INSIGHTS GAINED FROM THE HINDLIMB UNLOADED RAT MODEL FOR REPEATED SPACEFLIGHTS AND WITH EXERCISE ADDED DURING RECOVERY

Y. Shirazi-Fard\textsuperscript{2}, R.A. Anthony\textsuperscript{2}, A.T. Kwaczała\textsuperscript{3}, S. Judex\textsuperscript{4}, C.E. Metzger\textsuperscript{3}, A.V. Mantri\textsuperscript{4}, J.S. Kupke\textsuperscript{2}, J.M. Davis\textsuperscript{1}, S.D. Morgan\textsuperscript{1}, E. Gonzalez\textsuperscript{1}, S.A. Bloomfield\textsuperscript{1}, H.A. Hogan\textsuperscript{1,2}

Departments of 1Mechanical Engineering, 2Biomedical Engineering, 3Health & Kinesiology, 4Texas A&M University Health Science Center College of Medicine, Texas A&M University, College Station, TX

1Department of Biomedical Engineering, State University, Stony Brook, NY

INTRODUCTION

Encouraging results have been reported recently for ISS crew members as a result of improved nutrition, better exercise equipment, and/or administration of osteoporosis drugs (bisphosphonates) [1,2]. Important questions still remain, however, regarding the relative roles of, and interactions between, such factors as nutrition, exercise, genetics, pharmacologic countermeasures, duration of unloading, effects of repeat missions, and even radiation exposure. Animal models allow for destructive testing of bone and numerous other invasive assays that cannot be conducted on crew members, but that will provide deeper insights into basic mechanisms and broader effects. We have recently completed a series of ground-based animal studies characterizing bone loss and recovery trends for single and repeated exposures to simulated microgravity [3-5]. Adult (6 mo.) male rats were used as the animal model, with the classic hindlimb unloading (HU) protocol used to simulate microgravity [6].

METHODS

A series of three studies was undertaken. In the first study, animals were exposed to a single bout of HU (28d) and tracked for 84 days after return to weight-bearing. For the second study, animals recovered for 56 days following an initial HU and were then exposed to a second HU plus 56 days of reambulation. A third study added exercise during the 56 days of recovery between two HU exposures. Bone densitometric variables were measured in vivo at 28d intervals at the proximal tibia metaphysis (PTM). The PTM was also assessed by ex vivo microCT. Bone strength was measured ex vivo for both cortical and cancellous bone in both the tibia and femur. For the third study, bone formation dynamics were assessed by histomorphometry, and serum markers of bone formation and resorption were measured.

RESULTS AND DISCUSSION

Bone mass and density at the PTM of the rat exhibited similar loss and recovery trends as reported by Lang et al. [7] for the proximal femur of ISS crew members; in particular, recovery of density lagged that of mass. The femoral neck of the rat did not match the human data as well, and this complicates interpretation of the biomechanical strength testing results. For the double-HU study, losses of both mass and density were milder for the second HU. These results suggest that repeat missions for crew members may not be more detrimental as there was no evidence of an exacerbating effect. Adding exercise during recovery between the two HU bouts enhanced bone mass and density to levels exceeding aging controls but did not alter the reductions due to the second HU. The net effect remained positive, however, as the absolute values following the second HU were higher due to the elevations from exercise pre-exposure. Exercise had an especially potent anabolic effect in the trabecular bone of the PTM, as reflected by vigorous increases in trabecular thickness and mechanical properties. Both histology and serum markers confirmed severely reduced bone formation at the end of the second HU. A new study has also been initiated to assess how bisphosphonate drugs given during the first HU may affect recovery during reambulation and perhaps even alter the response to the second HU.

ACKNOWLEDGEMENTS. Support provided by NASA grant NNX08AQ35G is gratefully appreciated.

REFERENCES