| | | | |
|---|---|---|---|
| **Fiscal Year:** | FY 2015 | **Task Last Updated:** | FY 10/29/2015 |
| **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 | | |
| **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:** | 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:** | 2 | **Monitoring Center:** | NASA JSC |
| **Contact Monitor:** | Ploeger, Stephanne | **Contact Phone:** | |
| **Contact Email:** | stephanne.l.ploeger22@nasa.gov | | |
| **Flight Program:** | | | |
| **Flight Assignment:** | NOTE: Extended to 6/30/2016 per NSSC information (Ed., 9/28/15)<br>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 )<br>Haussler, Kevin ( Colorado State University )<br>McGilvray, Kirk ( Colorado State University )<br>Santoni, Brandon ( Foundation for Orthopaedic Research and Education )<br>Palmer, Ross ( Colorado State University )<br>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.<br>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.<br><br>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.<br>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:** | Simulated microgravity-related alterations in fracture healing were investigated in this study. The employed methodology was based on (1) in vivo experimentation on skeletally mature female ewes to interrogate fracture healing and possible therapeutic countermeasures, and (2) finite element modeling of the ovine hindlimb under simulated microgravity and Earth gravity loading conditions to characterize the micromechanical environment of healing fractures. In Specific Aim 1, a ground-based, ovine model of skeletal unloading was developed in order to simulate a microgravity loading condition. The external fixation unloading technique utilized in this model was able to induce mechanical unloading of the metatarsus and significant alterations in the relevant radiographical, biomechanical, and histomorphometric parameters characteristic of spaceflight. Specifically, the newly developed ovine model captured the characteristic decrease in osteoblast numbers and increase in osteoclast activity associated with human spaceflight. The unloading methodology developed in Specific Aim 1 was extended to the investigation of fracture healing in a simulated microgravity loading environment in Specific Aim 2. The findings of this study revealed that the mechanical loading environment dramatically affects the fracture healing cascade and resultant mineralized tissue strength, and that animals that healed in a reduced loading environment demonstrated significant reductions in healing rate and callus mechanical competency as compared to animals healing in a 1G Earth gravitational environment.<br><br>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. External fixation componentry was modeled to mimic the experimental methodology of Specific Aim 2 and correlate model predictions to experimental outcomes. The findings indicate that simulated microgravity unloading decreases hydrostatic stress and principal strain within the callus and fracture gap, resulting in primarily intramembranous bone formation rather than the endochondral bone formation pathway characteristic of Earth-based fracture healing.<br><br>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.<br><br>While the results reported in this dissertation work provide an initial foundation to the understanding of fracture healing in reduced gravitational loading environments and possible countermeasures to the negative effects of reduced mechanical loading, additional investigations are warranted. Further investigation of the dose-dependent relationship and long-term healing characteristics of shock wave therapy and low-intensity pulsed will provide valuable information regarding their efficacy as a countermeasure during long-duration spaceflight. These efforts, as well as the investigation of other countermeasures, should be part of future simulated microgravity fracture healing work. |

| Bibliography Type: | Description: (Last Updated: 03/25/2020) |
|---|---|
| Abstracts for Journals and Proceedings | Gadomski BC, McGilvray KC, Easley JT, Palmer RH, Ruehlman D, Roberts M, Puttlitz CM. "Shock wave therapy does not enhance acute fracture strength but may accelerate formation rates under simulated microgravity conditions." 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015.<br>2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. , Jan-2015 |
| Abstracts for Journals and Proceedings | Gadomski BC, Lerner ZF, Browning RC, Puttlitz CM. "Finite element modeling of the ovine hindlimb for the investigation of microgravity-related mechaniobiological alterations." 61st Annual Meeting of the Orthopedic Research Society, Las Vegas, Nevada, March 28-31, 2015.<br>Proceedings of the 61st Annual Meeting of the Orthopedic Research Society, Las Vegas, Nevada, March 28-31, 2015. Poster 1530. , Mar-2015 |
| 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 Orthpaed Res. In Review, as of October 2015. , Oct-2015 |
| Articles in Peer-reviewed Journals | Lerner ZF, Gadomski BC, Ipson A, Haussler KK, Puttlitz CM, Browning RC. "Modulating tibiofemoral contact force in the sheep hindlimb via treadmill walking: Predictions from an OpenSim musculoskeltal model." J Orthop Res. 2015 Aug;33(8):1128-33. Epub 2015 May 28. http://dx.doi.org/10.1002/jor.22829 ; PubMed PMID: 25721318 , Aug-2015 |
| Articles in Peer-reviewed Journals | Gadomski BC, McGilvray KC, Easley JT, Palmer RH, Santoni BG, Puttlitz CM. "Partial gravity unloading inhibits bone healing responses in a large animal model." J Biomech. 2014 Sep 22;47(12):2836-42. Epub 2014 Aug 7. http://dx.doi.org/10.1016/j.jbiomech.2014.07.031 ; PubMed PMID: 25138631 , Sep-2014 |
| Papers from Meeting Proceedings | Gadomski BC, Lerner ZF, Browning RC, Puttlitz CM. "A finite element investigation of fracture healing under simulated microgravity loading conditions." Presented at the Summer Biomechanics, Bioengineering, and Biotransport Conference, Snowbird, Utah, June 17-20, 2015.<br>Proceedings of the 2015 Summer Biomechanics, Bioengineering, and Biotransport Conference, Snowbird, Utah, June 17-20, 2015. Paper 2015-422. ISBN: 978-0-692-45599-9. , Jun-2015 |