Fiscal Year:	FY 2021	**Task Last Updated:**	FY 03/21/2021
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		
PI Email:	ahargens@ucsd.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	858-534-7837
Organization Name:	University of California, San Diego		
PI Address 1:	Altman Clinical and Translational Research Institute		
PI Address 2:	9452 Medical Center Drive/0863		
PI Web Page:			
City:	La Jolla	**State:**	CA
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:**	10/31/2021
No. of Post Docs:	2	**No. of PhD Degrees:**	
No. of PhD Candidates:		**No. of Master' Degrees:**	1
No. of Master's Candidates:	2	**No. of Bachelor's Degrees:**	3
No. of Bachelor's Candidates:	3	**Monitoring Center:**	NASA JSC
Contact Monitor:	Brocato, Becky	**Contact Phone:**	
Contact Email:	becky.brocato@nasa.gov		
Flight Program:	ISS		
Flight Assignment:	NOTE: Project end date changed to 10/31/2021 per L. Barnes-Moten / NASA JSC. (Ed., 12/7/21) 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:	March 2021 report: Dr. Steven Laurie is now Co-Principal Investigator on the project.		
COI Name (Institution):	Arbeille, Phillipe M.D., Ph.D. (CERCOM, France) Liu, John Ph.D. (University of California, San Diego) Macias, Brandon Ph.D. (NASA Johnson Space Center) Stenger, Micheal Ph.D. (NASA Johnson Space Center) Ebert, Douglas Ph.D. (KBR/NASA Johnson Space Center) Laurie, Steven 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 who was replaced by Steve Laurie (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" by testing 13 astronauts. Moreover, we have updated and renewed our NASA and University of California - San Diego (UCSD) Institutional Review Board (IRB) approvals. To date, all pre/in/post-flight data collection are completed on 13 subjects for this experiment. Partial results from our spaceflight and other related investigation are available as part of three publications and three chapters 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 (PIs): Mike Stenger/Cardiovascular and Vision Laboratory-Johnson Space Center (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, European Space Agency (ESA), and the Japan Aerospace Exploration Agency (JAXA), as well as Russian Cosmonauts. The primary goal of this study was to (1) characterize the fluid shift that occurs during spaceflight, (2) determine if measurements obtained preflight could be used to predict ocular changes during spaceflight, and (3) evaluate the

effectiveness of lower body negative pressure (LBNP) during spaceflight 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) spaceflight. Before and after spaceflight 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 spaceflight 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.

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 (Marshall-Goebel K, Laurie SS, Alferova IV, Arbeille P, Auñón-Chancellor SM, Ebert DJ, Lee SMC, Macias BR, Martin DS, Pattarini JM, Ploutz-Snyder R, Ribeiro LC, Tarver WJ, Dulchavsky SA, Hargens AR, Stenger MB. "Assessment of jugular venous blood flow stasis and thrombosis during spaceflight." JAMA Netw Open. 2019 Nov 1;2(11):e1915011). In addition to 2 of 11 subjects demonstrating thrombosis in the left IJV, this publication also revealed that IJV cross-sectional area during spaceflight 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.

Task Progress:

Cardiovascular Responses to LBNP during Spaceflight. While use of LBNP during spaceflight has been studied in astronauts during short-duration spaceflight missions, long-duration astronauts have not been systematically evaluated during exposure to a sustained mild level of LBNP during spaceflight. Russian Cosmonauts routinely use LBNP during various research studies, as well as during the final 21 days of spaceflight 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 spaceflight when there are known musculoskeletal and cardiovascular changes that could limit the physiological responses to the LBNP stressor. The preliminary data below 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 spaceflight 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 spaceflight, compared to that with occurs in a gravitational environment on Earth.

LBNP Effect on Ocular Venous Drainage. We and others have hypothesized that the cerebral venous congestion that develops during spaceflight may contribute to the development of optic disc edema in astronauts. A key question is whether use of LBNP, which we have demonstrated reduces IJV cross-sectional area thereby reducing cerebral venous congestion, effectively reaches the eye. We are currently drafting a manuscript that explores the ability for LBNP during spaceflight to reduce venous pressure draining the eye, as quantified by a fall in intraocular pressure (IOP). However, if this same hypothesis holds for the veins draining the choroidal vasculature, then the observation that choroid thickness during application of LBNP does not change suggests choroid thickness measures may represent fluid both within and external to the choroidal vasculature.

Ocular Structural Changes During Spaceflight. Recent publications by members of the Cardiovascular and Vision Laboratory reveal early signs of edema develop in most crewmembers during long-duration spaceflight and this can take up to 1 year post-flight to fully resolve. Similarly, in the Fluid Shifts study astronauts and Cosmonauts developed increased retinal thickening. These data will serve as the backbone of a publication in FY21 that will explore if there are other outcome data collected within the Fluid Shifts study that can predict these changes in total retinal thickness.

Fluid Shift Characterization. A primary aim of the original grant proposal submitted by the Cardiovascular and Vision Laboratory centered on the shift of fluids both towards the head, as quantified through ultrasound measures of the cerebral venous system, as well as shifts of fluid between intracellular and extracellular, and intravascular and extravascular fluid compartments. To accomplish this collaborators from the Nutritional Biochemistry Laboratory have developed dilution measure techniques that will provide assessment of total body water and intracellular and extracellular fluid volume preflight, inflight, and postflight. Plasma volume measured during preflight and postflight testing will also allow for quantification of intravascular and extravascular fluid volumes as well. The data from the dilution measures will be batch processed and combined with other ocular outcome data to determine if variability in fluid distributions may provide insight into the variability of the ocular findings.

Noninvasive Measures of Intracranial Pressure. At the start of the Fluid Shifts study in 2012 there was a desire to use noninvasive approaches to measure intracranial pressure during spaceflight. Because any single approach has the potential for errors or pitfalls, we took the strategy of using multiple approaches with the goal of improving the likelihood of correctly interpreting the data if all the techniques demonstrated similar trends. Data collected with the Cerebral and Cochlear Fluid Pressure (CCFP) analyzer, shifts in otoacoustic emissions, and measures of optic nerve sheath diameter will all be incorporated into a single manuscript in FY21. Preliminary review of these data suggest that noninvasive estimates of ICP do not reveal pathologically elevated ICP during spaceflight.

Magnetic Resonance Imaging Reveals Brain Structural Changes. Multiple groups from around the world, including members of the Fluid Shifts team, have reported on brain ventricular enlargement on MRI following spaceflight. These data reveal ~10.7% to 14.6% increase in lateral ventricular volume, which is ~2-3 ml increase in volume. These measures have been obtained on Fluid Shifts subjects and reveal similar magnitude increase as previously reported. In FY21 we will combine these measures with other outcome measures obtained on these crewmembers to gain insight into possible etiology of the brain structural change. Preliminary data in the Fluid Shifts subjects reveal substantial variability between subjects, including a single subject demonstrating no change in lateral ventricular volume. There has been speculation that the brain and eye structural changes are related, although the limited data that have been published suggest that a lack of change in lateral ventricular volume is related to the development of SANS as determined based on presence of a subjective optic disc edema or choroidal folds. Quantitative data collected in this Fluid Shifts study cohort suggest there is not a relationship between the brain structural changes and total retinal thickness changes as quantified from OCT images. These data will be incorporated into a manuscript planned for FY21.

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 summits 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 spaceflight, (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. These analyses and results will inform the OMB Milestone to characterize SANS by the end of FY21.

Bibliography Type:	Description: (Last Updated: 06/30/2025)
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Articles in Peer-reviewed Journals	Khossravi EA, Hargens AR. "Visual disturbances during prolonged space missions." Curr Opin Ophthalmol. 2021 Jan;32(1):69-73. https://doi.org/10.1097/ICU.0000000000000724 ; PMID: 33196542 , Jan-2021
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