Fiscal Year:	FY 2013	**Task Last Updated:**	FY 06/23/2013
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) **Fracture**:Risk of Bone Fracture due to Spaceflight-induced Changes to Bone (IRP Rev F)		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	puttlitz@engr.colostate.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	970-224-9743
Organization Name:	Colorado State University		
PI Address 1:	1374 Campus Delivery		
PI Address 2:	Department of Mechanical Engineering and School of Biomedical Engineering		
PI Web Page:			
City:	Fort Collins	**State:**	CO
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:**	08/23/2014
No. of Post Docs:	0	**No. of PhD Degrees:**	0
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:	2	**Monitoring Center:**	NASA JSC
Contact Monitor:	Mullenax, Carol	**Contact Phone:**	281.244.7068
Contact Email:	carol.a.mullenax@nasa.gov		
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Browning, Raymond (Colorado State University) Haussler, Kevin (Colorado State University) McGilvray, Kirk (Colorado State University) Ryan, Stewart (Colorado State University) Santoni, Brandon (Foundation for Orthopaedic Research and Education)		
Grant/Contract No.:	NNX11AQ81G		
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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 microgravities 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) develop treadmill protocols that enhance bone fracture healing in the presence of simulated microgravity.
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 addresses 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:	Aim 1 (completed): To date, the work for Specific Aim 1 is 100% complete. The findings of Specific Aim 1 have been presented at the 2012 and 2013 NASA Human Research Program Investigators’ Workshops, the 2013 American Society of Mechanical Engineers Summer Bioengineering Conference, and have been submitted for publications to the Journal of Biomechanics. Aim 2: Solid progress has been made in determining the effects of simulated microgravity on haversian bone healing in Specific Aim 2. Utilizing the previously characterized external fixation device, simulated microgravity was induced for a period of 3 weeks in an animal model resulting in a mean 18% loss in metatarsal bone mineral density. Following the 3-week simulated microgravity exposure period, a 3.0 mm ostectomy was created at the mid-diaphysis of the metatarsal bone and stabilized via an orthopaedic locking plate instrumented with a strain gage. Inhibited in vivo fracture healing occurred in the Microgravity Group as evidenced by an 18% percent increase in orthopaedic plate strain over the 4-week healing period versus a 98% decrease in orthopaedic plate strain in the Earth gravity control group. These findings were further substantiated by biomechanical four-point bending and micro-computed tomography results (μCT) which displayed a statistically significant 88% (pAim 3: Computational models of the sheep hindlimb were created in order to delineate the specific mechanical signals responsible for directing the fracture healing cascade. A musculoskeletal model of the full ovine hindlimb was created from the phalanges to the hip complete with all relevant muscular structures. Physiologic muscle moment arms and attachment sites of the limb were experimentally determined, and proper anthropometric properties of the hindlimb were acquired via dual-energy x-ray absorptiometry (DEXA) scans. In order to validate the musculoskeletal model, a treadmill experiment was performed wherein in vivo hindlimb motion were quantified via three-dimensional stereophotogrammetry, ground-reaction forces of the limb were acquired via a force plate positioned beneath the treadmill belt, and muscle activation was measured via electromyography (EMG) for speeds ranging from 0.25m/s to 1.0 m/s. Muscle activation predictions from the musculoskeletal model were then compared to the experimentally-derived EMG measurements for the various gate speeds in order to verify the model. A finite element model of the hindlimb was created consisting of the phalanges, metatarsus, hock joint, tibia, and relevant ligamentous structures. Transversely isotropic material properties were assigned to the cortical and cancellous bone constituents while the articular cartilage was modeled with a mooney-rivlin hyperelastic material definition. The finite element model was validated via comparison to experimentally-derived metatarsal surface strain readings as well as three-dimensional stereophotogrammetry motion tracking during simulated hindlimb compression. Metatarsal surface strain and joint rotation predictions of the finite element model were within one standard deviation of the experimental values indicating satisfactory validation of the model. The remaining three months in Year 2 will be utilized to complete the sample size of the in vivo fracture healing study. Additionally, decalcified and undecalcified histomorphometric analysis will be performed to quantify bone volume, mineralizing surface, mineral apposition rate, bone formation rate, and osteoblast and osteoclast numbers in the fracture callus and within the fracture gap. Computationally, model validation will be completed, and muscle forces predicted by the musculoskeletal model will be incorporated into the finite element model to begin ascertaining which specific mechanical signals are responsible for driving the fracture healing cascade.

	Based upon the data generated to date, it is expected that the additional specimens of Specific Aim 2 will conclusively and statistically demonstrate that the mechanical unloading associated with spaceflight significantly inhibits haversian bone healing. The findings of Specific Aim 2 will motivate Specific Aim 4 in which therapeutic interventions capable of increasing the fracture healing cascade during simulated microgravity will be investigated with the direct application to human spaceflight.
Bibliography Type:	Description: (Last Updated: 03/25/2020)
Abstracts for Journals and Proceedings	Gadomski BC, McGilvray KC, Easley JT, Palmer RH, Puttlitz CM. "Evaluation of a ground-based ovine model of simulated microgravity." 2013 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-14, 2013. 2013 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-14, 2013. , Feb-2013
Papers from Meeting Proceedings	Gadomski B, McGilvray K, Easley J, Palmer R, Puttlitz C. "Simulating microgravity in a large animal model." Presented at the American Society of Mechanical Engineers 2013 Summer Bioengineering Conference, Sunriver, OR, June 26-29, 2013. American Society of Mechanical Engineers 2013 Summer Bioengineering Conference, Sunriver, OR, June 26-29, 2013. Conference Proceedings. Paper SBC2013-14215. , Jun-2013