Fiscal Year:	FY 2016	**Task Last Updated:**	FY 09/26/2016
PI Name:	Puttlitz, Christian Ph.D.		
Project Title:	Fracture Healing in Haversian Bone under Conditions of Simulated Microgravity		
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) **Bone Fracture**:Risk of Bone Fracture due to Spaceflight-induced Changes to Bone		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	80523-1374	**Congressional District:**	4
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2010 Crew Health NNJ10ZSA003N
Start Date:	08/24/2011	**End Date:**	06/30/2016
No. of Post Docs:	0	**No. of PhD Degrees:**	1
No. of PhD Candidates:	1	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	6	**Monitoring Center:**	NASA JSC
Contact Monitor:	Ploeger, Stephanne	**Contact Phone:**	
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Flight Program:			
Flight Assignment:	NOTE: Extended to 6/30/2016 per NSSC information (Ed., 9/28/15) NOTE: Extended to 8/23/2015 per HRP and NSSC information (Ed., 10/21/2014)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Browning, Raymond (Colorado State University) Haussler, Kevin (Colorado State University) McGilvray, Kirk (Colorado State University) Santoni, Brandon (Foundation for Orthopaedic Research and Education) Palmer, Ross (Colorado State University) Easley, Jeremiah (Colorado State University)		
Grant/Contract No.:	NNX11AQ81G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	There is a need for information regarding hard and soft tissue healing in microgravity environments, and if impaired healing exists, what countermeasures can be called upon to enhance healing. Research on fracture healing using the rodent hindlimb suspension model shows healing is impaired in simulated microgravity, while clinical research shows that moderate, early mechanical loading caused by weight bearing induces osteogenesis and aids in repair of bone fracture. Further research is needed to determine what loads, if any, should be applied during spaceflight to promote fracture healing. Most ground-based microgravity models utilize rodent hindlimb suspension to simulate how reduced loading affects isolated physiologic systems. Unfortunately, results derived from these studies are difficult to directly translate to the human condition due to major anatomic and physiologic differences between rodents and humans. Specifically, the differences in rodent and human bone structures become increasingly important when studying orthopaedic issues such as bone maintenance and healing during spaceflight. For example, the basic microstructure of rodent bone, known as “plexiform” bone, lacks the osteons (Haversion systems) that are the main micro-architectural feature of human cortical bone. Furthermore, it is known that the osteogenic and healing potential of rodent bone far exceeds that of adult human tissue. Due to these limitations in current ground-based microgravity models, there exists a need to develop a ground-based, large animal model of fracture healing in simulated weightlessness that more closely approximates the human condition as has been done in the first year of this study. This animal model should be capable of simulating a wide spectrum of microgravity and able to investigate exercise protocols that may aid in the optimization of the fracture healing cascade. Four specific aims were defined to meet these goals: 1) Develop a ground-based large animal model of bone unloading in order to simulate full weightlessness; 2) interrogate the effects of a simulated microgravity environment on bone fracture healing in a large animal model; 3) develop a computational model of weightbearing in ovine bone under different experimental conditions in order to characterize the loads experienced by the fracture site; and 4) investigate possible countermeasures to the deleterious effects of weightlessness on fracture healing.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The data collected during the first year of this study clearly demonstrate that the ovine model of ground-based microgravity effectively simulates the bone loss experienced by astronauts in space and ground-based rodent hindlimb suspension. This model has a major advantage over rodent hindlimb suspension models in that the mature ovine bone structure is nearly identical to that of humans, and future studies utilizing this large animal model (i.e., how hard and soft tissues heal in a microgravity environment, which will be executed in year two of this grant) will be easily translated to the human condition. Furthermore, the study of fracture healing will benefit from the use of a large animal model rather than a rodent model since the healing potential of sheep more closely matches that of humans than rodents. The ground-based experiments utilizing this large animal (ovine) model directly address the need to know how varying microgravity environments affect fracture healing, as well as determining the applied loads at the fracture healing site through inverse dynamics and finite element simulations. The fracture rehabilitation protocols explored within this study will also aid in determining which mechanical environment leads to enhanced bone healing under microgravity conditions. The data produced during this study will significantly advance the basic mechanobiology of fracture healing by discerning which mechanical signals and environments facilitate enhanced bone healing.
Task Progress:	Specific Aim 3 outlined the development of a finite element of the ovine hindlimb in order to characterize the localized mechanical environment of a healing fracture in simulated microgravity and Earth gravitational environments. A high fidelity finite element (FE) model of the ovine hindlimb extending from the tibia to proximal phalanges was constructed and external fixation componentry was modeled to mimic the experimental methodology of Specific Aim 2. Additionally, a control model was created in which no external fixation componentry was included. Each model underwent a thorough validation process using experimental data from Specific Aims 1 and 2 to ensure model fidelity and robustness of model predictions. In order to simulate the fracture healing process of Specific Aim 2, histological data was utilized to create geometrically-matching fracture calluses on the Microgravity and Control models. Each model was then loaded with ground reaction forces measured during Specific Aim 2 and the local maximum and minimum principal strain as well as hydrostatic pressure predictions for each model were quantified. The findings indicated that the mechanical unloading experienced during simulated microgravity resulted in inhibited fracture healing by inducing fundamental changes in the bone formation processes, specifically by reducing hydrostatic pressure and strain of the healing fracture. These reductions resulted in alterations in the healing process, with animals exposed to a simulated microgravity environment subsequently healing primarily via intramembranous bone formation rather than the typical endochondral ossification process experienced by animals healing in an Earth gravitational environment. Finally, in Specific Aim 4, two therapeutic countermeasures to the inhibited fracture healing of simulated microgravity unloading were investigated. The methodology of Specific Aim 2 was replicated, and shock wave therapy and low-intensity pulsed ultrasound were administered to animals healing in simulated microgravity and Earth gravitational loading environments. While fracture mechanical competency was not significantly altered following either countermeasure, both treatments significantly elevated osteoblast numbers and bone formation rates in simulated microgravity animals. The outcome of this study suggests that shock wave therapy and low-intensity pulsed ultrasound may be beneficial in situations involving aberrant fracture healing but elicit minimal modifications to the normal healing sequelae.
Bibliography Type:	Description: (Last Updated: 03/25/2020)
Abstracts for Journals and Proceedings	Gadomski BC, Qin Y-X, Jiao J, McGilvray KC, Easley JT, Palmer RH, Puttlitz CM. "Shock wave therapy and low-intensity pulsed ultrasound accelerate bone formation rates under simulated microgravity conditions." Presented at the 2016 NASA Human Research Program Investigators’ Workshop, Galveston, TX, February 8-11, 2016. 2016 NASA Human Research Program Investigators’ Workshop, Galveston, TX, February 8-11, 2016. , Feb-2016

Abstracts for Journals and Proceedings	Gadomski BC, Lerner ZF, Browning RC, Puttlitz CM. "A finite element investigation of fracture healing under simulated microgravity loading conditions." Summer Biomechanics, Bioengineering and Biotransport Conference, Snowbird, UT, July 17-20, 2015. Proceedings of the Summer Biomechanics, Bioengineering and Biotransport Conference, Snowbird, UT, July 17-20, 2015. , Jul-2015
Articles in Peer-reviewed Journals	Gadomski BC, McGilvray KC, Easley JT, Palmer RH, Jiao J, Li X, Qin Y-X, Puttlitz CM. "An investigation of shock wave therapy and low-intensity pulsed ultrasound on fracture healing under reduced loading conditions in an ovine model." J Orthop Res. 2018 Mar;36(3):921-9. Epub 2017 Aug 11. https://doi.org/10.1002/jor.23666 ; PubMed PMID: 28762588 [Note reported originally in Sept 2016 as in review at Bone with title "Shock wave therapy and low-intensity pulsed ultrasound accelerate bone formation rates under simulated microgravity loading conditions."] , Mar-2018
Articles in Peer-reviewed Journals	Gadomski BC, Lerner ZF, Browning RC, Easley JT, Palmer RH, Puttlitz CM. "Computational characterization of fracture healing under reduced gravity loading conditions." J Orthop Res. 2016 Jul;34(7):1206-15. Epub 2016 Jan 8. https://dx.doi.org/10.1002/jor.23143 ; PubMed PMID: 26704186 , Jul-2016