressed erythropoiesis is considered the main driver of the persistent decline in Hb mass, there is also evidence suggesting a potential increase in red blood cell destruction

(hemolysis) early in spaceflight [23]. The mechanisms for this are not fully understood but could involve mechanical stress on red blood cells due to fluid shifts or other factors related to the space environment. However, the contribution of increased destruction to the overall Hb mass reduction appears to be less significant than that of suppressed production over longer periods [24].Other factors that may influence erythropoiesis in space and during simulation include:

- **Inflammation:** Spaceflight is associated with changes in the immune system and inflammatory markers, which could potentially affect bone marrow function [25].
- **Oxidative Stress:** Increased exposure to radiation and other stressors in space could lead to oxidative damage, potentially affecting red blood cell lifespan or bone marrow activity [26].
- **Nutritional Factors:** Adequate intake of iron, vitamin B12, and folate is essential for erythropoiesis. While nutritional support is provided during spaceflight, subtle deficiencies or altered metabolism could play a role [27-30].
- **Carbon Dioxide Levels:** Elevated CO$_2$ levels in the spacecraft environment could potentially influence oxygen sensing and EPO production, although the precise effects are complex [31].

HDTBR allows for controlled investigation of some of these factors, but replicating the full spectrum of spaceflight stressors (e.g., radiation, altered atmospheric composition) on Earth is challenging.

Implications for Crew Health and Performance

The reduction in Hb mass during spaceflight, while often termed "space anemia," is typically not associated with overt clinical symptoms in microgravity due to the reduced metabolic demand and altered fluid distribution [32]. However, the decreased oxygen-carrying capacity can have implications for crew health and performance, particularly during specific mission phases and activities.

Re-adaptation to Gravity: Upon return to Earth's gravity, the cardiovascular system undergoes significant changes to readapt. The reduced Hb mass, combined with other factors like cardiovascular deconditioning, can contribute to orthostatic intolerance (difficulty standing up without feeling dizzy or fainting) and reduced exercise capacity. The body's ability to deliver oxygen to the muscles and brain is compromised, making the transition back to a 1-g environment more challenging [33].

Physical Performance in Space: While microgravity reduces the load on the musculoskeletal system, astronauts still perform physically demanding tasks, including exercise for countermeasure purposes, extravehicular activities (EVAs or spacewalks), and operational duties. A reduced Hb mass could potentially limit aerobic capacity and increase fatigue during these activities, although the extent of this impact can vary depending on the individual and the specific task.

Long-Duration Missions: For extended missions to the Moon, Mars, or beyond, the cumulative effects of reduced Hb mass over many months or years become a greater concern. The potential for chronic tissue hypoxia, impaired wound healing, or reduced resilience to other stressors needs to be carefully considered [34].

Understanding the functional consequences of reduced Hb mass is critical for setting appropriate medical standards for crew selection and for developing effective strategies to maintain crew health and performance throughout long-duration missions.

Implications for Crew Health and Performance

Given the potential implications of reduced Hb mass for crew health and performance, particularly during and after long-duration missions, the development and implementation of effective countermeasures have been a focus of space medicine research.

Exercise: Exercise is a cornerstone of spaceflight countermeasures for maintaining musculoskeletal and cardiovascular health [34]. While exercise in space helps mitigate muscle atrophy and bone loss, its effect on Hb mass is less clear. Some studies suggested that exercise might help attenuate the decline in Hb mass, possibly by stimulating erythropoiesis through increased metabolic demand, but the evidence was not entirely consistent [35]. Ground-based HDTBR studies incorporating exercise have provided mixed results on its efficacy in preserving Hb mass.

Nutritional Support: Ensuring adequate intake of essential nutrients for red blood cell production, such as iron, vitamin B12, and folate, is a standard practice [32]. However, simply providing these nutrients may not be sufficient to overcome the suppressed erythropoiesis driven by reduced EPO levels.

Pharmacological Interventions: The use of recombinant human erythropoietin (rhEPO) was considered and explored in ground-based studies as a potential countermeasure to stimulate red blood cell production [36]. However, the use of rhEPO in healthy individuals raises concerns about potential side effects (e.g., increased blood viscosity, thrombotic risk) and requires careful consideration of the risk-benefit profile in the spaceflight context [36].

Artificial Gravity: Exposure to artificial gravity, such as through centrifugation, is a potential countermeasure for multiple physiological systems affected by microgravity [37]. By reintroducing gravitational loading, artificial gravity could potentially restore the stimulus for EPO production and help maintain Hb mass [37].

Discussion

The significant impact of altered gravity on the erythropoietic system. The primary mechanism, suppressed erythropoiesis likely mediated by decreased EPO production, is well-supported by the available evidence. The initial rapid decline in Hb mass suggests an acute adaptation, possibly involving fluid shifts and early red blood cell destruction, followed by a more gradual reduction driven by chronic suppression of production. The value of HDTBR as a ground-based analog for studying spaceflight-induced changes in Hb mass is evident from the comparable patterns of reduction and recovery observed in both environments. HDTBR provides a controlled setting to investigate mechanisms and test countermeasures, although it does not replicate all aspects of the spaceflight environment, such as radiation exposure or psychological stress.These changes and identifying key mechanisms, several questions remained. The precise time course of adaptation in Hb mass during very long-duration missions (e.g., beyond one year) was not fully elucidated. The long-term functional consequences of reduced Hb mass for crew health and performance during extended exploration-class missions, particularly in combination with other physiological deconditioning, required further investigation. The optimal strategies and dosages for potential pharmacological countermeasures, such as rhEPO, needed careful evaluation

to balance efficacy with safety concerns. Furthermore, the potential for individual variability in the magnitude and time course of Hb mass changes and the factors contributing to this variability were areas of ongoing research.

Future research building upon the foundation should focus on longitudinal studies during extended space missions to better understand the long-term dynamics of Hb mass regulation. Investigating the interplay between the erythropoietic system and other physiological systems affected by spaceflight, such as the cardiovascular and musculoskeletal systems, is crucial for a holistic understanding of adaptation. Advanced molecular and cellular techniques could provide deeper insights into the regulation of erythropoiesis at the bone marrow level in response to microgravity. Continued research using ground-based analogs, incorporating multi-system countermeasures and novel technologies, will be essential for developing effective strategies to preserve Hb mass and ensure crew health and performance during future space exploration endeavors.

Conclusion

Humans experience a significant reduction in hemoglobin mass during spaceflight, a phenomenon largely replicated in head-down tilt bed rest simulation studies. This decrease is primarily driven by suppressed erythropoiesis, likely due to reduced erythropoietin production in response to altered fluid distribution and reduced metabolic demand in microgravity. While the "space anemia" is often an adaptation, the reduced oxygen-carrying capacity has implications for crew health and performance, particularly during re-adaptation to gravity and physically demanding tasks. Ground-based simulations have been invaluable for investigating the mechanisms and testing potential countermeasures. Despite significant progress, challenges remained in fully understanding the long-term dynamics of Hb mass changes and developing optimal strategies to mitigate the decline for future long-duration space missions. Continued research in this area is vital for ensuring the health, safety, and success of human space exploration.

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