Fiscal Year:	FY 2015	**Task Last Updated:**	FY 07/29/2014
PI Name:	Ethier, Christopher Ph.D.		
Project Title:	Microgravity-driven Optic Nerve/Sheath Remodeling Simulator (MONSTR Sim)		
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) **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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Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2012 Crew Health NNJ12ZSA002N
Start Date:	10/01/2013	**End Date:**	09/30/2016
No. of Post Docs:	2	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NASA GRC
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	none		
COI Name (Institution):	Gleason, Rudolph (Georgia Institute of Technology) Myers, Jerry (NASA Glenn Research Center) Samuels, Brian (Indiana University) Nelson, Emily (NASA Glenn Research Center)		
Grant/Contract No.:	NNX13AP91G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Visual Impairment/Intracranial Pressure (VIIP) syndrome occurs in a significant fraction of astronauts undergoing long-duration space flight. VIIP is characterized by a spectrum of ophthalmic changes, including optic nerve sheath distention and kinking, optic disc edema, choroidal folds, and flattening of the posterior eye globe. Most significantly, astronauts with VIIP can suffer permanent loss of visual acuity. The cause(s) of VIIP are not well understood, but the syndrome has ophthalmic features similar to those seen in patients with idiopathic intracranial hypertension, strongly suggesting that elevations in intracranial pressure and/or reductions in intraocular pressure play an important role in VIIP. Notably, observations in VIIP are consistent with a major alteration in the pressure difference across the lamina cribrosa. Given the probable role of these altered pressures in VIIP, any VIIP computational model should include biomechanical models of the relevant ocular tissues. Importantly, VIIP develops slowly (over weeks); further, the anatomic changes observed in ocular connective tissues (e.g. the optic nerve sheath) appear to be permanent in some cases. This strongly suggests that tissue remodeling is an important aspect of VIIP, and thus any attempt to understand VIIP must consider remodeling effects. In view of the above, we hypothesize that cephalad fluid shifts in microgravity affect intracranial pressure (ICP) and intraocular pressure (IOP), leading to altered biomechanical loads on the tissues of the posterior globe and optic sheath. This altered biomechanical environment in turn causes connective tissue remodeling, an important contributing factor to vision changes in the VIIP syndrome. We will develop modeling tools to allow the above hypothesis to be tested, and which will provide a test bed for identification of which clinically observable attributes play key roles in the development of the VIIP syndrome. These tools will be developed through 4 specific aims: SA1: Develop validated tools for computing IOP and ICP in microgravity. These tools will be based on modeling of fluid shifts between the eye and various compartments in the cardiovascular, cerebrospinal and lymphatic systems. SA2: Develop validated finite element-based tools for computing the biomechanical environment and subsequent connective tissue remodeling in the optic nerve head, optic nerve sheath, and posterior globe. These tools will be complemented by a model of the eye's optical performance. SA3: Integrate the models from SA1 and SA2 to produce a unified, open, and extensible software package that can predict ocular biomechanics and ocular connective tissue remodeling under microgravity conditions. SA4: Use the integrated model of SA3 to study clinically observable attributes and determine the role they may play in the development of VIIP. This proposal directly addresses an explicit requirement of NASA Research Announcement NNJ12ZSA002N, namely to "… develop and deliver numerical model(s) of the visual system quantifying the biomechanical pathways by which gravitational unloading could affect the distribution of hydrodynamic pressures within the CVS and CNS, and their impact on the structure of the eye." Our models will provide a powerful platform for better understanding VIIP and, eventually, for suggesting VIIP screening and mitigation strategies, thus contributing to astronaut health. Our team has highly complementary skills that together address all relevant aspects of this complex, interdisciplinary problem. In addition to Ethier (PI at Georgia Tech; expertise in modeling optic nerve head and ocular biomechanics), co-investigators include Myers, Best, and Nelson (NASA Glenn; expertise in cephalad fluid shift models and space physiology); Samuels (Indiana; expertise in clinical ophthalmology and neuroscience); and Gleason (Georgia Tech; expertise in soft tissue biomechanics and tissue remodeling).
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	
Task Progress:	This grant studies the causes of Visual Impairment/Intracranial Pressure (VIIP) syndrome, with the eventual goal of identifying mitigation strategies. Our specific objective is to develop and use a finite element model (FEM) to simulate the biomechanical environment of the posterior eye and optic nerve sheath (dura mater), since biomechanical factors are hypothesized to play an important role in VIIP. This FEM will be coupled with a lumped-parameter model that describes fluid shifts and pressure changes under microgravity. Eventually, our FEM will incorporate growth and remodeling algorithms to assess how fluid pressure changes lead to alterations in tissue properties/geometry in the eye and optic nerve. Before undertaking finite element modeling, it was necessary to carry out experiments to measure relevant parameters of the optic nerve sheath (dura mater). Specifically, we characterized the mechanical behavior (stiffness) and fluid permeability of the dura mater, and determined its collagen orientation. Stiffness measurements showed significant hysteresis, typical of soft tissues, and strain-induced stiffening. From measured pressure-diameter curves we derived stress-strain relationship for the sheath and calculated the tangent modulus at various levels of intracranial ICP. At ICP = 7 mmHg, the tangent modulus was approximately 400 kPa, increasing to c. 2 MPa at ICP = 30 mmHg. The measured fluid permeability of the dura was approximately 0.8 µL/min/cm2/mmHg (n=17), which in turn predicts that a significant volume of CSF crosses the dura each day. Microscopy showed that the collagen fibers in the dura mater have an initial crimp, or wave-like, pattern when unloaded but become elongated and straighten as ICP is increased. We then created a finite element model of the posterior eye. This model includes the posterior sclera, peripapillary sclera, optic nerve, lamina cribrosa, dura mater, pia mater, and a simplified central retinal vessel. In this initial model we treated all the constituent tissues as linearly elastic and isotropic, simplifications which we will shortly relax. Utilizing this model we examined the effect of increasing intracranial pressure from 0 to 30 mmHg, based on the CSF pressures at the posterior eye expected in upright posture (walking and standing, 0 mmHg) to those in space flight (30 mmHg). For these simulations we held intraocular and retinal vessel pressures constant at normal values (15 mmHg and 55 mmHg, respectively) to isolate the effects of increasing ICP. A significant finding from these results was that strains within the lamina cribrosa and post-laminar neural tissue change as ICP increases. This is important because changes in strains have been hypothesized to play a role in other visual diseases (e.g. glaucoma) and may explain some of the connective tissue changes observed in VIIP.
Bibliography Type:	Description: (Last Updated: 11/26/2021)
Abstracts for Journals and Proceedings	Raykin J, Best L, Gleason R, Mulugeta L, Myers J, Nelson E, Samuels B, Ethier CR. "Experimental Measurements Driving Modeling of VIIP Syndrome." 2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014. 2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014. http://www.hou.usra.edu/meetings/hrp2014/pdf/3209.pdf , Feb-2014

Abstracts for Journals and Proceedings	Ethier CR, Best L, Gleason R, Mulugeta L, Myers JG, Nelson ES, Samuels B. "A Framework for Modeling Connective Tissue Changes in VIIP Syndrome." 2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014. 2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014. http://www.hou.usra.edu/meetings/hrp2014/pdf/3210.pdf , Feb-2014
Abstracts for Journals and Proceedings	Ethier CR, Raykin J, Gleason R, Mulugeta L, Myers J, Nelson E, Samuels B. "Biomechanics of the Optic Nerve Sheath in VIIP Syndrome." 7th World Congress of Biomechanics., Boston, MA, July 6-11, 2014. 7th World Congress of Biomechanics., Boston, MA, July 6-11, 2014. , Jul-2014
Abstracts for Journals and Proceedings	Raykin J, Best L, Gleason R, Mulugeta L, Myers J, Nelson E, Samuels B, Ethier CR. "Optic Nerve Sheath Mechanics and Permeability in VIIP Syndrome." Annual Association for Research in Vision and Ophthalmology (ARVO) Meeting, Orlando, FL, May 4-8, 2014. Annual Association for Research in Vision and Ophthalmology (ARVO) Meeting, Orlando, FL, May 4-8, 2014. ARVO 2014 Annual Meeting Abstracts http://www.arvo.org/webs/am2014/abstract/sessions/436.pdf , May-2014