Fiscal Year:	FY 2019	**Task Last Updated:**	FY 06/21/2019
PI Name:	Dulchavsky, Scott A. M.D., Ph.D.		
Project Title:	Fluid Shifts		
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:	48202-2608	**Congressional District:**	13
Comments:			
Project Type:	FLIGHT	**Solicitation / Funding Source:**	2011 Crew Health NNJ11ZSA002NA
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No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
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Flight Program:	ISS		
Flight Assignment:	NOTE: Extended to 1/31/2021 per NSSC information (Ed., 10/16/18)		
Key Personnel Changes/Previous PI:	none		
COI Name (Institution):	Ebert, Douglas Ph.D. (Wyle Laboratories, Inc.) Sargsyan, Ashot M.D. (Wyle Laboratories, Inc.)		
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Task Description:

Editor's Note (7/11/2013): NOTE THIS IS A CONTINUATION OF FUNDING FOR NNX13AB42G (Microgravity Associated Compartmental Equilibration (MACE)) WITH THE SAME PRINCIPAL INVESTIGATOR.
Fifty percent of American astronauts have developed ocular refraction change after long duration space flight on the International Space Station (ISS). Recent findings have also included structural changes of the eye (papilledema, globe flattening, choroidal folds) and the optic nerve (sheath dilatation, tortuosity, and kinking), as well as imaging signs and lumbar puncture data indicative of elevated intracranial pressure (ICP). While short duration space flight is also characterized by vision disturbances, these are generally transient and do not appear to have lasting impacts on the structure or function of the eye. Changes in vision, eye, and adnexa morphology are hypothesized to be the result of space flight-induced cephalad fluid shifts and transiently elevated intracranial pressure. This hypothesis, however, has not been systematically tested. In earlier anecdotal publications, ICP elevation in long-duration space flight has been inferred but without association with structural or functional changes of the eye. Furthermore, while fluid shifts and compartmentalization during short-duration space flight (Space Shuttle missions) have been studied, the fluid distribution patterns and their effects on intracranial pressure or the structure and function of the sensory organs in the course of long-duration space flight are not well known.

Several ISS crewmembers have reported consistent worsening of nasal congestion and associated symptoms in late afternoon hours, necessitating topical and systemic decongestant use. Although several explanations have been entertained, food (salt) and water intake are likely to have provoked these symptoms through postprandial modification of fluid balance or increase in the circulating volume that manifests in the most susceptible individuals.

The purpose of the proposed work is to objectively characterize the changes in fluid distribution, including intra/extracellular and intra/extravascular fluid shifts, by applying advanced non-invasive assessment technologies before, during, and after long duration space flight. Additionally, we will examine the relationship between the type and magnitude of the fluid shift with any effects on eye morphology and vision disturbances, intraocular pressure (IOP), and measures of intracranial pressure. Further, we seek to determine whether the magnitude of fluid shifts during space flight, as well as the above effects of those shifts can be predicted based upon crewmember baseline data and responses to acute head-down tilt tests performed before launch. Finally, we propose to evaluate the effect of lower body negative pressure (LBNP) on the above parameters.

To our knowledge, this is the first attempt to systematically determine the impact of the fluid distribution in microgravity on a comprehensive set of structural and functional measures including, but not limited to, those related to intracranial pressure, vision, morphology of the eye and its adnexa, and the vascular systems of the head and neck, during and after long duration space flight. The study design and methodology are based on the extensive relevant experience of the Investigators, including many successful ground-based, space flight analogue, and space flight projects and investigations.

Primary Hypothesis

Prolonged microgravity-induced, headward volume, and pressure shifts promote elevation of intracranial pressure and result in alterations in crewmembers' vision.

Specific Aims

Specific Aim I: To characterize fluid distribution and compartmentalization before, during, and after long-duration space flight.

Hypothesis 1: Fluid distribution measured by dilution techniques will reflect a headward fluid shift and an intra- to extra-vascular fluid shift during space flight, returning to pre-flight condition after landing.

Hypothesis 2: Regional headward fluid shifts in-flight are documented by increased cephalad venous dimensions (jugular veins) and flow characteristics, skin and soft tissue thickness.

Hypothesis 3: Fluid re-distribution towards the eye (detected in choroid, retina, and optic nerve head using ultrasonography and optical coherence tomography), and in arteries supplying ocular vascular beds, contributes to vision alterations.

Hypothesis 4: Splanchnic venous congestion (detected by portal vein size) contributes to headward volume shift, but is not in communication with the veins of head and neck. Thus, there should be a different level of venous congestion in these two compartments.

Specific Aim II: To correlate in-flight alterations of eye structure, ocular vascular parameters, and vision with headward fluid shifts, vascular dimensions, and flow patterns.

Hypothesis 5: Space flight-induced fluid shifts will have an upregulating effect on ICP and will alter ocular refraction / visual acuity. These changes will vary in magnitude and respectively, in their resolution pattern after space flight.

Hypothesis 6: In-flight ICP-related measures, IOP (intraocular pressure), venous and arterial morphometric and flow characteristics, vascular resistance of ocular vascular beds, and optic nerve anatomy will trend towards normal-gravity levels temporarily during and residually after fluid sequestration (LBNP) interventions.

Specific Aim III: To determine systemic and ocular factors of individual susceptibility to the development of ICP elevation and/or vision alterations.

Hypothesis 7: Subjects with greater fluid shifts (as measured by the ultrasound method in Aim 1) during pre-flight testing will experience greater fluid shifts in-flight and will be more susceptible to flight-induced vision alterations.

Hypothesis 8: Subjects who are resistant to the reversal of in-flight symptoms and physiological status through the application of LBNP will be more susceptible to persistent flight-induced vision alterations.

Hypothesis 9: Propensity towards more severe changes in-flight and the more indolent postflight resolution pattern will correlate with a range of individual characteristics of the crewmembers, such as anatomical and microanatomical and physiological features and potentially, hitherto unsuspected factors.

NOTE: This study was merged with investigations from Dr. Alan Hargens (Fluid distribution before, during and after prolonged space flight) and Dr. Michael Stenger (Distribution of Body Fluids during Long Duration Space Flight and Subsequent Effects on Intraocular Pressure and Vision Disturbance) 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:	Current means of measuring increased intracranial pressure require an invasive monitoring system with skilled medical personnel. The techniques outlined in this proposal, if verified, would provide a rapid, accurate, non-invasive, and scalable solution to measure increases in intracranial pressure for a number of critical medical conditions. These studies will also provide physiological insight to the mechanisms of fluid shifts and their relationship to intracranial pressure. This information could be relevant to terrestrial disorders of intracranial pressure such as idiopathic intracranial hypertension (IIH).
Task Progress:	We have continued to make significant progress over the past year in all dimensions of the Fluid Shifts (FS) experiment. To date the team has performed preflight baseline data collection on fifteen crewmembers (one with a repeated session as backup), completed all inflight sessions for 11 subjects, and three sessions remain to complete inflight testing on all 13 subjects. Postflight sessions ranging from return plus 10 days (R+10) to R+180 have been completed for the first 10 subjects, including upright and 3 Tesla (3T) postflight MRI. Postflight sessions for the remaining three subjects will begin once they land. Hardware and procedures have run smoothly this past year, with no major failures. However, the FS team has continued to collectively respond to changes in circumstances, most notably the ascent abort of Soyuz MS-10 which was to carry the Expedition 57 crew to the ISS. This event necessitated adjustment of inflight and postflight data collection schedules. Supine and tilted 3T MRI data collections continued at the Victory Lakes facility (University of Texas Medical Branch-UTMB) facility, taking advantage of the existing MRID (MED B) pulse sequences. Subjects continued to tolerate the procedure well and all early assessments of data quality gave satisfactory results. Since 2016, the team includes Dr. Larry Kramer (University of Texas Health Science Center-Houston (UTHSC-H)) for general MRI advising and assistance with data analysis. Specifically, work is underway for CSF (cerebrospinal fluid) flow quantification in the Sylvian aqueduct and determination of pre- and postflight CSF production rates. Other MRI analysis methods continue to be refined to optimize data analysis in terms of quality and resources. Notwithstanding the decision by Medical Operations to use IV contrast during MED B MRI scans as the preferred version for venography, none of the Fluid Shifts subjects has received contrast injections and data collections are likely to continue with non-contrast techniques. Dr. Mark Haacke has recently been added to the team, who is a specialist in the collection and analysis of MRI venography data. He will complete the MRI analysis team, adding expertise in the analysis of susceptibility weighted imaging (SWI), and time of flight (TOF venography) in the head and neck. The subcontract has been established for this work and analysis will begin in the near future. The remaining three subjects are US crewmembers; therefore, challenges that the team experienced with remote (Moscow and Cologne) postflight MRI and physiological testing are not a concern. The "free-floating" use of the optical coherence tomography (OCT) device for inflight Chibis sessions continues to work well for crewmembers, resulting in similar exam times and data quality when compared to the traditional chinrest method. The Johnson Space Center (JSC) Cardiovascular and Vision Laboratory upgraded to the Heidelberg Engineering OCT2 in 2017, and the ISS unit was upgraded in 2018. OCT2 provides faster scanning time, and better image depth and resolution. Similar to other measures, ultrasound data are collected in the inflight baseline state (Columbus module) and again during Chibis (Russian Service Module), which allows us to contrast space normal to the lower negative pressure state induced by the Chibis device. Transcranial Doppler, optic nerve sheath diameter (ONSD), central retinal and ophthalmic artery Doppler, among other parameters, are being analyzed to compare conditions and individual subject variation. Our team has continued to make advances in the analysis of otoacoustic emission (OAE) data over the past year. Dr. David Kemp continues to provide invaluable OAE expertise, streamlining and refining the OAE analysis methods. We have focused our analysis on transient evoked OAE (TEOAE) phase shifts, which have been highly systematic in response to posture change and lower body negative pressure during preflight testing. TEOAE phase shifts are consistent with expected intracranial pressure changes due to HDT (head down tilt), and appear to be consistent across multiple subjects. OAE results indicate that overall, oval window tension (a surrogate for intracranial pressure) is not systematically elevated during space flight. Our team attended the NASA Human Research Program (HRP) Investigators' Workshop in Galveston, TX in January 2019, presenting an overall project poster for Fluid Shifts and participating in many Spaceflight Associated Neuro-ocular Syndrome (SANS)-related sessions and discussions. Our team also presented a poster highlighting our otoacoustic emissions findings in FS subjects. These findings were combined with prior data collected in collaboration with our 2016 summer intern (T. Caldwell), as well as with data from the impedance threshold device (ITD) project, to present the mechanistic relationships between TEOAE stimulation and response phases, middle ear pressure, and intracranial pressure. Tympanometry data from the Fluid Shifts study indicates a trend toward negative middle ear pressure in flight, and therefore there has been increased interest in the effects of middle ear pressure on OAE and cerebral and cochlear fluid pressure (CCFP) measures. Presentations (past year): 1) Kemp D, Ebert D, Melgoza R, Danielson R, Stenger M, Hargens A, Dulchavsky S. Otoacoustic Emissions Phase as an Indicator of Intracranial Pressure Change: Basis and Optimization for Fluid Shifts Studies. Presented at the Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. 2) Stenger MB, Hargens AR, Dulchavsky SA, Arbielle P, Danielson RW, Ebert DJ, Johnston SL, Laurie SS, Lee SMC, Liu J, Macias B, Martin DS, Minkoff L, Ploutz-Snyder R, Ribeiro LC, Sargsyan A, Smith SM. Fluid Shifts. Presented at the Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. 3) Macias BR, Laurie SS, Lee SMC, Martin DS, Ploutz-Snyder R, Sargsyan A, Marshall-Goebel K, Ebert DJ, Dulchavsky SA, Hargens AR, Stenger MB. Elevated Intracranial Pressure Does Not Explain Spaceflight-Induced Optic Disc Edema. Presented at the Association for Research in Vision and Ophthalmology Annual Meeting, Vancouver, B.C., April 28-May 2, 2019.

	Related Publication: 1) Garrett-Bakelman F.E., et al. (including D. Ebert). The NASA Twins Study: A multi-dimensional analysis of a year-long human spaceflight. Science. 2019 Apr 12;364 (6436).
Bibliography Type:	Description: (Last Updated: 02/23/2023)