59-52 N95-15136 108722

MUSCULOSKELETAL ADAPTATION TO MECHANICAL FORCES ON EARTH AND IN SPACE

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INTRODUCTION

A major concern of the US and Soviet (Russian) space programs is the health and safety of astronauts and cosmonauts. One of the areas receiving the most attention has been the effects of long duration space flight on the musculoskeletal system.

During the Skylab period exercise programs and bone densitometry equipment were evolving. No treadmills were included on either Skylab-1 or Skylab-2, and only a teflon pad and elastic cords were available on Skylab-4 [1]. During the same period the Russians were beginning to experiment with longer duration space flight culminating in a milestone flight of 366 days in 1987-1988. Development of exercise protocols and equipment was an important part of their program [2].

Early Skylab results were not considered encouraging. In spite of daily exercise, calcium balance studies measured significant increases in urinary calcium [3]. And while calcaneal bone density adaptation on Skylab flights was not particularly high (+1% to -8%), the longest flight was only 84 days. Short duration shuttle flights have been the only other source of information on humans from the US space program. The fact that daily exercise protocols were not rigorously followed nor sufficiently intense likely contributed to their limited success. Interestingly, reduced muscle strength and bone loss were only detected in the lower limbs.

According to published data and Joint US/USSR Working Group (JWG) reports, the health of cosmonauts returning from space is not related to the length of stay in microgravity but is directly related to the "intensity" with which they exercised in space [4]. Pre- and post-flight bone density measurements of recent MIR crews have been taken with a Hologic QDR-1000/W dual energy x-ray absorptiometry (DXA) machine supplied by the US space program. DXA machines have a precision for repeated bone density measurements of 1-2%. These data are our best source of information on the effects of long duration space flight with exercise on regional changes in bone density. Regional lower limb bone density and muscle strength were reduced in most cosmonauts on their return. However, lumbar spine bone density measurements have been mixed. Vertebral body trabecular bone, measured by quantitative computed tomography (QCT), increased or remained unchanged in 6 of 7 cosmonauts [5]; DXA data show a mean decrease in lumbar density (vertebra plus posterior elements) in a different group of cosmonauts.

After three decades of space flight and research, questions continue: Can exercise in space maintain musculoskeletal tissue mass and function in an adult? The objective of this paper is to address this question in a way that hopefully provides a rational basis for *quantifying* and *evaluating* the influence of daily activity on muscle and bone on Earth and in space.

Gravity and Activity

In addition to supporting body weight, living structures must also accommodate and *adapt to* dynamic forces generated during activity. A number of examples illustrate the important regulatory function of dynamic forces. For example, vascular wall thickness is greater in vessels exposed to higher cyclic fluid pressures and thinner in walls subjected to lower pressures. In an analogous way, cross-sections are significantly thicker in muscles and bones subjected to higher levels of dynamic loading. In general the adaptive response is "localized" to the sites exposed to more "intense" mechanical loading.

Bone density and muscle mass remain relatively constant in adults between 25 and 35 years of age and then gradually decline with age. One possible explanation for the time course of muscle and bone loss with age is that weekly and even yearly physical activity levels initially remain fairly constant and then gradually decline with age. That is, musculoskeletal tissue morphology and physiology are maintained by a relatively constant level of daily mechanical stimulus.

External Forces and Internal Musculoskeletal Forces

Normal daily activities such as standing, walking, and running impose two external forces on the body: body weight (constant) and the ground reaction force (GRF) composed of body weight and the inertia force accelerating and decelerating the center of mass of the body during activity (see Figure 1). The magnitude of the GRF is determined by the force-time histories of the muscles accelerating the major limb segments. We can measure the GRF, but muscle forces must be estimated from complex dynamic musculoskeletal models [6,7] or measured invasively in animals [8].

High GRFs produce large internal muscle and bone forces. Mechanical strains in animal leg bones, monitored with strain gages bonded to the bone, indicate that for a wide range of gait speeds and modes of locomotion surface patterns of bone strain are similar and follow the magnitude of the GRF. These results suggest that the musculoskeletal forces in these limb bones are approximately scaled by the magnitude of the GRF during steady state activities [9,10]. (Notable exceptions are the walk/run transition in humans and trot/gallop transition in quadrupeds. Other exceptions include lifting and sitting down (getting up) in humans that can generate relatively high forces in the knee and hip without increasing the GRFz significantly.) It follows that monitoring daily GRFs may provide a good approximation to lower body muscle and bone loading histories.

Muscle Fiber and Bone Tissue Loading Histories

Different gait speeds, modes of locomotion, and activities such as ascending and descending stairs or rising from a chair will produce different, but reasonably characteristic, muscle, tendon, and bone *force* or *loading histories*. Individual

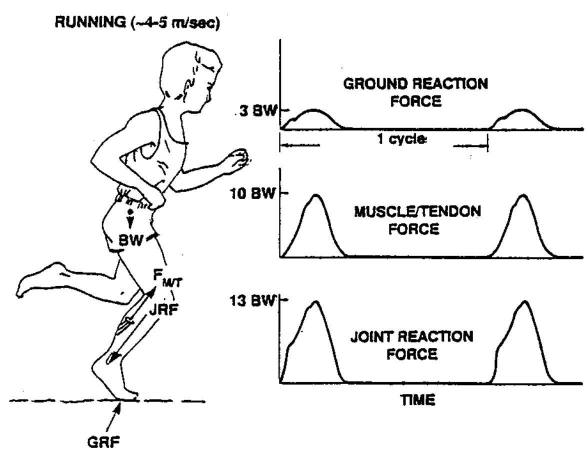


Figure 1. External and internal forces acting on the body during gait. GRF= ground reaction force, $F_{M/T}$= plantar flexion muscle/tendon force, JRF= joint reaction force, BW= body weight.

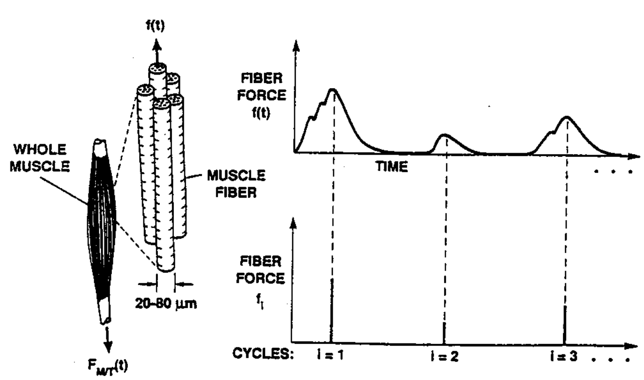


Figure 2. Definition of muscle fiber force-time (loading) history. Three cycles are shown; the model uses only peak force levels.

muscle *fiber* force, a contributor to the total muscle force, is controlled by fiber activation level, fiber type (i.e., force-velocity property), and cross-sectional area. It follows then that each muscle *fiber* has a daily *stress* (fiber force divided by fiber cross-sectional area) *history* which differs from the tendon and whole muscle stress history (see Figure 2). Similarly, bone tissue has a daily *stress (strain) history* determined in large part by the levels of muscle force exerted on the bone.

Mechanisms of Maintenance and Adaptation

Muscle and bone have similar adaptive responses to functional loading and altered tissue loading histories. Both hypertrophy in response to overload [11,12,13] and atrophy [14,15] in response to immobilization and disuse. Furthermore, electrical stimulation of muscle without force development does *not* maintain fiber cross-sectional area [16]. Little work has been done to quantify muscle mass and fiber contractile properties in terms of tissue loading histories.

Bone density and morphology may depend upon a number of characteristics of the loading history. These include (1) minimum effective and time-averaged bone strain [17,18,19], ((2) peak stress levels achieved during dominant activities [20,21], (3) strain distributions produced by atypical loads [22], (4) strain rate and frequency content of the tissue strain histories [23], and (5) cumulative daily peak cyclic strain energy density (SED) [24,25].

Functional loading of bone induces electrical fields, fluid flow in bone microchannels, and fatigue damage. Each of these has been proposed as a mechanism which activates bone remodeling. Cyclical fluid flow stimulates the biochemical activity of cells by fluid shear forces and creates streaming potentials by ion transport. The higher the strain rate the greater the effect.

Several investigators have proposed that the accumulation and repair of fatigue damage or cumulative strain energy density (SED) may be the driving force for bone remodeling [24,25,26,27,28,29]. Fatigue accumulation is most sensitive to load magnitude and stress state, followed by number of loading cycles and loading (stress or strain) rate. An attractive feature of using a "damage" accumulation model is that it can be applied equally to muscle and bone to build a consistent theory of musculoskeletal tissue adaptation. (See Martin and Burr [30] for a review of functional adaptation.)

MATHEMATICAL MODEL OF ADAPTATION

We have derived mathematical expressions for bone density [24,25] and muscle cross-sectional area [25,31] as functions of average daily cumulative strain energy densities. (See [32,33,34] for extensions of the model to osteogenesis, time-dependency and cortical bone remodeling.)

We have hypothesized that musculoskeletal tissues are regulated in order to maintain a constant level of average daily *tissue* mechanical stimulus, Ψ_t, where

$$\Psi_t = K [\Sigma \sigma_{ti}{}^{\alpha}]^{1/\alpha}. \quad (1)$$

In this expression K is a tissue-specific constant, σ_{ti} is the peak *tissue* level effective stress for each *i*th daily loading cycle. Contributions from all daily loading cycles are summed to give the total tissue stimulus, Ψ_t. A tissue-specific weighting factor, α, determines the relative importance of the effective stress magnitude compared to the number of loading cycles. The tissue effective stress is a scalar quantity computed from the peak continuum SED and local bone apparent density.

The following expressions for bone density, ρ, and muscle fiber cross-sectional area, a_x, can be derived

$$\rho = K_b [\Sigma \sigma_{ci}{}^m]^{1/2m} \quad \text{and} \quad a_x = K_m [\Sigma f_i{}^k]^{1/k} \quad (2)$$

where σ_{ci} is the peak *continuum* cyclic effective stress in bone, and f_i is the peak cyclic fiber force (see Figure 2). The exponent m for bone is estimated to be between 4 and 8 [10]. Values for k have not been estimated from literature data, but high values (k > 8) are consistent with high force, low cycle exercise increasing fiber cross-sectional area more effectively than low force, high cycle exercise.

Several consequences of the model are noteworthy. First, bone density and fiber area are predicted to be non-linear functions of their respective tissue loading histories. Second, many distinct tissue loading histories can provide the *equivalent* tissue level stimulus. However, because the expressions and parameters are tissue-specific, a change in activity pattern and level will affect each tissue differently.

MAINTENANCE AND ADAPTATION IN SPACE

The most significant factor affecting human physiology during space flight is the loss or reduction in the level of the daily external loading history (primarily body weight and the GRF). Parvin *et al.* [2] and Thornton [1] emphasized the importance of periodic impact loads provided by normal Earth activities that develop high force levels and hydrodynamic pressures in lower limb musculoskeletal tissues and vessels. We can now address with our model whether changes in cosmonaut bone density are at least consistent with cosmonaut exercise intensity.

Daily Loading Histories in Hypogravity

It is possible to estimate daily external loading histories in space for treadmill exercise from simulations of hypogravity locomotion on Earth. He *et al.* [35] simulated hypogravity locomotion with a treadmill and an adjustable overhead spring attached at the waist. Running speed was 3.0 m/s which is approximately the jogging speed in space.

Peak GRFz levels for one subject have been plotted in Figure 3 as a function of gravity ratio. Peak GRFz magnitude decreased with decreasing "g-level" while the shape of the GRFz curve remained nearly unchanged (Figure 4) indicating that internal muscle activation histories are similar in hypogravity, but proportionally reduced in force magnitude. Slightly shorter foot contact times at lower g levels imply that load rate, and therefore bone tissue strain rates, will be closer to normal than the peak force levels.

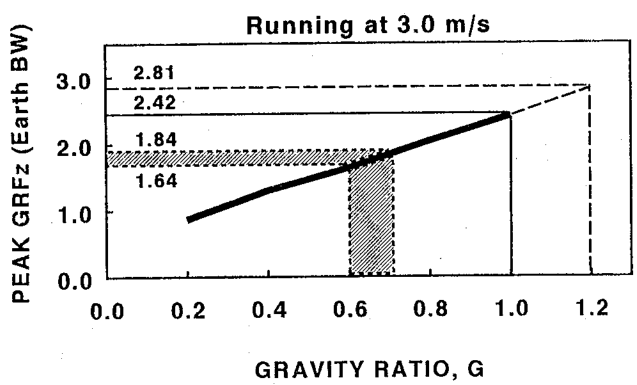


Figure 3. Peak GRFz versus gravity ratio for running at 3.0 m/s. From [35]. Cosmonauts may run differently, but differences cancel if peak values are proportionally reduced.

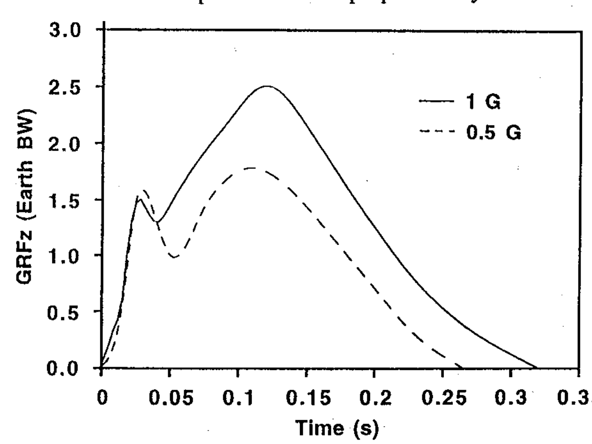


Figure 4. GRF comparison between running at 0.5 g and 1.0 g. Adapted from [35]. Different subject for Figure 3.

Elastic cords, attached at the waist and shoulders, pull the cosmonauts toward the treadmill with a force between 0.6 to 0.7 Earth BW (see shaded region of Figure 3). GRFz force levels during running are nearly proportional to g level. Peak running GRFz at 0.6 g is ~ 67 % of normal 1.0 g running and ~76 % of normal at 0.7 g. To a first approximation lower limb musculoskeletal forces and tissue stresses will be equivalently reduced.

Cosmonaut External Daily Loading Histories

Recommended treadmill exercise on Mir follows a special program of alternate strength and velocity training. Evidently, cosmonauts are also given some latitude and flexibility to change their exercise protocols. For example, some cosmonauts intensify their exercise routine by increasing the elastic tension during brief bouts of jumping on the treadmill. Others are known to reduce their exercise level [personal communication].

Detailed records of cosmonaut daily treadmill activity are kept, but, unfortunately, these logs have not been published along with bone density data. Therefore, it is not possible to examine the effectiveness of specific exercise programs in relation to individual bone density data. The following analysis uses treadmill exercise data from the Mir Prime Crew-5, 166 day flight [36] as representative of the recommended level of in-flight exercise. Activities not significantly loading the lower body have not been included. Table I lists the cosmonauts' average exercise per session (daily exercise equals two sessions per day). Walking speed of 1.2 m/s was assumed and running speeds were computed from the data. Peak walking GRFz at "0.7 g" was assumed to be 70 % of normal, peak running GRFz was taken from Figure 3. Daily loading cycles were computed based on estimates of stride frequency. Figure 5 graphs the estimated external loading history in space for each cosmonaut in terms of peak GRFz levels and daily loading cycles. An "idealized" normal activity level on Earth (including ~20 minutes daily jogging) is plotted for comparison.

	COSMONAUT C1		COSMONAUT C2	
	Walking	Running	Walking	Running
DISTANCE (m)	1080	3317	1273	2673
SPEED (m/s)	1.2 (assumed)	3.15	1.2 (assumed)	2.8

*JWG on Space Biology and Medicine, San Francisco, CA September 16-22, 1990

Table I. One average session of cosmonaut treadmill exercise. Daily treadmill exercise: two sessions per day.

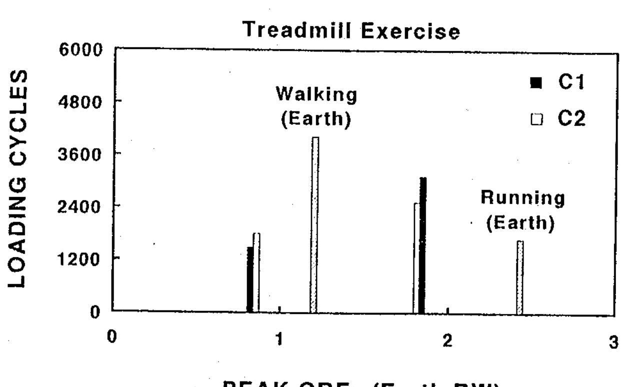


Figure 5. Estimated daily external loading histories for *each* leg expressed in terms of the GRFz. (Approximate history. Earth: ~4000 cycles @ 1.2 BW, 1800 cycles @ 2.42 BW; Space: ~1600 cycles @ .85 BW, 3200 cycles @ 1.84 BW)

Cosmonaut Bone Density and Muscle Strength

Calcaneal bone density data from two Salyut-6 crews (175 days, n=2; 184 days, n=2) showed a mean change of -6.7% [37]. Data from a 140 day flight were not used here since the baseline measurement was taken 1.5 to 2.0 years post-flight. All measurements were taken with a Studsvik (Sweden) radioisotope Bone Scanner Model #7102.

More recent regional and whole body bone density data are presented in Table II. Mir Prime Crew 6 and 7 data were obtained from a JWG report [38]. Densitometry results from tests on 9 Mir cosmonauts were recently presented by Schneider *et al.* [39].

Regional bone density losses presented in Table II are not overly severe, although a 9 to 11% loss in the trochanter is troublesome. One might have anticipated decreased levels 2 to 3 times higher based on immobilization data from long term studies of 6 months or more. (Disuse [40] and spinal cord injury studies [41] have shown bone loss to be non-linear with the greatest change occurring within the first 6 months.) The decrease in trochanter density compared to femoral neck density in cosmonauts is puzzling. It would be very interesting to investigate the spatial distribution of loss within the trochanter and femoral neck. It would also be interesting to compare *absolute* values of areal density of returning cosmonauts with male normative data on Earth.

Force-velocity properties of plantar flexion muscles in returning cosmonauts, measured isokinetically, vary greatly. Isometric plantar flexor (calf) muscle strength decreased 20% to 50% after 160 to 366 days on the Mir station. The Mir crew of 1987 (326, 175, and 160 days) showed isometric strength decreases of 25-40 %, but only 15-25 % 2 weeks post-flight. Losses were least in cosmonauts performing the greatest amount of exercise [4]. Isometric strength was maintained in one crew member [36].

FLIGHT	PELVIS	FEMORAL NECK	TRO-CHANTER	TIBIAL EPIPHYSIS	WHOLE BODY
*Mir PC-6, n=2 (179 days)	-6.6	-5.3	-11.0	-2.6	-1.23
*Mir PC-7, n=2 (131 days)	-7.6	-3.6	-7.3	-1.3	-0.9
**Mir, n=9 (131-312 days)	-7.4	-5.0	-9.1	NA	no change

* Hologic QDR-1000W DXA

** Scanner type not given for all cosmonauts

Table II. Cosmonaut bone density data taken from the literature. Percent change from pre-flight.

Model Predictions

The following analysis assumes that the majority of regional bone loss has occurred within the first 6 months of flight, and that bone density values have stabilized even though they may be slowly drifting lower. Cosmonaut data give no indication that bone density is related to flight duration. In fact Kozlovskaya *et al.* [4] found physical exercise "intensity", not flight duration, to be the primary determinant of cosmonaut health. (No data on bone density were presented, however.).

If lower limb musculoskeletal loading is proportional to the GRFz, then bone density and muscle fiber area from equations (2) (m=4, k=8) reduce to

$$\rho \propto [\Sigma\, GRFz_i^{\,4}]^{1/8} \quad \text{and} \quad a_x \propto [\Sigma\, GRFz_i^{\,8}]^{1/8} \quad (3)$$

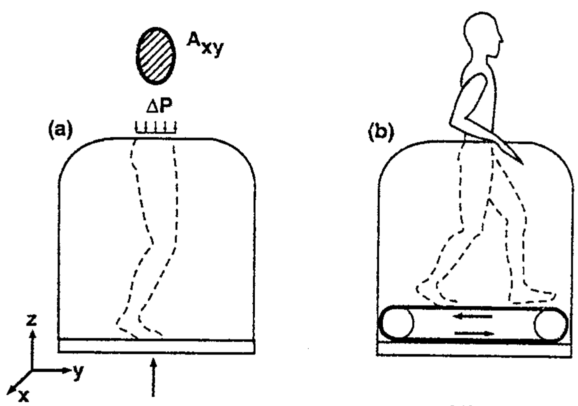
An estimated representative daily pre- and in-flight cosmonaut daily GRFz history is given in the Figure 5 caption. Percent change is predicted by taking the ratio of in-flight to pre-flight loading histories using equation (3). The predicted decrease in bone density in trabecular regions of the lower body is approximately 8%. Muscle strength (proportional to cross-sectional area) is expected to decrease by 18%. Other scenarios are also possible. For example, if cosmonauts exercised only one session per day, bone density and muscle strength would be reduced 17% and 25%, respectively. Predictions are also sensitive to estimates of activity level on Earth.

Comparison with Table II shows that predicted change compares favorably with cosmonaut data. The sensitivity of model predictions to different estimates of the external loading history underscores the need to quantify activity levels on Earth and in space.

TREADMILL+LBNP AS A COUNTERMEASURE

We have proposed a novel method of exercising in space that we believe will produce near Earth-equivalent (1) ground reaction forces, (2) limb segment kinematics, (3) internal muscle and bone forces, and (4) transient lower limb hydrodynamic pressures during walking and running in microgravity [42]. The device and theory are presented in Figure 6 which shows a treadmill inside a lower body negative pressure (LBNP) chamber. A frictionless, air-tight, flexible waist high seal isolates the upper body from the lower body.

We have confirmed that a negative pressure of ~100 mmHg (~13 KPa or ~2psi) imposes a constant force of one Earth BW [43]. Similar to gravity, the line of action of the force passes (approximately) through the center of mass of the body during upright activities. The force is distributed as a pressure difference over the upper and lower body and is not sensed as a contact or "pulling" force. Compression devices ("anti-g" suits) may be used during exercise to compensate partially for the negative pressure. We believe walking and running in this device will generate fully equivalent daily loading histories in space compared to daily activity on Earth.



$$GRF_z = F_{BW} + \Delta P \cdot A_{xy} + M \cdot a_z^{cm}$$

Figure 6. Treadmill and lower body negative pressure chamber. On Earth three forces contribute to the GRFz: (1) body weight, (2) force from the differential pressure, and (3) inertia force accelerating the body center of mass. In space the body weight force term is absent and only the last two terms contribute.

DISCUSSION

The objective of this paper was to present a limited analysis of musculoskeletal maintenance in space *only* from the perspective of altered musculoskeletal loading histories. Discussions of perturbed blood flow, fluid shifts, eccentric versus concentric exercise, fiber transformation, etc., are beyond the scope of the paper. The reason for the choice of treadmill exercise in space [1,2,4] was to simulate as closely as possible daily activity on Earth, thereby avoiding some of the above issues.

The paper presents a method for *quantifying* and *evaluating* activity levels. With the model the importance of "intensity" versus duration of exercise can be examined. Our results suggest that the countermeasures are, in fact, working but that higher force levels are needed if bone and muscle mass in the lower body are to be maintained [1,4].

A major assumption of this analysis is that the GRF magnitude serves as a good measure of lower limb musculoskeletal loading. This assumption is probably better in the ankle and tibial regions than the hip where body weight and body position combine to produce high (nearly) *static* reaction forces during activities such as lifting. The spine has also not been include in this analysis since it is very effectively loaded by resistance (elastic cord) exercise.

We are now investigating treadmill exercise in a LBNP chamber as a method of applying an equivalent 1.0 g force to the center of mass of the body while walking and running in space. We have also begun development of instrumentation to monitor GRFzs during daily activity (see Whalen and Quintana this issue). We believe these new devices and techniques, coupled with our mathematical model and new methods of analyzing DXA scans (see Whalen and Cleek this issue), will enhance our understanding of the influence of mechanical forces on musculoskeletal tissue adaptation on Earth and in space.

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