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PI Name:	Shea, Steven Ph.D.		
Project Title:	Identification of cardiometabolic vulnerabilities caused by effects of synergistic stressors that are commonly encountered during space missions		
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Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
Joint Agency Name:		**TechPort:**	No
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Human Research Program Risks:	(1) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	02115-5804	**Congressional District:**	8
Comments:	NOTE: PI currently at Oregon Health & Science University as of June 2016.		
Project Type:	GROUND	**Solicitation / Funding Source:**	2009 Crew Health NNJ09ZSA002N
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No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	July 2013: Since the last annual report, Dr. Melanie Rueger has left the group. Dr. Matthew Butler has assumed project leader duties.		
COI Name (Institution):	Barger, Laura (Brigham And Women's Hospital, Inc.) Lockley, Steven (Brigham And Women's Hospital, Inc.) Scheer, Frank Ph.D. (Brigham And Women's Hospital, Inc.) Wang, Wei (Brigham And Women's Hospital, Inc.) Matthew, Butler (Brigham and Women's Hospital, Inc.)		
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Task Description:

The risk of adverse cardiac events has been listed as Priority 1 in the NASA Bioastronautics Roadmap (Risk Areas 5 and 6; 2005; http://bioastroroadmap.nasa.gov). Under extremely physiologically challenging circumstances, i.e. microgravity, astronauts are expected to perform tasks that add additional physical and mental stress to their cardiovascular system such as space walks or robotic operations during EVAs. To date we know little to nothing about the synergetic effects of chronic sleep restriction, circadian misalignment, and physical and mental stressors on cardiovascular functioning. The main goals of this four year NASA project are (1) to characterize the alterations (and potential maladaptations) of cardiovascular function (i.e. hemodynamic, autonomous nervous functioning, cardiac vulnerability) associated with chronic sleep restriction and circadian misalignment potentially occurring during space missions; (2) to characterize the effects of different types of stressors (postural, exercise, and mental stressors; except microgravity) on cardiovascular functioning; and (3) to identify the synergetic effects of chronic sleep restriction, circadian misalignment, and different stressors, potentially identifying in vulnerable periods with an increased likelihood of adverse cardiac events during space missions.

During space missions astronauts are exposed to unusual light-dark cycles (e.g. Martian day length: 24.65 hrs) that would be expected to cause circadian misalignment resulting in sleep disturbances, sleep loss, and poor quality sleep. In addition, almost all astronauts report chronic sleep curtailment due to mission requirements such as working 'slam shifts' before EVAs and extended shifts during EVAs. The sleeping conditions on the ISS, e.g. cramped crew quarters, noise, and heat, also add to the reported sleep curtailment. Data from laboratory and epidemiological studies have shown that chronic sleep curtailment and circadian misalignment changes endocrine, inflammatory, and cardiovascular function; changes that potentially result in adverse health events, including cardiac arrhythmias, myocardial and peripheral vascular dysfunction, risk of syncope, hypertension, diabetes, and metabolic syndrome. Moreover, adverse cardiac events show a clear day-night pattern, with a peak in the morning. In addition, it is well know than microgravity itself impacts cardiovascular functioning resulting in decreased circulating blood volume, decreased central venous blood pressure, increased stroke volume and increased cardiac output, potentially leading to cardiac rhythm disturbances that have been documented during spaceflight previously. Our studies of sleep and circadian stressors on cardiovascular performance are relevant to astronauts in space flight as well as the many workers on Earth who experience similar conditions, albeit with gravity, during shift work.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

Curtailed sleep and circadian disruptions are common features of modern life, on Earth as well as in space. Shift workers include factory workers, police, fire fighters, and nurses, and such work has been identified as a risk factor for a host of diseases, including cardiovascular disease, strokes, and metabolic disorders. Our work therefore stands to impact health in astronauts, health in workers on Earth, and may point to countermeasures and improvements in work schedule design.
The risk of adverse cardiac events has been listed as Priority 1 in the NASA Bioastronautics Roadmap (Risk Areas 5 and 6; 2005; http://bioastroroadmap.nasa.gov). This project specially aims to address gaps CV1 which asks "What are the in-flight alterations in cardiac structure and function?" and Gap CV8 which asks "Can manifestations of sub-clinical or environmentally induced cardiovascular diseases during spaceflight be predicted? Cardiac arrhythmias have been observed in astronauts and are considered a major risk endangering the success of space missions. In addition to structural changes, such arrhythmias can be triggered by numerous interacting and summating stressors (e.g., exercise, sleep deprivation, working during the biological night ['circadian misalignment']) causing changes in cardiovascular risk markers, such as increased blood pressure, cardiac vagal withdrawal, sympathetic activation, and promotion of hemostatic mechanisms. Current research in this focus area examines the clinical expression of cardiac atrophy by using in-flight Holter monitoring and ultrasound assessment of potentially long-term changes in cardiac structure and function with spaceflight (e.g., pre-flight, every 2-4 weeks during flight, and post-flight). Our current study complements these prior research activities by elucidating the effects on cardiovascular risk markers of two of the most debilitating aspects of space flight: circadian misalignment and chronic sleep loss. Moreover, to realistically simulate the stresses encountered by astronauts, we are assessing the synergistic effect of behavioral stressors together with the effects of circadian misalignment and prolonged sleep loss.

Our project has implications to Risk #27 - Risk of Performance Errors Due to Sleep Loss, Circadian Desynchronization, Fatigue, and Work Overload [Behavioral Health and Performance (BHP) Element of the HRP]. BHP focuses on the effects of sleep loss, fatigue, circadian misalignment and work overload on performance. Current countermeasures under investigation include recommendations concerning sleep hygiene, work-rest schedules, and optimal lighting requirements for the space vehicle, as well as safe and efficacious methods for implementing lighting as a countermeasure. Specifically, we share interest with the following identified gaps:

•Sleep 4 - How can individual astronauts' vulnerabilities to sleep loss and circadian rhythms best be determined?; •Sleep 5 - How can light be used to optimally minimize circadian problems in space; •Sleep 8 - How are physical and cognitive workloads managed optimally in space relative to fatigue and recovery?

Knowledge about impaired cardiovascular function and periods of vulnerability for adverse cardiac events would contribute substantially to the above mentioned gaps and would enable knowledge integration between the Cardiovascular Alterations Team and the Human Factors and Performance team.

Astronauts experience circadian misalignment, sleep deprivation, and different mental and physical stressors during missions; it is possible that these conditions contribute to sub-optimal cardiovascular function and that these effects will be exacerbated by stressors such as exercise during EVAs and postural stresses on return to earth. Nevertheless, to date, we have little to no knowledge about how the relevant hemodynamic, autonomic, hemostatic, vascular, and endothelial biomarkers that comprise our dependent variables, react to challenging circumstances of circadian misalignment, sleep loss and physical or mental exertion/stress. Once the effects of circadian misalignment, sleep deprivation, and different stressors are determined and vulnerable periods are identified, we hope to develop measures to alleviate or limit the risks by both ensuring proper circadian entrainment and sleep, and by ensuring activities that particularly challenge the cardiovascular system are avoided at specific vulnerable states of circadian misalignment and sleep deprivation. This could inform a new gap related to 'inter-individual vulnerabilities' to challenging work environments, including countermeasures and improvements of already existing challenging work environments (space flight and shift work), and better screening tools for future employees experiencing these work environments.

Finally, our previous work with healthy volunteers on Earth has shows that circadian disruption adversely affects metabolism and cardiovascular reactivity to stressors; two results with broad impact for society on Earth. This project extends these work to consider the impact of short sleep, common across modern society, on how the circadian clock controls times of metabolic and cardiovascular vulnerability.

Task Progress:

1. Introduction
The risk of adverse cardiac events has been listed as Priority 1 in the NASA Bioastronautics Roadmap (Risk Areas 5 and 6; 2005; http://bioastroroadmap.nasa.gov). Several factors impact cardiovascular functioning in space, including microgravity, sleep loss, sleeping or remaining awake at the 'wrong' times according to the internal body clock (circadian misalignment), physical, and mental stress. The project is assessing the contributions of reduced sleep, circadian misalignment, and varied physical and mental stresses on cardiovascular function, simulating many of the physiological stresses that occur throughout long missions.

This ground-based research will help to determine whether long-duration spaceflight (exclusive of radiation effects) leads to important changes in cardiovascular structure and function. This has been identified as an important concern for the Cardiac Alterations research area focusing on research and technology development to support crew health and performance in space explorations missions.

1.1. Specific aims

The specific aims of the protocol are to determine:

1. The effect of circadian misalignment on cardiovascular function. 2. The effect of chronic sleep loss on cardiovascular function. 3. The synergetic effects of circadian misalignment, chronic sleep loss, plus different stressors (postural, exercise, and mental stress) on cardiovascular function.

1.2. Background

In the past, we found that the internal circadian system modulates many important cardiovascular risk markers at rest, and that behavioral stressors have different effects when they occur at different times of day. For example, circulating adrenalin is high during the day and low at night, but additionally, the adrenalin response to exercise varies across the day, with peaks in exercise reactivity in the morning and evening. Thus, the circadian system modulates numerous cardiovascular risk markers at rest as well as their reactivity to exercise, with resultant profiles that could potentially contribute to the day/night pattern of adverse cardiovascular events. We now wish to study the additional effect of sleep loss on these variables, better simulating the anticipated stresses of space flight.

1.3. Critical Path Roadmap questions addressed with this project

The risk of adverse cardiac events has been listed as Priority 1 in the NASA Bioastronautics Roadmap (Risk Areas 5 and 6; 2005; http://bioastroroadmap.nasa.gov). This project specially aims to address gaps CV1 which asks "What are the in-flight alterations in cardiac structure and function?" and Gap CV8 which asks "Can manifestations of sub-clinical or environmentally induced cardiovascular diseases during spaceflight be predicted? Cardiac arrhythmias have been observed in astronauts and are considered a major risk endangering the success of space missions. To realistically simulate the stresses encountered by astronauts, we are assessing the synergistic effect of behavioral stressors together with the effects of circadian misalignment and prolonged sleep loss.

Our project also has implications to Risk #27 - Risk of Performance Errors Due to Sleep Loss, Circadian Desynchronization, Fatigue, and Work Overload [Behavioral Health and Performance (BHP) Element of the HRP]. BHP focuses on the effects of sleep loss, fatigue, circadian misalignment and work overload on performance. Current countermeasures under investigation include recommendations concerning sleep hygiene, work-rest schedules, and optimal lighting requirements for the space vehicle, as well as safe and efficacious methods for implementing lighting as a countermeasure. Specifically, we share interest with the following identified gaps:

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Knowledge about impaired cardiovascular function and periods of vulnerability for adverse cardiac events would contribute substantially to the above mentioned gaps and would enable knowledge integration between the Cardiovascular Alterations Team and the Human Factors and Performance team.

1.4. Potential benefits to society (e.g. increased understanding of disease process, etc)

This project will help identify the synergistic contributions of sleep loss, circadian misalignment, and three different stressors on cardiovascular alterations, thereby simulating many of the physiological stresses that occur throughout long missions. Characterizing these effects on cardiovascular function may help us develop appropriate countermeasures to limit and/or alleviate adverse cardiovascular function during long and short duration space missions. Identifying vulnerable periods in which sleep loss, circadian misalignment, and different stressors lead to malfunctioning of the cardiovascular system may help us to improve work schedules and life-style interventions for shift workers as circadian misalignment and sleep deprivation are hallmarks of shift work.

2. Materials and Methods

Healthy non-obese participants, age 30-55, are being studied in a within-subject design, with each subject undergoing two 11-day circadian misalignment protocols, achieved by advancing sleep periods by 4 hours every day (i.e., recurring 20 h 'days'). One protocol provides adequate sleep (equivalent to 10 h of sleep opportunity per 24 h day) while the other protocol restricts sleep (equivalent to 6 h of sleep opportunity per 24 h day), thereby mimicking the average reported sleep duration of astronauts. In both protocols, subjects perform a sequence of standardized stresses each experimental 'day' including mental, exercise (bicycle), and postural (tilt-table) stresses. For each stressor we record baseline, stress-related and recovery data. Cardiovascular function is assessed by markers of hemodynamic, hemostatic, autonomic and vascular endothelial function, for example with beat-to-beat blood pressure, EKG, and sampling of blood, urine, and saliva for hormone and biomarker analysis. Using this approach, with subjects in conditions free of time cues, the effects of the stressors are being assessed at all phases of the internal biological clock.

In addition to these variables, obtained daily, all subjects participate in an extensive clinically relevant cardiovascular function test battery before and after the sleep and circadian treatments. These include echocardiography to measure heart function and structure, brachial artery ultrasound to examine blood vessel function and stiffness, a maximum exercise test, and a longer postural stress to assess blood pressure regulation. Combining the day-by-day results and the longer changes over the course of the experiment will yield information about both the short-term and longer-term nature of these stressors. For example, an immediate time of day vulnerability may explain why heart attacks cluster in the morning, but a long term exposure to sleep loss and circadian disruption may exacerbate this vulnerability.

3. Results

This grant covers one experiment with two randomized, single blind conditions; the study is ongoing and results are blinded to reduce the risk of bias throughout the analysis phase. Thus, we cannot yet report unblinded results for our primary outcome variables. Secondary analyses performed by co-investigators at JSC in Houston, are ongoing and unblinded.

Recruiting Report and Subject Completion Timeline. Because of the extended in-lab commitment that participants must make, health screening is rigorous and attrition during the screening process due to ineligibility (physiological, medical, or psychological) and difficulty in committing the time is high. To date we have received calls from 1494 people, of whom 103 were deemed eligible, available to participate, and were sufficiently interested to give their consent to start the screening procedures. Of these 103 people, 19 subjects matched our criteria for study, and provided informed consent to participate. Of these 19, thirteen initiated the study, and ten completed both 11-day visits. Participant completion is therefore on schedule.

Immune Function. In collaboration with Dr. Crucian and Dr. Satish, at NASA's JSC in Houston, immune function parameters have been investigated in blood samples taken during and after each circadian misalignment protocol. We found alterations in the bulk leukocyte subsets following the short sleep protocol, which were qualitatively similar to immune alterations observed during space flight. These results were presented at the NASA Human Research Program Investigators' Workshop (February 12–14, 2013, Galveston, Texas) and at the annual international SLEEP 2013 meeting in Baltimore, MD, 1-5 June 2013 (see below).

Other Assays. The plasma samples from all participants studied so far are currently being assayed together as a batch for markers of blood clotting (tPA, PAI-1) and autonomic function (epinephrine, and norephinephrine). Samples from the remaining six subjects will be assayed together as a second batch after completion of the remaining 6 participants.

Data Analysis Plans. We anticipate finishing data collection on all subjects during the winter/spring of 2014, after which full unblinded data analysis will commence.

Bibliography Type:	Description: (Last Updated: 08/14/2018)
Abstracts for Journals and Proceedings	Rueger M, Crucian B, Mehta SK, Pierson DL, Sams C, Scheer FA, Butler MP, Tzigantcheva AD, Smales C, Shea SA. "Effects of sleep deprivation and circadian misalignment on immunological markers in humans." SLEEP 2013--27th Associated Professional Sleep Societies LLC (APSS) Annual Meeting, Baltimore, MD, June 1-5, 2013. Sleep. 2013;36(Abstract Suppl):A101. Abstract 279. http://www.journalsleep.org/Resources/Documents/2013AbstractSupplement.pdf , Jun-2013
Abstracts for Journals and Proceedings	Ruger M, Crucian B, Mehta SK, Pierson DL, Sams C, Scheer FAJL, Butler MP, Tzigantcheva AD, Smales C, Shea SA. "Preliminary results on the effects of sleep deprivation and circadian misalingment on immunological markers in habitually active particpants." 2013 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-14, 2013. 2013 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-14, 2013. , Feb-2013