Fracture healing in spaceflight and in a ground-based hypogravity analog

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**Issue:** accidental bone trauma will eventually happen on long duration space missions.

**Question:** Will trauma to a weight-bearing bone heal normally during a period of extended microgravity?
Relevant Spaceflight Literature

Juvenile bone growth arrests during spaceflight:

Inhibition of Bone Formation During Space Flight

Abstract. Parameters of bone formation and resorption were measured in rats orbited for 19.5 days aboard the Soviet Cosmos 782 biological satellite. The most striking effects were on bone formation. During flight, rats formed significantly less periosteal bone than did control rats on the ground. An arrest line at both the periosteum and the endosteum of flight animals suggests that a complete cessation of bone growth occurred. During a 26-day postflight period, the defect in bone formation was corrected. No significant changes in bone resorption were observed.

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Relevant Spaceflight Literature

Bone Healing May be Impaired During Spaceflight:

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THE EFFECT OF MICROGRAVITY ON BONE FRACTURE HEALING IN RATS FLOWN ON COSMOS-2044

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In summary, the following conclusions can be made:

1. The healing process of fractures of long tubular bones in microgravity is inhibited due to which the callus size decreases and consolidation strength declines;

2. An increase in the relative osteoid volume in callus trabecules and a simultaneous decrease of the amount of active osteoblasts point to disorders in the mineralization of bone newly formed in microgravity;

3. A 14-day exposure of rats to microgravity leads to osteoporosis of spongy bone of tibia metaphyses; moreover, osteoporosis is induced not only by inhibition of bone formation but also by stimulation of bone resorption;

4. Similarity of changes that occur in untreated and treated bones of flight and suspended rats suggests that tail suspension can be viewed as an adequate model of the effects of microgravity for the study of alterations in hind-limb bones.
Bone healing was investigated histologically in a rat fibular osteotomy model subjected to microgravity (shuttle flight STS-29) and the tail suspension microgravity simulation model. Exposure to microgravity or tail suspension occurred during the last 5 days of a 10-day healing period. Periosteal osteogenesis and the development of vascular channels in both experimental groups were similar to that observed in a weightbearing control group. Chondrogenesis was more advanced in weightbearing rats than in either flight or tail-suspended rats. Angiogenesis in the osteotomy gap was more advanced in weightbearing and tail-suspended rats than in the flight group. These findings suggest that bone healing may be impaired during space travel. Interpretation of the findings is complicated by observations that flight and suspended rats lost weight during the flight period and that suspended rats consumed less water than control rats. Tail suspension did not produce the same pattern of healing as spaceflight; therefore, long-term studies of bone healing, conducted entirely in the microgravity environment, are needed to distinguish metabolic from mechanical influences and to determine whether effective fracture consolidation will occur in the absence of gravitational forces.
   - “…non-weight bearing delays and alters the process of fracture healing in rats … characterized by increased osteopenia, delayed callus remodeling and abnormal remodeling of the…cortex.”

   - “…healing is impaired at the stage of chondrogenesis in a microgravity environment or tail suspension model.”

   - “Hindlimb suspension leads to decreased cartilage formation and a smaller callus. Decreased cartilage formation did not, however, lead to decreased callus strength or to impaired fracture healing.”
Hypothesis

• *Cortical bone healing will be impaired by chronic unloading.*


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1. Simulated weightlessness analog
   • Hind limb unloading (HLU)

2. Reproducible, well-defined fracture
   • Minimally invasive, mid-diaphyseal fibular osteotomy
Experimental Design

Sprague Dawley female rats, 6 months (280-300 g BW) at delivery

Weight Bearing, **WB** *(cage activity)*
Non-Weight Bearing, **NWB** *(HLU)*
Monitoring *In Vivo* Bone Healing

*In Vivo Micro-CT Imaging*

Days after Surgery

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WB Group

NWB Group

40 μm isotropic voxels

1-cm fibular region surrounding the osteotomy

Healing Callus: gray scale values 115-175
Cortical reaction: gray scale values 176-190
Longitudinal Measures of Bone Healing

*In Vivo Micro-CT Imaging*

NWB ~19% WB callus formation rate

NWB ~22% WB max. callus volume

Gray scale values 115-175

Mean ± SD

N = 10 rats/group

*P < 0.01, ANOVA
Increase in Cortical Bone Volume
(*Surface Reaction Leading to Secondary Cortex*)

In Vivo Micro-CT Imaging

Gray scale values 176-190

Starting volume of the 1-cm cortical ROI = 5.2 ± 0.7 mm³

NWB ~16% of WB cortical bone volume increase

Mean ±SD
N = 10 rats/group
* P < 0.01, ANOVA
Extent of Hard Callus Bridging

*Ex Vivo Micro-CT Imaging at 5-weeks*

**Mid-longitudinal Cut-Away Views**
“Non-Union” Criteria

1. Inspection to determine if the recovered bone can hold its own weight.

Bridging tissue cannot support the weight of the bone itself

Bridging tissue can support the weight of the bone itself
“Non-Union” Criteria

2. Extent of hard tissue bridging across fracture site via micro-CT imaging.

[Images of bone scans labeled WB and NWB]
“Non-Union” Criteria

3. Histological assessment of fibrous tissues around and within the fracture site.

Decalcified paraffin sectioning at 5-weeks

Mid-longitudinal section
Toluidine blue stain
Incidence of Non-Union

- **WB bone healing**
  - 0/10 “non-unions”

- **NWB bone healing**
  - 6/13 “non-unions” (46%)
Quantifying Bone Strength

Load-Displacement Curve

Slope ~ Stiffness
**Bending Strength Tests**

**WB - 303R**

**NWB - 702L**

**NWB - 808R**
Callus Bend Stiffness for Testable Bones

NWB is 16% of WB stiffness

*N P < 0.01; ANOVA
Summary

Comparing chronic HLU to normal weight-bearing fibular fractures:

• More variable healing response
• On average, the rate of hard callus formation and extent of callus size was diminished to 20-30% of WB values
  - Partial hard callus bridging across the osteotomy gap
  - Hard callus has low X-ray attenuation ("density")
  - Remainder of bridging callus is soft tissue
• Relative bending strength averaged ~16% of WB values after 5-weeks of healing
• Non-union incidence was 46% (6/13) compared to 0% (0/10) for WB rats
Conclusion

Fibular fracture healing in a chronically unloaded condition is impaired when compared to the healing response in a weight-bearing condition.
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Closed femoral fracture

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