

Artificial Gravity: Will it Preserve Bone Health on Long-Duration Missions?

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Summary

Prolonged microgravity exposure disrupts bone, muscle, and cardiovascular homeostasis, sensory-motor coordination, immune function, and behavioral performance. Bone loss, in particular, remains a serious impediment to the success of exploration-class missions by increasing the risks of bone fracture and renal stone formation for crew members. Current countermeasures, consisting primarily of resistive and aerobic exercise, have not yet proven fully successful for preventing bone loss during long-duration spaceflight. While other bone-specific countermeasures, such as pharmacological therapy and dietary modifications, are under consideration, countermeasure approaches that simultaneously address multiple physiologic systems may be more desirable for exploration-class missions, particularly if they can provide effective protection at reduced mission resource requirements (up-mass, power, crew time, etc). The most robust of the multi-system approaches under consideration, artificial gravity (AG), could prevent all of the microgravity-related physiological changes from occurring. The potential methods for realizing an artificial gravity countermeasure are reviewed, as well as selected animal and human studies evaluating the effects of artificial gravity on bone function. Future plans for the study of the multi-system effects of artificial gravity include a joint, cooperative international effort that will systematically seek an optimal prescription for intermittent AG to preserve bone, muscle, and cardiovascular function in human subjects deconditioned by 6° head-down-tilt-bed rest. It is concluded that AG has great promise as a multi-system countermeasure, but that further research is required to determine the appropriate parameters for implementation of such a countermeasure for exploration-class missions.

BACKGROUND

Prolonged microgravity exposure disrupts bone, muscle, and cardiovascular homeostasis, sensory-motor coordination, immune function, and behavioral performance. Exposure to decreased gravity during exploration-class missions is expected to far exceed that of our space flight experience to date. For instance, microgravity exposure during transit to Mars is expected to last 6-9 months during both the outbound and return segments, while decreased gravity on the Martian surface (~3/8 g) between transits is expected to last from 1-18 months. Extrapolating from our long-duration space flight experience to date (typically 3-6 month missions), it seems clear that physiological deconditioning may present a serious risk to the success of exploration-class space flight missions. For example, despite the availability and utilization of increasingly sophisticated resistive and aerobic exercise countermeasure devices, deterioration of the musculoskeletal system has been consistently observed in long-duration missions aboard Skylab, Mir, and the International Space Station.¹⁻⁴ Bone mineral density losses during 3-6 month space flight missions vary widely between individuals and from region-to-region within an individual;^{1,2,4} however, these losses average 1 to 3% per month and range up to 20% total loss in some regions. While this degree of demineralization may not be functionally significant after 3-6 month missions, if it continues at this rate, it may reach clinically significant levels during exploration-class missions. The consequences of clinically significant bone loss include an increased risk of fracture, which could be magnified by concomitant muscle atrophy/deconditioning and/or neuro-motor coordination decrements. Moreover, since the demineralization results in hypercalciuria, there may be an increased risk of renal stone formation.⁵

The failure of exercise countermeasures to fully preserve bone mineral density during long-duration missions may be related to inadequate equipment, prescriptions or compliance, or it may be related to insufficient neuromuscular stimulation in the microgravity environment. It

seems more likely that 1-2 hrs per day (the duration of typical exercise regimens) is insufficient to provide a loading equivalent to that normally experienced during 16 hrs per day on Earth. Researchers are currently developing new exercise equipment and prescriptions, as well as pharmacological (e.g., bisphosphonates), dietary (e.g., vitamin K), and mechanical (e.g., vibration, lower body negative pressure) countermeasures;⁶ however, the effectiveness of these approaches is unknown.

NASA's primary approach to protecting crew members from the untoward effects of decreased gravity has focused on developing system-specific countermeasures. An alternative approach is to bring (artificial) gravity along. Artificial Gravity (AG) has long been considered a viable countermeasure to all of the adaptive physiological responses to the absence of gravity during space flight.^{7,8} AG produced by continuously rotating the transit vehicle throughout a long-duration mission would have the advantage of providing a passive, omnipresent, inertial loading that could closely replicate the gravitational environment of Earth (or Mars) with minimal mission resource requirements.⁹ Continuous AG loading would provide Earth-like stimulation of the musculo-skeletal system, the cardiovascular system, and the graviceptors responsible for neuro-muscular activation. While maintenance of pre-flight fitness levels would require supplemental exercise (just as it does on Earth), conventional terrestrial exercise devices could be used to accomplish this, obviating the need for the complicated devices currently required to provide subject loading or coupling in microgravity. Unfortunately, the rotating environment would not be identical to the terrestrial environment. Coriolis forces and cross-coupled angular velocities proportional to the angular velocity of the vehicle might affect sensory-motor adaptation and/or the ability of the crewmember to effectively use the exercise devices. Also, the cost or technical complexity of developing a rotating space vehicle may outweigh the benefits. Even without a rotating vehicle AG could be employed as a countermeasure, but it would be discontinuous, requiring crew members to intermittently ride aboard a short-radius centrifuge

within the habitable volume of the vehicle. For improved effectiveness and resource efficiencies, such short-radius centrifuges would most likely incorporate aerobic and/or resistive exercise devices.

PREVIOUS INVESTIGATIONS OF ARTIFICIAL GRAVITY AND BONE

AG is not a new countermeasure concept. In the latter part of the 19th century, Konstantin Tsiolkovsky envisioned rotating spacecraft that would provide gravity-equivalent centrifugal force to protect humans from the effects of weightlessness⁷. The US and Russia have frequently considered AG in program definition phases, and have supported limited studies of AG. Some results relevant to bone function are presented below.

Animal studies

Shipov¹⁰ suggested that the optimal approach to investigating the efficacy of AG as a countermeasure is to determine the mechanisms underlying the physiological consequences of AG, an approach best accomplished by animal studies. Indeed, animal studies using AG have provided data that support a positive effect of centrifugal force on bone. For instance, Biosatellite studies have demonstrated in rodents that the development of microgravity-induced osteoporosis and concomitant decreases in bone structural properties and strength could be mitigated by hypergravity produced by centrifugation.¹¹⁻¹⁴ Ground-based hypergravity studies in rodents have also demonstrated the sensitivity of bone to changes in gravity. Some of these studies suggest that age, duration of centrifugation, and the degree of hypergravity (G level) are critical factors in determining the effects of centrifugation on bone.¹⁵⁻¹⁷

Other ground-based studies have taken advantage of a rodent space flight analog model, which demonstrated that skeletal unloading for 2 weeks by hind limb suspension decreased tibial and vertebral calcium levels, and that subsequent reloading increased calcium accretion.¹⁸ The time needed to restore bone deficits caused by unloading exceeded the time needed to induce the

deficits, which is consistent with calcium kinetics studies of astronauts aboard the Mir space station that showed it would take about 2.5 times the mission length to restore bone lost after about 3 months in orbit.¹⁹ Studies using the hind limb suspension model have primarily evaluated the role of intermittent hypergravity exposures in ameliorating disuse-induced bone loss. Two hours of normal loading each day did not prevent calcium loss and reduction of collagen matrix in the tibia²⁰ and humerus²¹ of rats hind limb-unloaded for 15 and 35 days, respectively. However, in another study,²² one hour of standing or centrifugation at 1.5 g and 2.6 g partly alleviated decrements in bone mechanical and physical properties of rats during 28 days of hind limb unloading. In yet another study, unloading was found to decrease differentiation of cartilage cells, but this decreased differentiation was reversed in unloaded rats, intermittently reloaded via centrifuge during the suspension periods.²³ Reversal of the decreased differentiation appeared to proceed with increased reloading up to a threshold, above which differentiation decreased. In a review of in vivo mechanical loading models for bone, the consensus appears to be that osteogenic signals are initiated during loading by both biochemical and mechanical signals.²⁴ Further, excessive G forces (above threshold) result in decreased expression of osteocalcin, suggesting that moderate mechanical stress is sufficient to produce positive effects on bone.²⁵

Endocrine and physiological responses

Metabolic changes induced by centrifugation may also point to a positive role for AG in ameliorating unloading-induced bone loss. Glucocorticoid use in a variety of clinical conditions has been described as the “most common secondary cause of osteoporosis”.²⁶ Strong evidence suggests that blood cortisol levels are increased in astronauts, especially during the early part of their missions,²⁷⁻²⁹ with possible negative consequences for bone.

Bone also responds to changes in blood flow, and microgravity-induced changes in bone have been hypothesized to be partially mediated by changes in blood flow. Primates exposed to head-down tilt for 28 days with periodic centrifugation (1.2 to 1.6 g) had some alleviation of the

decreased blood flow in the muscles of the lower extremities ($-19\pm 3.1\%$) compared with non-centrifuged animals ($-40\pm 2.7\%$).³⁰ Similar changes may exist in blood flow to bone. A study using lower-body negative pressure with exercise to ameliorate bed rest-induced changes in bone also suggests that changes in blood flow are related to prevention of bone loss.³¹ Physiological changes in bone during space flight are likely caused by a combination of hormonal changes, blood flow changes, and the lack of mechanical stress at the cellular level. It is logical to assume that continuous or intermittent AG would have a positive effect on these processes. Cellular and animal studies will be important for evaluating the effects of AG on these processes in bone.

Human studies

Data that demonstrate a positive effect of AG on bone in humans are limited. Although bed rest is a valuable tool for simulating microgravity, longer-term studies than those typically used to investigate the effects of centrifugation on cardiovascular and muscular changes are required to detect changes in bone mineral density caused by unloading. However, biochemical markers indicate that changes occur in bone metabolism within days to weeks of starting bed rest.³²⁻³⁴ During 4 days of 6° head-down bed rest, intermittent exposure to 1g plus exercise prevented the increase in urinary calcium excretion typically seen during simulated microgravity.^{35,36} During a 6-week bed rest study,³⁷ ambulation for 4 hours per day maintained calcium balance. These studies³⁵⁻³⁷ suggest that the intermittent addition of gravity (standing for 3 or 4 hours) may be more effective than exercise in modulating bed rest-induced calcium excretion.³⁷⁻³⁹ Nevertheless, it is likely that concomitant exercise and AG may be the optimal approach to developing countermeasures for space flight-induced deconditioning.

FUTURE STUDIES

To explore the utility of AG as a multi-system countermeasure during long-duration, exploration-class space flight, 83 members of the international space life science and space flight

community participated in a workshop convened by NASA and NSBRI in 1999.⁴⁰ The participants concluded unanimously that the potential of AG as a multi-system countermeasure is indeed worth pursuing, that the requisite AG research needs to be supported more systematically, and noted that more than 30 years of sporadic activity in AG research has not elucidated the fundamental operating parameters for an AG countermeasure. They went on to identify a series of specific AG research questions to be answered, and recommended an approach to answering these questions through a program of coordinated scientific research projects.

A variety of AG approaches have also been proposed independently of the 1999 workshop, including the design and development of a rotating vehicle and a variety of human centrifuge devices.⁴¹ Future biomedical research in AG in microgravity and on Earth should focus on both human and animal studies, to maximize the scientific return. Critical questions that remain to be considered in planning for AG research include whether AG should be continuous or intermittent. Regardless of the approach chosen, questions remain about the amount of AG needed to maintain acceptable crew health and performance, the impact of continuous versus intermittent AG on other space flight environmental factors, living and working conditions, and the requirements for supplemental countermeasures, such as exercise.

In response to the 1999 workshop, NASA has recently begun a vigorous program in AG research. The first project in this program is a joint, cooperative effort between the US, Germany, and Russia that will systematically seek an optimal prescription for intermittent AG to preserve bone, muscle, and cardiovascular function in human subjects deconditioned by 6° head-down-tilt-bed rest. The pilot study for this project is scheduled to begin in 2005 at the University of Texas Medical Branch in Galveston and will evaluate calcium and bone metabolism in subjects before, during, and after 21 days of 6° head-down bed rest, with and without daily 1-hour bouts of AG (2.5 g at the feet with 1g/m G-gradient along the body). Investigators will evaluate whether significant decrements in bone are observed in the control group (no AG), and whether these

decrements are attenuated in subjects exposed to the AG treatment. Biochemical markers of bone and calcium homeostasis will be measured in urine and blood before, during, and after bed rest. In addition, studies of calcium excretion and balance (throughout the study) and calcium kinetics (before and during bed rest) will be performed. Dual energy X-ray absorptiometry measurements will be performed before and after the study to evaluate any changes in bone mineral density. In addition, peripheral quantitative computerized tomography will be used to evaluate bone mineral content and bone strength of the tibia before and after bed rest. Magnetic resonance imaging will be performed before and after bed rest, to assess bone structure and strength in the distal tibia and/or calcaneus.

Future projects being planned for NASA's AG program include systematic evaluation of human factors and sensory-motor adaptations associated with living aboard a rotating structure, and integrated, multi-system animal studies to supplement and guide the human research studies.

CONCLUSION

Development of safe, effective, efficient, and non-invasive approaches to ameliorating the negative physiological costs of space flight will be important for the success of exploration missions to the moon, Mars, and beyond. Countermeasures that address multiple systems simultaneously offer the additional benefit of being cost-effective. AG has been proposed as one such multi-system approach that can influence multiple physiological systems.^{10,42-45} At this point it seems clear that a rotating vehicle that provides 1g loading throughout the transit phases of exploration-class missions would have a salutary effect on preserving bone health by eliminating the primary physical stimulus of bone loss during space flight. While this would not obviate the requirement for exercise equipment to maintain fitness, the complexity of exercise devices and prescription development would likely be simplified for a 1g environment. What seems less clear is whether the Coriolis and cross-coupling side effects would interfere with this effectiveness and whether intermittent AG (plus exercise) could be effective in preserving bone health in a non-

rotating vehicle (or upon a planetary surface). Therefore, while AG shows significant promise as a multi-system countermeasure, more research is necessary to develop optimal prescriptions for its application. Accordingly, a rigorous, systematic research program has been put into place to investigate these issues.

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