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Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
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This project investigated the impact of sleep loss and circadian disruption on the cardiovascular (CV) system, including the CV responses to mental and physical challenges that are commonly encountered during space flight.
Microgravity affects CV function by decreasing circulating blood volume and central venous blood pressure and increasing stroke volume and cardiac output, potentially leading to cardiac rhythm disturbances, which have been documented during spaceflight [1]. On top of this, astronauts experience additional CV stress, for example, during space walks or robotic operations during Extravehicular Activities (EVAs) [2]. In addition, during any space mission, astronauts experience unusual light-dark cycles (currently the 90 min cycle on board of the ISS) [3] leading to some degree of chronic circadian disruption which can take the form of: (a) the whole body being at the 'wrong time' given the prevailing behaviors. For example, astronauts are often awake, eat and perform activities at the time when their internal biological clocks are preparing the body for optimal physiological rest and sleep; or they may be trying to sleep during the biological day when their circadian clock normally prepares the body for activities; or (b) parts of the body can be set to suboptimal times, such 'internal desynchrony' when varied cells and organs are shifting to new time zones at different rates. Thus, circadian disruption may result in maladaptive physiological responses. In addition, the inevitable sleep loss that accompanies circadian disruption itself can further stress the CV system. Undoubtedly, mission requirements, such as 'slam shifting' before EVAs and working extended shifts during EVAs will contribute to sleep loss. The environmental conditions on the International Space Station (ISS), e.g., noise, and heat, also contribute to sleep loss. Data from laboratory and epidemiological studies have shown that unfavorable changes in endocrine, inflammatory, and CV function occur in individuals as a result of chronic sleep restriction [4] and circadian disruption [5, 6]; changes that potentially result in adverse health events, including cardiac arrhythmias, myocardial and peripheral vascular dysfunction, risk of syncope [7], hypertension, diabetes, and metabolic syndrome. With the possibility of longer space exploration missions in the future, the effect of sleep loss and circadian disruption on health, performance and safety is paramount. Adverse CV events can be triggered by numerous stressors (e.g., exercise, sleep loss, circadian disruption) causing changes in CV risk markers, such as increased blood pressure, cardiac vagal withdrawal, sympathetic activation, and promotion of hemostatic mechanisms.

Task Description:

Cardiac arrhythmias have been observed in astronauts and are considered a major risk endangering the success of space missions [8]. In addition to structural changes, such arrhythmias can be triggered by numerous interacting and summating stressors [9, 10] (e.g., exercise, sleep loss, working during the biological night ['circadian disruption']) causing changes in cardiovascular risk markers, such as increased blood pressure, cardiac vagal withdrawal, sympathetic activation, and promotion of hemostatic mechanisms. While such responses can be vital homeostatic responses to such challenges, chronic activation of these mechanisms, or activation in individuals with underlying susceptibilities (e.g., with possibly sub-clinical but vulnerable atherosclerotic plaques) can be counterproductive and lead to adverse cardiovascular events, including stroke or myocardial infarction [9, 11].

Therefore, the aims of this project were to identify, in ostensibly healthy individuals of a similar age range as astronauts, the influences of sleep loss and circadian disruption on CV responses to physiological stresses that may occur throughout long missions. Characterizing these effects may help us determine if countermeasures would be recommended in order to limit adverse CV effects during long and short duration space missions.

SPECIFIC AIMS:

1. The effect of circadian disruption on CV function, including the CV responses to physical and mental challenges commonly encountered during spaceflight.

2. The effect of sleep loss on CV function, including the CV responses to physical and mental challenges commonly encountered during spaceflight.

3. The synergetic effects of circadian disruption plus sleep loss on CV function, including the CV responses to physical and mental challenges commonly encountered during spaceflight.

Our studies of sleep and circadian stressors on cardiovascular performance are relevant to astronauts in spaceflight as well as the many workers on Earth who experience similar conditions, albeit with gravity, during shift work.

NOTE: References available in the Task Progress section below.

Rationale for HRP Directed Research:

Research Impact:
Astronauts experience circadian misalignment, sleep loss, 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 simultaneous challenging circumstances of circadian misalignment, sleep loss and physical or mental exertion/stress. Once the effects of circadian misalignment, sleep loss, 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 loss. 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 (spaceflight and shift work), and better screening tools for future employees experiencing these work environments.

The research project has considerable relevance to a number of parts of NASA's current Human Research Program (HRP) Integrated Path to Risk Reduction. In the HRP element of Human Health Countermeasures (HHC), the research is relevant to the following risks:

1. Arrhythmia: Risk of Cardiac Rhythm Problems;

2. Immune: Risk of Adverse Health Event Due to Altered Immune Response (IRP Rev F) In the HRP element of Behavioral Health and Performance (BHP), the research is relevant to the following risk:

3. Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload

Research Impact/Earth Benefits:

The research has relevance to the following specific HRP gaps:

CV01: What are the in-flight alterations in cardiac structure and function?

CV03: Is orthostatic intolerance a potential hazard?

CV08: Can manifestations of sub-clinical or environmentally induced cardiovascular diseases during spaceflight be predicted?

IM03: We have not defined and validated a terrestrial human analog for spaceflight-associated immune system dysregulation (IRP Rev E).

IM08: We do not know the influence, direct, or synergistic, on the immune system of other physiological changes associated with spaceflight (IRP Rev E).

Sleep 2: We need to understand the contribution of sleep loss, circadian desynchronization, extended wakefulness, and work overload on individual health (physical and behavioral), team functioning, and performance (including operational performance), for spaceflight.

Sleep 4: We need to identify indicators of individual vulnerabilities and resiliencies to sleep loss and circadian rhythm disruption, to aid with individualized countermeasure regimens, for autonomous, long duration and/or distance exploration missions.

Sleep 10: We need to identify the spaceflight environmental and mission factors that contribute to sleep decrements and circadian misalignment, and their acceptable levels of risk.

Earth Benefits:

Curtailed sleep and circadian disruptions are common features of modern life, on Earth as well as in space. Night-shift work is common among 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, stroke, 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.

To address the aims we studied volunteer healthy participants throughout two 11-day ‘inpatient’ protocols that combined circadian disruption with extended sleep opportunity (i.e., sufficient sleep) or short sleep (i.e., insufficient sleep). We sought healthy, non-obese, habitually active, male and female volunteers, aged 35-55 years, with no history of chronic medical disorders, no medications, and no substance abuse. This profile was designed to emulate the typical astronaut crew profile. Planned enrollment was 16 participants (8 male, 8 female). Based on flyers, plus newspaper, transportation and web based advertising, we received 2148 inquires. Overall 14 healthy, habitually active participants completed all of the screening and both of the in-laboratory phases of the study (8 male; 6 female).
Each participant was studied in both the Short Sleep and Long Sleep conditions (randomized). These two protocols were called ‘forced desynchrony’ protocols because the day length was shorter than 24 hours (h) such that the behavioral rest/activity cycle became desynchronized from the internal circadian cycle. This was achieved by scheduling participants to live on recurring 20 h ‘days’ in dim light (<3 lux), allowing the endogenous circadian pacemaker to oscillate at its inherent period rather than being reset by daily exposure to the light-dark cycle [12]. One protocol (Short Sleep) permitted sleep for 5 h per 20 h ‘day’, which is equivalent to 6 h sleep opportunity per 24 h for an entire week. The other protocol (Long Sleep) allowed 8 h 20 min sleep per 20 h-‘day’, which is equivalent to 10 h sleep opportunity per 24 h for an entire week. This approach allows us to uniformly distribute the sleep/wake cycle across the circadian cycle to quantify the independent influences of the circadian system and behaviors and also their interacting effects. Under these carefully controlled conditions we tested the hypothesis that circadian disruption combined with sleep restriction would result in unfavorable changes in cardiovascular (CV) function during behavioral challenges commonly faced by astronauts. A behavioral test battery was performed at the same time relative to time since scheduled waking during each laboratory protocol (starting at 2 h after scheduled wake time). Before each test battery, participants had been supine for at least 5 h during the sleep periods in both the Long Sleep and Short Sleep conditions. Subsequently, when lights were switched from darkness to the dim light condition (3 lux), participants remained in a semi-recumbent posture (upper body at 45º) for 2 h during which time they were provided with a urinal or bedpan as needed. During this time participants consumed breakfast 1 h after scheduled wake time. An identical behavioral test battery was repeated on each 20 h ‘day’ and included three standardized stressors performed in the following order: (i) a mental challenge; (ii) a postural challenge; and (iii) an exercise stressor.

Physiological Measurements

In brief, the following dependent variables were assessed at the beginning and at the end of each protocol (i.e., without and with sleep loss, and before and after circadian disruption):

• Maximal oxygen consumption (incremental treadmill exercise to maximal tolerable level

• Hemodynamic response to a strong postural challenge (passive 80° head-up tilt for 30 minutes)

• Cardiac structure and function (echocardiography)

• Endothelial function (reactive hyperemia index and endothelial-independent vasodilation)

• ECG arrhythmias (24 hour Holter recording)

For practical reasons or due to concerns that invasive or intensive tests would affect subsequent measurements (e.g., maximal exercise challenge can induce training effects), for the middle parts of the study (i.e., during the forced desynchrony) the following less invasive/ intensive identical test battery sessions were performed throughout each 20 h forced desynchrony:

• Core body temperature (CBT) for assessment of internal circadian phase

• Wrist actigraphy (and polysomnography is 4 participants) for estimation of sleep duration

Task Progress:

• Hemodynamic, autonomic and endocrine responses to:

• Mental Stress (serial addition test for 10 minutes)

• Mild autonomic [postural) challenge (passive 60° head-up tilt for 15 minutes)

• Aerobic exercise challenge (bicycle exercise at 60% maximal heart rate for 15 minutes)

Additional measurements:

• Circadian Phase Assessment from core body temperature.

• Blood pressure and heart rate.

• Blood Sampling for autonomic, fibrinolytic and metabolic assays.

• Immune function: Astronauts experience various stressors that may result in inhibition of cell mediated immunity and increased reactivation of latent viruses [15,16]. Thus, comprehensive immune assessment was performed from whole blood samples collected with heparin at the beginning of study before either protocol, and twice during each of the short sleep and the long sleep protocols. Immune function was assessed by Dr. Brian E. Crucian and colleagues at NASA Johnson Space Center using standard techniques including peripheral leukocyte distribution by flow cytometry, T cell function, intracellular cytokine profiles, and secreted cytokine production profiles following T cell or monocyte stimulation [15]. In addition, innate reactivation of latent EBV (Epstein Barr Virus), HSV1 (herpes simplex virus 1), and VZV (Varicella Zoster Virus) was assessed from the DNA in liquid saliva samples taken at the beginning of study before either protocol, and every alternate day across both the short and long sleep protocols. These assays were performed by Dr. Satish K. Mehta and colleagues at NASA Johnson Space Center using real time polymerase chain reaction techniques [16].

• Rest/Activity cycles and Sleep (Actigraphy and Polysomnography): Verification of the rest/activity cycles imposed by the protocols and estimation of sleep was made throughout the entire study (baseline and in-laboratory phases) by wrist actigraphy worn on the non-dominant arm. In a subset of 4 participants, sleep was assessed on each study sleep opportunity during the laboratory phases by using polysomnography. Sleep data were visually scored according to standard criteria [13].

Statistical Comparisons: The main comparisons were between CV outcome measurements collected at baseline (Wake Periods 3 or 4 from each protocol) and after circadian disruption [with or without sleep loss] (Wake Periods 10 or 11 from each protocol). Differences across the long sleep protocol are attributed to a week of circadian disruption. Differences across the short sleep protocol relative to differences across the long sleep protocol are attributable to sleep loss. This sleep loss effect is seen as a significant statistical interaction between Condition [long sleep vs. short sleep] and Wake Period [beginning vs. end of protocol].

RESULTS

At time of this final report, no results have been published in peer-reviewed scientific journals, although updates were presented as posters at the NASA Human Research Program (HRP) Investigators' Workshops in 2013 and 2014, and the main results were presented in an oral presentation at the HRP Investigators' Workshop in 2015. It is anticipated that publications will appear in 2016 or 2017.

References

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Bibliography Type:	Description: (Last Updated: 08/14/2018)
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