TOPICAL: THE SCIENTIFIC RATIONALE TO STUDY THE EFFECT OF THE SPACE ENVIRONMENT ON HEMODYNAMICS, COAGULATION, AND VASCULAR MECHANOTRANSDUCTION

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I. Abstract

Changes in cardiovascular physiology due to microgravity include redistribution of blood from the lower to upper body; decrease in blood volume and pressure; vasodilation; and changes in heart rate. These changes manifest as orthostatic intolerance, spaceflight associated neuro-ocular syndrome, and recently reported incipient thrombosis, however, the underlying mechanisms are unknown. It is important that we understand the effect of spaceflight on cardiovascular physiology from the molecular, cellular, and organ-level perspectives to benefit flight crew and terrestrial cardiovascular health.

II. Introduction/Background

With the goal to increase the duration of space exploration missions, it is critical to understand the role of the space environment on the human body and organ systems. This is particularly true for the cardiovascular system, the hemodynamics of flowing blood which ultimately affects all the tissues throughout the body as well as overall crew health and functioning. On earth, there is a homeostatic state of blood flow, blood pressure, and vessel mechanics that is tightly regulated. During space flight microgravity or low gravity there is a significant redistribution of fluid in the tissues and extracellular spaces throughout the body. These adaptations induced by microgravity include hypovolemia[1], cardiac atrophy[2-6], and region-specific vascular remodeling[7-9]. Additionally, some of these adaptations may become maladaptive, notably leading to postflight orthostatic intolerance[6], sensory-neural adaptation, and spaceflight-associated neuro-ocular syndrome[10-12]. In general, mechanisms involved with microgravity induced cardiovascular adaptations include: 1) loss of hydrostatic pressure gradients within the fluid columns of the body (e.g., artery, veins, lymphatics, cerebrospinal fluid), 2) loss of bodyweight and mechanical loading, 3) decreased sensory inputs, and 4) changes in interstitial tissue pressures and compliance. In turn, the tissues (e.g., heart, arteries, veins, and lymphatics) and cells (e.g. endothelium, smooth muscle) of the cardiovascular system are affected. Increase in jugular vein, portal vein, and femoral vein diameter have been observed during spaceflight and microgravity analogs, which indicates venous pooling in cephalic, splanchnic, and pelvic regions.[13] This shift in blood volume is accompanied by an increase in venous blood pressure as well.[13, 14]

Recent evidence has also shown stagnant and retrograde (reversed) blood flow in the jugular vein, makes the astronauts susceptible to thrombosis or formation of blood clots without injury.[15] In 2019, approximately two months into an International Space Station (ISS) mission, an obstructive thrombus was revealed in the internal jugular vein of an astronaut during an ultrasound examination for a vascular research study.[15] The thrombus was treated with traditional anticoagulants while in space, and interestingly, only a small residual thrombus was revealed 24 h after landing which disappeared 10 days later. Although an isolated incident, this case study reveals fundamental differences in mechanisms of thrombosis between spaceflight and earth.[16] Since on earth, unprovoked isolated internal jugular vein (IJV) thrombosis is uncommon, this recent observation has brought to light the potentially serious consequences that disrupted hemodynamics can have in otherwise healthy astronauts.

Hemodynamic changes due to spaceflight may impact the biophysical and biochemical pathways which regulate the cellular and enzymatic systems responsible for cardiovascular homeostasis as we know on earth. This homeostasis is maintained by mechanoresponsive vascular cells, namely, the hematopoietic stem cells from which the blood cells originate, endothelial cells that line the vasculature, smooth muscle cells that make up the vessel wall, and the platelets, red cells, and immune cells that are in circulation during space flight. Endothelial and smooth muscle cells are active participants in the complex interactions that occur between flowing blood in the lumen and the cells comprising the vascular wall. The endothelium plays a pivotal role in the maintenance of vascular hemodynamics in both healthy and pathological states, and a great deal of work has been done to better understand the impact of microgravity on these cells. Vascular smooth muscle cells maintain integrity of the arterial wall, as well as contract or relax to change both the volume of blood vessels and the local blood pressure, a mechanism that is responsible for the redistribution of the blood within the body to areas where it is needed. Forces associated with blood flow significantly affect vascular tissue morphogenesis and vascular physiology. These forces are altered in space with subsequent effects on various vascular cellular pathways, such as mechanotransducers. Endothelial cells are flow-sensitive, and alterations in flow-mediated shear stress, as a result of altered hemodynamics while in space, contribute to or activate different phenotypic, biochemical, and inflammatory responses. Studies over the past two decades have shown that laminar flow is essential to maintaining a healthy endothelial phenotype while stasis or oscillatory flow switches endothelial cells to an inflammatory and prothrombotic phenotype. Further, both ground-based analog and space flight studies have shown that microgravity influences endothelial gene expression through miRNA-based regulation, as well as protein expression of various cellular pathways involved in regulating endothelial function, including endothelial nitric oxide synthase (eNOS).[17, 18] However, the combined effects of fluid shear stress and pressure (surface forces), substrate properties (surface stiffness and compliance), and microgravity (body forces) on endothelial mechanotransduction is not known. These signaling effects determine the endothelial fate, and therefore may have implications in both normal physiology of hemostasis, and pathophysiology of thrombosis during space travel. Furthermore, there are significant changes in the vascular smooth muscle, such as decrements in vasoconstrictor responsiveness and vascular remodeling, all of which will effect vascular function.[7, 19] The effects of microgravity and spaceflight on all other mechanoresponsive cells of the vasculature are currently unknown or poorly understood. Therefore, a more comprehensive understanding on the impact of these changes on vascular health is important.

Elucidating the mechanisms of the role altered hemodynamics plays in vascular health will not only benefit space travel but will also allow us to understand the importance of altered hemodynamics on earth. Data generated and studied in space flights will help guide risk assessment, preventive, diagnostic and therapeutic countermeasure strategies in spaceflights as well in extreme environments on earth.

III. Significance/Impact for crew health

There are several cardiovascular adaptations from microgravity exposure, such as orthostatic intolerance, reduced aerobic exercise capacity, elevated heart rate, hypovolemia, etc. We are also still discovering new adaptations, such as spaceflight-associated neuro-ocular syndrome, and as spaceflight missions become longer (e.g. up to 1-year crewed missions now), more frequent (e.g. commercial crew), and also plans for returning to the Moon and Mars (e.g. longer missions and new environmental exposures such as deep space radiation), there may be more adaptations that we may learn of and have to consider with relation to crew health. For example, most studies of cardiovascular health have focused on the heart; however, blood flow is regulated by the arteries, which we are learning have significant adaptations to microgravity and radiation, while comparably there is a paucity of data for lymphatic adaptations to the spaceflight environment.[20] Increasing our knowledge and awareness of cardiovascular adaptations to the spaceflight environment will not only lead to mechanistic insights on the effect of spaceflight on blood flow and mechanoresponsive vascular cells as well as blood cells, but also may reveal targets for countermeasure development and/or therapeutic strategies in flight. Technological advances in the future like mobile ultrasound and doppler to study cardiovascular physiology in orbit with real time data transmission will impact our understanding of spaceflight effects on human biology, in general. Countermeasure development may focus on strategies to reduce the disturbances/changes in hemodynamics or mitigate the deleterious effects. In addition, advancement in technology to detect blood flow disturbances will allow for better therapeutic strategies. Understanding how space travel affects hemodynamics is not only important for defining the risk of thrombosis, and hence countermeasures to alleviate this risk; but also, for defining the new hemostatic normal in space. This phenomenon has been long overlooked.[21]

IV. Implementation/Research Priorities

To achieve the goal to better understand the effect of space flight on hemodynamics, coagulation system, and mechanotransduction, and develop countermeasures, a robust multi-disciplinary approach is warranted. We recommend the following:

- Develop both on earth and space flight platforms to support in vitro biomimetic organ on a chip
- Robust characterization of appropriate animal models that mimic the cardiovascular changes (e.g. hindlimb unloading, partial gravity suspension)
- Hardware development to recreate physiological stimuli to address this issue (e.g. shear stress, pressure profiles, cyclic stretch)
- Infrastructure to obtain real-time on-orbit data on the dynamics of crew blood flow as well as biomarkers to indicate cardiovascular dysfunction.
- Infrastructure that allows for both short- and long-term measurements on hematologic and coagulation parameters, and functional studies (e.g. ultrasound scans and measurement).
- Doppler technology and advances in on-orbit microscopy for both cells and whole animals
- Development of on-orbit assays to detect cardiovascular changes
- Studies that compare the changes in cardiovascular and lymphatic flow during spaceflight
- Increased opportunities to conduct rodent research and multi-PI/team projects.
- Studies to assess changes in coagulation parameters in humans subjected to -6° head-down tilt, and orthostatic stress.
- Advanced imaging technologies like venous duplex ultrasound and magnetic resonance direct thrombus imaging.
- Ground based animal studies to assess changes in coagulation parameters, and response to hemostatic insults.
- Understanding the effects of spaceflight on hematopoiesis through ground-based analogs and in-flight studies
- Robust assessments of molecular level changes through transcriptomics, proteomic with reference to coagulation systems. Advanced molecular studies will help develop a

personalized approach for each individual with risk mapping for blood clots and therapy if required.

- A robust communication system supporting real time diagnostic data transmission and telemedicine units that can promptly resolve a medical crisis during long term missions with limited in-flight medical support.

As would be expected, this challenge is multidisciplinary and would benefit from input from researchers in the areas of cardiovascular medicine, mechanobiology, bioengineering, and pathology.

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