Fiscal Year:	FY 2020	**Task Last Updated:**	FY 10/31/2020
PI Name:	Hargens, Alan R. Ph.D.		
Project Title:	Fluid Distribution before, during and after Prolonged Space Flight		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes (2) **SANS**:Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS)		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	92037-0863	**Congressional District:**	52
Comments:			
Project Type:	Flight	**Solicitation / Funding Source:**	2011 Crew Health NNJ11ZSA002NA
Start Date:	04/05/2013	**End Date:**	01/31/2022
No. of Post Docs:	2	**No. of PhD Degrees:**	
No. of PhD Candidates:	1	**No. of Master' Degrees:**	2
No. of Master's Candidates:	3	**No. of Bachelor's Degrees:**	5
No. of Bachelor's Candidates:	4	**Monitoring Center:**	NASA JSC
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Flight Program:	ISS		
Flight Assignment:	NOTE: Extended to 1/31/2022 per NSSC information (Ed., 1/6/21) NOTE: Extended to 1/31/2021 per NSSC information (Ed., 10/16/18)		
Key Personnel Changes/Previous PI:	2020 report: Dr. Lonnie Peterson and Dr. Douglas Chang are no longer CoInvestigators.		
COI Name (Institution):	Arbeille, Phillipe M.D., Ph.D. (CERCOM, France) Liu, John Ph.D. (University of California, San Diego) Macias, Brandon Ph.D. (KBR/NASA Johnson Space Center) Stenger, Micheal Ph.D. (KBR/NASA Johnson Space Center) Ebert, Douglas Ph.D. (KBR/NASA Johnson Space Center)		
Grant/Contract No.:	NNX13AJ12G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

Editor's Note (4/24/2013): NOTE THIS IS A CONTINUATION OF FUNDING FOR NNX12AL66G WITH THE SAME TITLE AND PRINCIPAL INVESTIGATOR.
We will use state-of-the-art, non-invasive technologies to quantify upper-body compartmental volumes and pressures in crewmembers before, during, and after prolonged space flight. Importantly, we will correlate these data with vision deficits that occur in order to establish pathophysiologic mechanisms that will serve as a basis for future countermeasure development. After successful completion of our investigation, we will deliver a comprehensive database of microgravity-induced, head-ward volume and pressure changes (type and magnitude), and a prioritization of these changes as to their deleterious effects on vision in crewmembers during and after prolonged space flight. We are proposing a well-documented and validated battery of non-invasive or minimally-invasive, image-based tests developed to identify and quantify microgravity-induced, head-ward volume and pressure changes. We hypothesize that prolonged microgravity-induced, head-ward volume and pressure shifts are responsible for elevating intracranial pressure (ICP) and producing deficits in crewmembers’ vision. Our project directly addresses Critical Path Roadmap Risks and Questions regarding "Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS)" (previously called “Risk of Microgravity-Induced Visual Alterations and Intracranial Pressure”), specifically Integrated Research Plan (IRP) Gap Cardiovascular (CV) 7: How are fluids redistributed in-flight? and IRP Gap We do not know the etiological mechanisms and contributing risk factors for ocular structural and functional changes seen in-flight and postflight (SANS1) [previoulsy VIIP 1: What is the etiology of visual acuity and ocular structural and functional changes seen in-flight and post-flight?]. Our first specific aim is to study periocular fluid volumes, intraocular pressure (IOP), upper-body compartment volumes before, during, and after prolonged microgravity exposure. The second specific aim is to measure jugular vein dimensions and blood flow using ultrasound before, during, and after prolonged microgravity exposure. The third specific aim is to quantify ventricular and cerebrospinal volumes using ultrasound before, during, and after prolonged microgravity exposure. A fourth specific aim is to perform retinal imaging to observe retinal venous distension in space. Tests of ocular structure will include optic nerve head tomography, nerve fiber layer thickness, axial length, and orbital retrolaminar subarachnoidal space. Tests of ocular function will include visual acuity, total retinal blood flow, and capillary blood flow in the optic nerve head and macula. Finally, changes in ICP, IOP, and ocular structures and functions will be investigated while applying a purely-mechanical countermeasure of low-level lower body negative pressure or thigh cuffs to counteract the head-ward fluid shift in space.

To our knowledge, this study will be the first to provide detailed and non-invasive measures of compartmental volume and pressure changes in the upper body induced by prolonged microgravity and to correlate these specific changes with decrements in vision for crewmembers. The proposed techniques represent the best available, state-of-the-art tools to quantify and document features that are clinically suspected as vision deficit generators. By correlating volume and pressure changes with vision problems, we expect to identify factors that will later motivate targeted development of effective physiologic countermeasures such as low-level lower body negative pressure exposure or thigh cuffs in space. This project has the potential to prevent loss of vision in crewmembers exposed to prolonged space flight and upon return to Earth.

NOTE: This study was merged with investigations from Dr. Michael Stenger (Distribution of Body Fluids during Long Duration Space Flight and Subsequent Effects on Intraocular Pressure and Vision Disturbance) and Dr. Scott Dulchavsky (Microgravity associated compartmental equilibration) resulting in a comprehensive study titled “Fluid Shifts Before, During and After Prolonged Space Flight and Their Association with Intracranial Pressure and Visual Impairment” (short title: Fluid Shifts).

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

Our proposed tests represent a comprehensive set of state-of-the-art, noninvasive technologies to quantify upper-body compartmental volumes and vascular parameters in crewmembers before, during, and after prolonged space flight. Importantly, we will correlate these data with vision deficits that occur in order to establish pathophysiologic mechanisms that will serve as a basis for future countermeasure development. After successful completion of our investigation, we will deliver a database of microgravity-induced, head-ward volume and vascular changes (type and magnitude) and a prioritization of these changes as to their deleterious effects on vision in crewmembers during and after prolonged space flight. Finally, our project includes use of lower body negative pressure (LBNP), which is known to sequester fluid in lower body tissues and counteract head-ward fluid shifts. Importantly, these procedures have the potential to reduce intracranial pressure and counteract papilledema, even if the proposed countermeasure acts transiently.
This research has strong Earth benefits such as development and validation of a noninvasive ICP device and greater understanding of glaucoma using the latest technology for measuring intraocular and intracranial pressures.

We have made significant progress over the past year on possible mechanisms of Spaceflight Associated Neuro-ocular Syndrome (SANS); all approvals were received and experimental schedules were optimized. We have completed most of our project NNX13AJ12G entitled “Fluid Distribution before, during and after Prolonged Space Flight” NASA Experimental Document and its revision. Likewise, we have updated and renewed our University of California - San Diego (UCSD) Institutional Review Board (IRB) approval.
To date, all pre/in/post-flight data collection has been completed on 12 subjects for this experiment. The final subject will require 1 more post-flight session, which will mark the completion of data collection for this study. This is expected to be completed by November 2020. Partial results from our space flight and other related investigation are available as part of three publications and one abstract.

INTRODUCTION

The Fluid Shifts flight study was funded starting in 2012 and resulted from the combination of three selected grant proposals into a single study (Principal Investigators: Mike Stenger/Cardiovascular and Vision Laboratory-JSC; Alan Hargens/University of California-San Diego; and Scott Dulchavsky/Henry Ford Health System). In 2013, the Cardiovascular & Vision Laboratory (CVL) portion of the project budget was re-scoped at the request of Human Health Countermeasures (HHC) management to increase the grant from 3 years to 7 years. Data collection on 10 subjects began in 2014, and 3 additional subjects were added to the CVL scope of work in 2017. This international investigation included astronauts from NASA, the European Space Agency (ESA), and the Japan Aerospace Exploration Agency (JAXA) , as well as Russian Cosmonauts.

Task Progress:

The primary goal of this study was to (1) characterize the fluid shift that occurs during space flight, (2) determine if measurements obtained preflight could be used to predict ocular changes during space flight, and (3) evaluate the effectiveness of lower body negative pressure (LBNP) during space flight to acutely reverse the headward fluid shift.

METHODS

Subjects were studied before (L-90), during (FD45, FD150), and after (R+10, R+30, R+180) space flight. Before and after space flight subjects were studied in the seated, supine, and 15° head-down tilt postures; before flight also included a posture of 15° head-down tilt plus 25 mmHg lower body negative pressure (LBNP). During space flight subjects were studied during nominal weightlessness, and again during use of 25 mmHg LBNP using the Russian Chibis device. Outcome measures included a variety of vascular, cardiac, and ocular ultrasound measures, noninvasive estimates of intracranial pressure, eye structural measures with optical coherence tomography, and intraocular pressure.

Fluid distribution measures included assessment of plasma volume (pre- and post-flight, supine), total body water, and intracellular and extracellular fluid volumes.

Magnetic resonance imaging (MRI) of the brain and eyes was obtained pre- and post-flight in the seated, supine, and 15° head-down tilt postures.

RESULTS

Data collected in the Fluid Shifts study have been published as part of two manuscripts, with multiple additional manuscripts being planned.

Early Signs of Optic Disc Edema: Optical coherence tomography (OCT) imaging provides quantitative measures of retinal thickness that can be used to identify the earliest signs of optic disc edema. We published a subset of the data collected in this study collected on ~flight day 30 and, combined with the same measures obtained in the Ocular Health study, compared to the same data collected in subjects exposed to 30 days of strict head-down tilt bed rest. This publication in the journal JAMA Ophthalmology highlighted similarities and differences in ocular changes between astronauts exposed to space flight and subjects exposed to a space flight analog.

Venous Thrombosis in Spaceflight. During a test session with a Fluid Shifts subject on ISS our ultrasound team discovered a venous thrombosis in the left internal jugular vein (IJV) of an astronaut participating in the Fluid Shifts study. This unexpected finding resulted in the PI team reviewing images of prior subjects and determined that a second earlier Fluid Shift subject also had an unconfirmed IJV thrombosis. These findings, along with IJV cross-sectional area and pressure data, were published in the journal JAMA Network. In addition to 2 of 11 subjects demonstrating thrombosis in the left IJV, this publication also revealed that IJV cross-sectional area during space flight is similar to that in the supine posture on Earth and that there are IJV flow pattern abnormalities during weightlessness that do not occur on Earth. These findings highlight that cerebral venous congestion occurs in weightlessness and underscore the need for additional characterization of all cerebral venous outflow pathways, including both left and right IJVs and left and right vertebral veins.

Cardiovascular Responses to LBNP during Space Flight

While use of LBNP during space flight has been studied in astronauts during short-duration space flight missions, long-duration astronauts have not been systematically evaluated during exposure to a sustained mild level of LBNP during space flight. Russian Cosmonauts routinely use LBNP during various research studies, as well as during the final 21 days of space flight as a countermeasures to prepare for re-adaptation to gravity. A key question being investigated here was how the cardiovascular system would respond to up to 60 minutes of LBNP during weightlessness during long-duration space flight when there are known musculoskeletal and cardiovascular changes that could limit the physiological responses to the LBNP stressor. The preliminary data will be included in an upcoming manuscript.

LBNP reduces venous return to the heart, thereby lowering cardiac output and ultimately arterial blood pressure. To compensate, heart rate increases in order to maintain appropriate blood pressure levels. If the negative pressure is increased far enough, or the physiological responses designed to prevent a fall in blood pressure are inadequate, syncope can occur. Here we report preliminary data on the change in mean arterial pressure (MAP) and heart rate (HR) during exposure to 25 mmHg LBNP in 12 subjects throughout long-duration space flight missions. These preliminary data reveal that all subjects tolerated the LBNP sessions without a substantial fall in MAP, yet HR was elevated in all subjects. During FY21 our team will continue analysis of these preliminary data and draft a manuscript with these and other data to highlight the similarities and differences in the LBNP response during space flight, compared to that with occurs in a gravitational environment on Earth.

DISCUSSION

Data collection will be completed on the final Fluid Shifts subjects in early FY21, and the continued analysis and reporting of findings are anticipated to continue through FY21 and FY22. Due to the international collaborations that make up the Fluid Shifts team, we are planning to hold a data summit to discuss data products and identify how multiple data sets link together to develop a comprehensive picture about (1) the fluid shift that occurs during long-duration space flight, (2) the ability for LBNP to reverse the fluid shift, and (3) if there are anatomic, physiologic, or other factors that can provide insight into which subjects may be most at risk for developing SANS findings.

OTHER RECENT RESULTS

FLUID DISTRIBUTION AND COMPARTMENTALIZATION DURING LONG-DURATION SPACE FLIGHT

INTRODUCTION. Visual acuity changes observed after short-duration missions are largely transient, but now up to 70% of ISS astronauts returning from long-duration missions demonstrate ocular structural changes such as optic disc edema, globe flattening, and/or choroidal folds. These structural and functional changes are referred to as the Spaceflight Associated Neuro-ocular Syndrome (SANS). The purpose of this study is to characterize the fluid distribution and compartmentalization associated with long-duration space flight and to determine whether a relationship exists between these fluid distribution measures and the ocular structural and functional changes associated with SANS. We also seek to determine whether headward fluid shifts during space flight, as well as any SANS-related effects of those shifts, can be predicted by preflight responses to acute hemodynamic manipulations, including posture changes with and without lower body negative pressure (LBNP).

METHODS. A variety of physiologic were investigated in 13 long-duration ISS crewmembers. Measures include (1) fluid compartmentalization (total body water by D2O, extracellular fluid by NaBr, intracellular fluid by calculation, plasma volume by carbon monoxide rebreathe, interstitial fluid by calculation); (2) upper and lower body skin tissue thickness by ultrasound; (3) vascular dimensions by ultrasound (jugular veins, cerebral and carotid arteries, vertebral arteries and veins, portal vein); (4) vascular dynamics by MRI (head/neck blood flow, cerebrospinal fluid pulsatility); (5) ocular measures (optical coherence tomography; intraocular pressure; 2-dimensional ultrasound including optic nerve sheath diameter, globe anterior-posterior diameter, and retina-choroid thickness; Doppler ultrasound of ophthalmic and retinal arteries and veins); (6) cardiac variables by ultrasound (inferior vena cava, stroke volume, right heart dimensions and function, four-chamber views); and (7) noninvasive ICP measures (tympanic membrane displacement, otoacoustic emissions). Before and after space flight, tests during acute posture changes included supine and head-down tilt (HDT) to induce headward fluid shifts, whereas LBNP (only preflight) will oppose these shifts. Through interventions applied before, during, and after flight, we intend to evaluate the relationship between headward fluid shifts, SANS, and possible SANS countermeasures.

DISCUSSION. Twelve subjects have completed all testing and all subjects have completed the flight phase of this experiment. Preliminary results suggest that relative to the seated posture, jugular vein cross-sectional area and pressure, intraocular pressure, and noninvasive indices of ICP increase in the supine and HDT conditions, yet choroid thickness does not change. Measures obtained during space flight generally are similar to supine values on Earth, but the choroid is thicker in weightlessness. Use of 25 mmHg LBNP appears to be partially effective in reducing the cephalad fluid shift both on Earth and in space, but does not affect choroid thickness measured within the first 15 min of LBNP. Analyses of the following outcomes are expected this year: blood pressure and heart rate responses to LBNP during space flight; total body water and extracellular fluid volume; optic nerve head morphology changes and their relationship to other variables; magnetic resonance imaging (MRI) of cerebral venous compartment; and MRI metrics of globe flattening.

JUGULAR, MIDDLE CEREBRAL AND PORTAL VEIN RESPONSES TO SIX MONTHS ISS SPACEFLIGHT AT REST AND WITH LBNP

BACKGROUND. Cephalad fluid shifts are suspected to cause ocular edema and increase ocular and intracranial pressures, likely resulting in the development of the SANS. Lower body negative pressure (LBNP) can be used as a method to shift fluid towards the legs in the absence of gravity. Our hypothesis was that inflight jugular and portal vein volumes would increase due to the fluid shift and that intracranial vein velocity would increase due a narrowing of the vessel lumen from increased intracranial pressure. LBNP was tested to restore these variables to preflight levels.

METHODS. During 6-month ISS spaceflights 13 astronauts performed echographic investigations with verbal remote guidance assistance from the ground. Jugular vein volume (JV vol, cm3), portal vein cross-sectional area (PV cm^2), and intracranial vein velocity (MCV; cm/s) were measured pre-flight, in-flight (FD45, FD150), and post-flight (R+40, R+180), at rest and during 25 mmHg LBNP with the Russian Chibis device.

RESULTS. With space flight, JV vol increased from pre-flight supine and seated values (46±48% from supine at FR45 & FD150) and 520±291%, from seated at FD45 & FD150. P<0.05), MCV increased (43±19% from supine and 109±110% from seated on FD45 and FD150, P<0.05). PV tended to increase but was not significant. Inflight LBNP of 25 mmHg restored JV vol, and MCV to pre-flight supine levels (P<0.05).

CONCLUSION. The increase in JV vol confirms the sustained headward fluid shift during the 6-month ISS flight. MCV increased, probably by compression of the vein (lumen reduction) or reduction in backpressure/interstitial resistance as neither cerebral nor carotid flows changed in space flight. The application of LBNP during the flight restored JV and MCV to pre-flight supine levels.

Bibliography Type:	Description: (Last Updated: 06/30/2025)
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