Fiscal Year:	FY 2015	**Task Last Updated:**	FY 03/23/2015
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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
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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, 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 made significant progress over the past year in all dimensions of the Fluid Shifts (FS) experiment, from preparing applications and receiving approvals from the NASA-Johnson Space Center (JSC) Institutional Review Board (IRB) to baseline data collection activities. Early in the reporting period, we made serious steps with optimizing and scheduling our pre-, in-, and postflight tests to maximize their scientific value and to minimize impacts and risks to ISS crewmembers. The "Fluid Shifts: Space Flight Study" was approved by the NASA JSC IRB on 1/28/2014. In addition, we received International Partner IRB approvals as well as Human Research Multilateral Review Board (HRMRB) approval. We helped finalize the NASA informed consent briefing for the first one-year astronaut. At the request of the NASA Element office we succeeded in merging three flight projects. We worked to integrate our proposed ground and flight measures among the combined research team (Dulchavsky et al., Hargens et al., and Stenger et al.), and have now finalized our research testing protocols for ISS crewmembers We have completed studies demonstrating that our proposed testing sessions can be successfully completed within the allotted crew time. Representatives from the entire Fluid Shifts (FS) team visited NASA-JSC in March 2014 for ground feasibility tests to successfully integrate vascular ultrasound and ocular measurements. In the process of developing our protocols, several "feasibility study" test subjects completed the protocols (or portions thereof). Erik Hougland, our International Space Station Medical Projects (ISSMP) flight project manager, has been coordinating our bi-weekly FS team telecons. We have provided input to the baseline version of the "Fluid Shifts" Experimental Document (ED) as well as updated versions, most recently approved in January 2015. The ISSMP team has also done an excellent job coordinating crew ICBs (inflight crew briefing), training, and testing as well as coordinating hardware development and Russian activities. We have worked with the University of Texans Medical Branch (UTMB) Victory Lakes 3T MRI (magnetic resonance imaging) facility to develop scanning protocols that maximize science return while capitalizing on the existing medically required MRI sequences. Additionally, we developed a 15 degree foam wedge that allows subjects to be scanned in the 15 degree head-down tilted position in the wide-bore Siemens 3T Verio instrument. The wedge fits securely into the patient table yet is lightweight and simple in design, allowing for rapid transitions during subject scanning. Terry Guess (Wyle STE) was instrumental in the design and construction of this wedge. We also visited the upright MRI facility to meet with the members of the FS team as well as Fonar and MRI facility personnel. We also participated in the protocol development and feasibility runs of the proposed MRI measures which include cerebral spinal fluid flow tests. Testing in the two MRI systems was coordinated to acquire mutually complementary data on central nervous system structure, vascular, and cerebrospinal fluid systems. We provided expertise and coordinated the acquisition of iCare intraocular pressure measurement devices (rebound tonometry). The team decided to use the iCare Pro for FS pre- and postflight studies due to its ability to collect tonometry data (eye pressure) in the supine position (without rolling the subject's head to the side), as well as the fact that it does not require eye anesthesia. The team would have preferred using the iCare TA01i inflight, however Human Research Program (HRP) and MedOps chose not to fly this additional hardware. Also, we provided feedback on acquisition and flight development of the Marchbanks Cerebral and Cochlear Fluid Pressure (CCFP) units. The Marchbanks device received a CE mark and the NASA research unit was shipped on 1/30/2014. In addition, two of the CCFP flight units arrived at NASA JSC on 12/29/2014. These flight units have now passed all flight hardware testing and certification and one unit has been delivered for packing onto the SpaceX6 vehicle in preparation for delivery to ISS. We have held conferences with Drs. Mike Williams and Bob Marchbanks to learn lessons from their experiments and assembly of our CCFP units to facilitate implementation of the CCFP hardware into our ISS flight project. In addition, we have worked with Dr. Alan Hargens' lab in developing the CCFP data analysis protocol. Parabolic flights were conducted in April 2014 under the Flight Opportunities Program "Microgravity Health Care" project to evaluate CCFP, Otoacoustic Emissions (OAE), and the iCare tonometer in microgravity. All three devices performed well in micro-, partial, and hypergravity, eliminating any concerns regarding proper operation once delivered to ISS. No major usability or ergonomic concerns were discovered. Physiological data was collected on multiple subjects, and a significant effect of gravity on intraocular pressure was found. OAE data quality was negatively affected by aircraft noise, but OAE and CCFP data are still being analyzed. Our study will utilize the Russian Chibis device; we have been in close contact with our Russian collaborators, Irina Alferova and Zhanna Yarmanova, to coordinate ISS Chibis operations and study implementation. We had a productive meeting with Drs. Alferova and Yarmanova to coordinate our planned physiological measures in the Russian ISS segment during Chibis operations at NASA JSC this past year. The ISSMP team continues to work Russian operational issues such as inverter use, safety certifications, and camera placements, among other topics. We provided feedback on the acquisition of the research Spectralis Optical Coherence Tomography (OCT) device with anterior segment module. A major milestone completed this year was acquisition and modification of an adjustable arm for OCT measurements in the upright, supine, and head-down-tilt positions. Terry Guess, a Wyle team member, did an excellent job working with the OCT manufacturer (Heidelberg Engineering) to verify that this was the correct solution and make the further modifications that made this an optimal OCT device for use in our experiment. We continue to work with Heidelberg to finalize automated, quantitative, and objective measures of ocular structures; however, it appears that automated choroid analysis will require a complete re-configuration of the current Heidelberg software. We understand that Heidelberg is still developing this software but the timeline has been significantly delayed. Therefore,

we are pursuing other options for choroid analysis including collaboration with Dr. Nimesh Patel at University of Houston (UH) School of Optometry, and potentially Dr. Brian Samuels at the University of Alabama at Birmingham (UAB).

Testing and training have been initiated to enable “free-floating” of the OCT device for in-flight measurements. Prior work by members of our group tested the feasibility of using the OCT scanner in free-float (without the use of the chin rest and stage); parabolic flights were conducted in November 2013 that established that this mode was feasible. This information opened up options for scanning locations other than the Maintenance Work Area (MWA) which would include scanning in the Russian Service Module while in Chibis. An inflight (ISS) free-float practice run is scheduled for April 2, 2015. All training sessions and preflight baseline data collection (BDC) have been completed for both one year mission crewmembers (including one cosmonaut); training and preflight BDC has also been completed for the one year mission US backup crewmember. These include MRI, dilution measures, ultrasound, OCT, tonometry, NIR (near infrared), CCFP, and OAE measures. Ocular and transcranial ultrasound analysis is complete on all data collected to date.

The team has also provided coordination with the Twins study to ensure the most efficient and effective data collection for both Fluid Shifts and Twins study can be accomplished.

Our team attended the NASA HRP Investigators’ Workshop in Galveston, TX in January 2015, presenting a poster on the FS project and participating in many Vision Impairment and Intracranial Pressure (VIIP) related sessions and discussions.

Bibliography Type:	Description: (Last Updated: 02/23/2023)
Abstracts for Journals and Proceedings	Stenger M, Hargens A, Dulchavsky S, Ebert D, Lee S, Laurie SS, Garcia KM, Sargsyan A, Martin D, Liu J, Macias BR, Arbeille P, Danielson R, Chang D, Gunga H, Johnston SL, Westby CM, Ploutz Synder RJ, Smith AM. "Fluid Shifts." 2015 NASA Human Research Program Investigators’ Workshop, Galveston, TX, January 13-15, 2015. 2015 NASA Human Research Program Investigators’ Workshop, Galveston, TX, January 13-15, 2015. Abstract #0020. , Jan-2015