Topic 1: Effects of Spaceflight Durations up to One Year in Low Earth Orbit on Cardiovascular Structure and Function in Astronauts

Summary
Results of previous studies on the ISS have indicated that six months of spaceflight increase stiffness of the carotid and femoral arteries and insulin resistance in astronauts (Hughson et al., 2016; Arbeille et al., 2016). Other aspects of the cardiovascular system’s adaptation to weightlessness have been studied, including for example systolic and diastolic function, cardiac chamber size and wall thickness, risk of arrhythmia, and risk of coronary artery atherosclerosis. The health and clinical effects of these findings are currently being debated and tested in space, and it is not known, whether longer duration flights could augment them. In addition, the efficiency of the in-flight exercise countermeasures to protect the cardiovascular system against increased vascular stiffness as well as against cardiac atrophy for one year in space is not known.

The purpose of this topic is therefore to understand if there are augmented cardiovascular health risk effects of extending missions to one year on ISS and the temporal profile of cardiovascular adaptation.

Background
As described in detail in the NASA Evidence Report documenting the foundation for the Risk of Cardiac Rhythm Problems (Lee et al., 2017), previous astronaut population studies have attempted to establish whether astronauts, who have flown in space for up to six months, are more susceptible to cardiovascular disease and whether spaceflight per se is a cardiovascular risk factor. No studies to date have convincingly revealed that this is the case. To date, too few astronauts have presented with chronic diseases to perform an accurate analysis of the risk of cardiovascular disease morbidity. Therefore, analyses regarding cardiovascular disease have been limited to cardiovascular mortality. Interpretations of the data, however, should be viewed with caution considering the low number of astronauts and that only a few astronaut deaths can be attributed to cardiovascular disease.

Some recent studies, however, have indicated that spaceflight for months in low Earth orbit may induce oxidative stress to the cardiovascular system and thus at least theoretically predispose to development of cardiovascular disease. Previous work has documented increased carotid intima media thickness (Arbeille et al., 2016) and carotid artery stiffness (Hughson et al., 2016) from before to after long-duration spaceflight. A current study on the International Space Station by Lee et al. is the first to acquire in-flight vascular measures and oxidative stress and damage biomarkers to characterize the time course of spaceflight-induced adaptations as well as to measure the long-term effects on vascular health with measures extending out to five years after landing. Given that ionizing radiation is a potent source of oxidative stress and has been associated with cardiovascular disease, even at relatively low doses (Lee et al., 2017), this study of astronauts in low Earth orbit also will serve as an important baseline to which to compare findings from astronauts who are exposed to space radiation during future exploration missions. Studying the physiologic and health consequences of different levels of radiation from low Earth orbit and travel beyond the van Allen belts is critical to the understanding of any synergistic effects of radiation and weightlessness and the appreciation of the risks associated with missions to Mars and other destinations.
Research Emphases
The main purpose of this topic is to characterize the temporal adaptation of the cardiovascular system and all its subcomponents to spaceflight of increasing duration (ranging from two month missions, through six month missions, and up to one-year missions in low-Earth orbit) and by extrapolation to understand, if extended durations in space beyond one year will induce a higher risk for developing cardiovascular disease and thus, to what degree this will be a factor in evaluating the health risk profiles of future long duration deep space missions, that will be around three years in duration. It is also the purpose to lay a foundation for later comparisons with study outcomes in astronauts during deep space Gateway missions for understanding effects of deep space radiation on human health.

HRP has a requirement for sufficient crewmember experience at one year in spaceflight to demonstrate the presence or absence of unacceptable deleterious physiological, psychological, and medical effects of spaceflight on human health and performance beyond the experience base of six-month expeditions and to permit extrapolation to early interplanetary expeditions with durations of up to two to three years. It is unlikely that there will be preliminary human spaceflight missions of that duration to provide statistically meaningful numbers of crewmembers before those interplanetary expeditions occur. Therefore, HRP is proposing a coordinated One-Year Mission Project (1YMP) on the International Space Station (ISS) consisting of five one-year missions (n=10 crewmember subjects), five standard-duration six-month missions (n=10) paralleling the year-long expeditions, and five short-duration crew vehicle exchange expeditions (n=10) lasting up to two months to occur at the mid-point of each 1YM. The first 1YMP expedition is expected to commence no earlier than Expedition 64, now planned for September 2020.

The intent of the HRP 1YMP is to 1) establish a baseline for proposed Deep Space Gateway expeditions of approximately six weeks’ duration; 2) establish a baseline for proposed year-long expeditions in the Deep Space Gateway in the late 2020s, using ISS as the spaceflight analog for the eventual interplanetary spacecraft; 3) allow the confident prediction of physiological and psychological trends out to two to three years of typical Mars conjunction-class missions; 4) understand the impacts of isolation, habitat, and environmental stressors on human health and mission performance; 5) demonstrate and verify the techniques needed to prevent, diagnose, treat, mitigate and cure the deleterious psychological and psychophysiological effects of prolonged isolation and confinement during spaceflight.

The HRP 1YMP is endorsed by the Multilateral Human Research Panel for Exploration (MHRPE) chartered by the ISS Program Managers and will include International Partner (IP) participation.

Building on the data collected during the first 1YM in one US astronaut and one Russian cosmonaut and concurrent Twins Study in FY15-16, the HRP 1YMP will include a consistent set of measures across 15 concurrent expeditions of three different durations on ISS (up to two months, six months and one year) to identify trends in adaptations to human health and performance. The Project is based on the principle of non-inferiority: if the observed physiological and psychological changes and frequency of medical events in the crewmembers
are no more deleterious after the year-long ISS expeditions than those documented after standard-duration ISS expeditions (six months), then HRP can claim adequate understanding of those changes and the relevant countermeasures to enable longer duration missions. If the extrapolation to two to three years based on results from the coordinated two-month, six-month, and year-long expeditions of the 1YMP predicts no significantly greater deleterious effects than observed previously, then HRP will have sufficient understanding of those changes to proceed confidently with countermeasure provision. It is also specifically intended to identify unresolved areas of greater concern for exploration missions.

**Deliverables**
- Time course of changes up to one year in key health related cardiovascular variables during spaceflight on ISS, including structure, function, and any relevant physiological parameter related to the heart and/or the blood vessels.
- Baselining of cardiovascular health variables in low Earth orbit for preparation of future long duration deep space missions.

**Research Platform**
ISS: Up to 2-, 6-, and 12-months missions.

Ground Analogs: In addition to the flight component, HRP is also proposing an integrated concurrent ground analog component to include three isolations of 4, 8, and 12 months. These expeditions will test countermeasures for psychological and psychophysiological problems associated with prolonged isolation and will be solicited for separately. Proposals, however, will also be considered that suggest the use of these analogs of varying durations as controls for the flight studies of almost similar durations.

**Please note that a maximum of $1,200,000 total ($200,000 per year for six years) is available for this topic.**

**Contact:**
Peter Norsk, M.D.
Element Scientist, Human Health Countermeasures
Telephone: 281-244-5405
E-mail: peter.norsk@nasa.gov

**References**


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<th>Primary Risk</th>
<th>Relevant Gap</th>
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<tr>
<td>Risk of Cardiac Rhythm Problems</td>
<td>CV1: What are the in-flight alterations in cardiac structure and function? CV7: How are fluids redistributed in flight? CV8: Can manifestations of sub-clinical or environmentally induced cardiovascular diseases during spaceflight be predicted?</td>
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<td>Risk of Cardiovascular Disease and Other Degenerative Tissue Effects From Radiation Exposure and Secondary Spaceflight Stressors</td>
<td>Degen-7: Are there synergistic effects from other spaceflight factors (e.g. altered gravity (µ-gravity), stress, altered immune function, altered circadian rhythms, or other) that modify space radiation-induced degenerative diseases in a clinically significant manner?</td>
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<td>Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS)</td>
<td>SANS1 - We do not know the etiological mechanisms and contributing risk factors for ocular structural and functional changes seen in-flight and post-flight. SANS 3 - We need a set of validated and minimally obtrusive diagnostic tools to measure and monitor changes in intracranial pressure, ocular structure, and ocular function. SANS 12 - We do not know whether ground-based analogs and/or models can simulate Spaceflight Associated Neuro-ocular Syndrome.</td>
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<td>Risk of Inadequate Nutrition</td>
<td>N6: What impact does the spaceflight environment have on oxidative damage? N7.2: We need to identify the most important nutritional factors for cardiovascular health. N15: We need to identify the most important nutritional factors for oxidative damage during spaceflight.</td>
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