Fiscal Year:	FY 2020	**Task Last Updated:**	FY 12/30/2020
PI Name:	Ethier, Christopher Ph.D.		
Project Title:	VIIP Simulations of CSF, Hemodynamics and Ocular Risk (VIIP SCHOLAR)		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
Joint Agency Name:		**TechPort:**	Yes
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:	ross.ethier@bme.gatech.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	404-385-0100
Organization Name:	Georgia Institute of Technology		
PI Address 1:	Biomedical Engineering		
PI Address 2:	315 Ferst Drive		
PI Web Page:	http://ethier.gatech.edu/		
City:	Atlanta	**State:**	GA
Zip Code:	30332-0363	**Congressional District:**	5
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2015-16 HERO NNJ15ZSA001N-Crew Health (FLAGSHIP, NSBRI, OMNIBUS). Appendix A-Crew Health, Appendix B-NSBRI, Appendix C-Omnibus
Start Date:	10/01/2016	**End Date:**	09/30/2020
No. of Post Docs:	1	**No. of PhD Degrees:**	
No. of PhD Candidates:	0	**No. of Master' Degrees:**	
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	3
No. of Bachelor's Candidates:	3	**Monitoring Center:**	NASA GRC
Contact Monitor:	Norsk, Peter	**Contact Phone:**	
Contact Email:	Peter.norsk@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: End date changed to 9/30/2020 per NSSC information (Ed., 10/9/19)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Martin, Bryn Ph.D. (University of Idaho, Moscow) Myers, Jerry Ph.D. (NASA Glenn Research Center) Oshinski, John Ph.D. (Emory University) Samuels, Brian M.D., Ph.D. (University of Alabama, Birmingham)		
Grant/Contract No.:	NNX16AT06G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

Visual Impairment/Intracranial Pressure (VIIP) syndrome [Ed. note July 2018: now referred to as Spaceflight Associated Neuro-ocular Syndrome (SANS)] occurs in a significant fraction of astronauts undergoing long-duration space flight, and is characterized by a spectrum of ophthalmic changes. Astronauts with VIIP can suffer permanent loss of visual acuity, and thus this condition is a major health concern for NASA. The pathophysiology of VIIP is poorly understood. However, evidence points to an important role for alterations in cerebrospinal fluid (CSF) and vascular flow dynamics/pressures in microgravity.
In view of the above, we hypothesize that the pathophysiology of VIIP involves alterations in biomechanical loads on the neural and connective tissues of the posterior globe/optic nerve due to changed CSF/blood pressures in microgravity. We further postulate that risk factors for VIIP can be identified through numerical modeling of these processes, and that such models can be used to evaluate proposed VIIP countermeasures.

In this proposal we will develop modeling tools that: (i) compute fluid shifts in microgravity; (ii) compute how these shifts lead to biomechanical insult to the optic nerve in astronauts; and (iii) estimate the effect that these insults have on optic nerve function. These tools will directly build upon, and interface with, models of ocular biomechanics and fluid shifts that we are currently developing in our NASA-funded MONSTR Sim project. Towards this end, we propose 4 specific aims:

SA1: Measure key physiologic parameters needed for modeling, including effects of intracranial pressure on optic nerve sheath diameter, optic nerve tortuosity, craniospinal volume, and cerebral blood flow.

SA2: Incorporate “quasi-1D” effects into existing compartment models, allowing us to evaluate the effects of microgravity and countermeasures on CSF and blood flows/pressures.

SA3: Extend finite element models of ocular biomechanics, specifically modeling: (i) optic nerve kinking, and (ii) compression of optic nerve fiber bundles in the lamina cribrosa; and relate kinking/compression to an index of axoplasmic insult/stasis.

SA4: Carry out parametric studies integrating the above models to identify individual-specific factors that: (i) predispose for the development of VIIP syndrome, and (ii) influence the efficacy of proposed countermeasures, both useful for risk profiling.

The resulting models will provide a powerful platform for better understanding individual-specific risks for VIIP and, eventually, for evaluating VIIP mitigation strategies, thus contributing to astronaut health. More specifically, these models will allow us to quantify the biomechanical environment of the optic nerve at the level of individual nerve fiber bundles, with outcome measures designed to predict the risk of two specific clinical features of VIIP: optic nerve kinking and papilledema.

This proposal directly addresses an explicit requirement of NASA Research Announcement NNJ15ZSA001N, namely to “...to develop and deliver detailed numerical models that quantify how CSF and vascular flow dynamics are altered in microgravity, and the propagative effects on the structure of the eye. The models must also be developed with the capability to interact with other pre-existing numerical models of the cardiovascular system, central nervous system, and eye ...”

The team assembled for this work has highly complementary skills that together address all relevant aspects of this complex, interdisciplinary problem. In addition to Ethier (Principal Investigator (PI) at Georgia Tech; expertise in modeling optic nerve head and ocular biomechanics), co-investigators include Myers (NASA Glenn; expertise in cephalad fluid shift models and space physiology); Samuels (Alabama; expertise in clinical ophthalmology and neuroscience); Oshinski (Georgia Tech/Emory; expertise in MR imaging of CSF and blood flow dynamics); and Martin (Idaho; expertise in modeling CSF dynamics).

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

May also help the understanding of idiopathic intracranial hypertension, an analogous condition that occurs in patients on Earth.

Task Progress:

FINAL REPORTING DECEMBER 2020
We acquired MRI scans of the eye and optic nerve sheath in 18 volunteers before and after head down tilt (HDT), as an acute analog of microgravity. Further, the MRI acquisition protocol was repeated in one subject, to assess test-retest variability. We acquired multiple pieces of information from each scan: (i) anatomic information (optic nerve sheath shape, globe shape), and (ii) flow in major cerebral arteries, veins, and CSF spaces.

We used this data for several purposes. First, we quantified optic nerve sheath (ONS) enlargement due to HDT, and then conducted finite element modeling to determine in vivo optic nerve sheath material properties. This work established a methodology for the determination of ONS mechanical properties in human subjects, opening the possibility of monitoring changes in such properties due to spaceflight. It also has provided much-improved values of such properties, correcting several errors in the literature. Second, we developed tools to quantify the anatomy of the optic nerve and ocular globe, including: 1) tortuosity, 2) vitreous chamber depth, 3) optic chiasm-to-ONH distance, 4) 3D bulbar subarachnoid space geometries, and 5) 3D posterior globe deformation. We applied these tools in both human volunteers and also astronauts who had undergone long-duration space flight, quantifying changes in ocular globe dimensions and their relationship to SANS. Third, we also measured blood flow and cerebrospinal fluid (CSF) flow in volunteers before and after HDT. We found that that acute application of 15° HDT caused a reduction in CSF flow variables (systolic peak flow and peak-to-peak pulse amplitude) which, when coupled with a decrease in average cerebral arterial flow, systolic peak flow, and peak-to-peak pulse amplitude, is consistent with a decrease in cardiac-related pulsatile CSF flow. These results suggest that decreases in cerebral arterial inflow were the principal drivers of decreases in CSF pulsatile flow.

In addition to the MRI data set, we conducted a meta-analysis of data in the literature on how intraocular pressure (IOP) depends on body position. We found a "universal" relationship between body posture and IOP, specifically determining that posturally induced IOP change can be explained by hydrostatic forcing plus an autoregulatory contribution that is dependent on hydrostatic effects. This study will be useful for future work considering postural change in relation to ocular physiology, intraocular pressure, ocular blood flow and aqueous humor dynamics. Finally, we have continued the development of a system model of regulation functions and validation studies with a Whole Body Model of fluid shifts,

	focusing on relevant pressures and volumes for space flight analogies. This work has been documented in 6 refereed journal papers (3 accepted and 3 in various stages of revision) and multiple conference presentations. ANNUAL REPORTING JULY 2019 We have acquired MRI scans of the eye and optic nerve sheath in 16 volunteers before and after head down tilt, and the acquisition protocol has been repeated in one subject. Using these data, we obtained 1) tortuosity, 2) vitreous chamber depth, 3) optic chiasm-to-ONH distance, 4) 3D bulbar subarachnoid space geometries, and 5) 3D posterior globe deformation parameters, which were used for subsequent finite element (FE) modeling. We have focused on estimating optic nerve sheath (ONS) stiffness using the subject-specific FEM models derived from MRI scans, necessary for future exploration of possible effects of microgravity and elevated CSF pressure on ocular function. We have also investigated the relationship between ONS stiffness and subject characteristics such as age, BMI (body mass index), and gender to obtain insight of risk factors for SANS. We have continued investigation of the system modeling of regulation functions and validation studies with a Whole Body Model of fluid shifts, focusing on relevant pressures and volumes for space flight analogies.
Bibliography Type:	Description: (Last Updated: 11/26/2021)
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Abstracts for Journals and Proceedings	Ethier CR, Feola AJ, Nelson ES, Meyers JG, Samuels BC. "Choroidal thickening imparts significant mechanical insult to ONH tissues." Poster presentation at 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. Program book 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019, p. 35. , Jan-2019
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Abstracts for Journals and Proceedings	Zahid A, Oshinski J, Martin B, Collins S, Ethier CR. "Changes in Arterial, Venous, and CSF Flow Dynamics Under Simulated Micro-Gravity Conditions." Presented at Georgia Clinical & Translational Science Conference 2019, Callaway Gardens, GA, February 28-March 1, 2019. Abstract book of the 2nd Annual Georgia Clinical & Translational Science Conference, Callaway Gardens, GA, February 28-March 1, 2019. , Feb-2019
Abstracts for Journals and Proceedings	Zahid A, Oshinski J, Martin B, Collins S, Ethier CR. "Changes in Arterial, Venous, and CSF Flow Dynamics Under Simulated Micro-Gravity Conditions." Presented at Translational Science 2019, Washington DC, March 5-8, 2019. Program and abstracts. Translational Science 2019, Washington DC, March 5-8, 2019. , Mar-2019
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Articles in Peer-reviewed Journals	Sater SH, Sass AM, Seiner A, Natividad GC, Shrestha D, Fu AQ, Oshinski JN, Ethier CR, Martin BA. "MRI-based quantification of ophthalmic changes in healthy volunteers during acute 15° head-down tilt as an analogue to microgravity." J R Soc Interface. 2021 Apr;18(177):20200920. https://doi.org/10.1098/rsif.2020.0920 ; PMID: 33906382 , Apr-2021
Awards	Zahid A. "TL1 Blue Ribbon Award for: A. Zahid, J. Oshinski, B. Martin, S. Collins and C.R. Ethier, Changes in Arterial, Venous, and CSF Flow Dynamics Under Simulated Micro-Gravity Conditions. Translational Science 2019, Washington DC, March 5-8, 2019." Mar-2019