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INVITED REVIEW

Space physiology VI: exercise, artificial gravity, and countermeasure development for prolonged space flight

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Abstract When applied individually, exercise countermeasures employed to date do not fully protect the cardiovascular and musculoskeletal systems during prolonged spaceflight. Recent ground-based research suggests that it is necessary to perform exercise countermeasures within some form of artificial gravity to prevent microgravity deconditioning. In this regard, it is important to provide normal foot-ward loading and intravascular hydrostatic-pressure gradients to maintain musculoskeletal and cardiovascular function. Aerobic exercise within a centrifuge restores cardiovascular function, while aerobic exercise within lower body negative pressure restores cardiovascular function and helps protect the musculoskeletal system. Resistive exercise with vibration stimulation may increase the effectiveness of resistive exercise by preserving muscle function, allowing lower intensity exercises, and possibly reducing risk of loss of vision during prolonged spaceflight. Inexpensive methods to induce artificial gravity alone (to counteract head-ward fluid shifts) and exercise during artificial gravity (for example, by short-arm centrifuge or exercise within lower body negative pressure) should be developed further and evaluated as multi-system countermeasures.

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Background

Human spaceflight has facilitated many key discoveries about our universe as well as medical insight into human physiology. During long-duration spaceflights, microgravity induces many adaptations within the human body that are similar to those that may occur with aging or disease. Unloading of normally weight-bearing joints causes deconditioning of musculoskeletal and cardiovascular functions that may or may not be fully recovered after spaceflight. Therefore, understanding mechanisms of physiologic deconditioning and developing countermeasures to mitigate this progression has become a central focus of space physiology research in the past several decades. Due to the inability to run comprehensive experiments during spaceflight with sufficient sample sizes, uninterrupted bed rest is a suitable model to study many physiological responses to microgravity. A recent review by Pavy-Le Traon et al. (2007) examines this field in greater detail than we provide in the present review. In our review, we examine recent ground-based research that documents the importance of exercise countermeasures with some form of artificial gravity to prevent microgravity deconditioning.

Head-down tilt (HDT) bed rest is specifically favored to induce the spectrum of adaptations associated with microgravity. For example, the subjects initially experience a rapid decline in aerobic capacity due primarily to decreased circulating blood volume that occurs in response to the head-ward body fluid shift (Convertino 1996).

Continued bed rest causes aerobic capacity to decline further, although at a slower rate, in association with other adaptations such as atrophy and biochemical changes of the active muscle, atrophy and altered mechanics of the myocardium, and impairment of vascular reflexes (Schneider et al. 1996). In addition to the loss of aerobic capacity, there are many other deconditioning responses that space crews must overcome, such as significant atrophy of the bones and muscles involved in posture and locomotion which can limit astronauts' ability to complete necessary tasks. Preventing deconditioning during spaceflight is important to enhance safety and to maintain the ability to perform extravehicular activities. The HDT bed rest model allows for the repeated testing and continued development of countermeasure protocols that can be implemented during spaceflight to mitigate these effects.

Physiological responses related to the head-ward fluid shift

Many of the initial adaptations to microgravity occur in response to head-ward fluid shifts. Healthy adults spend about two-thirds of their existence in upright, sitting, and standing postures. During upright posture on Earth, blood pressures are greater in the feet than at heart or head levels due to gravity's effects on columns of blood in the body (hydrostatic or gravitational pressures). For example, mean arterial pressure at heart level is normally about 100 mmHg, whereas that in the head is slightly lower (e.g. 70 mmHg) and that in the feet is much greater (e.g. 200 mmHg) (Katkov and Chestukhin 1980). During exposure to microgravity, gravitational blood pressure gradients (arterial, venous, and microcirculatory) are lost, and so blood volume is redistributed towards the head. Head-ward fluid shifts are associated with reduced intravascular volumes and pressures in the legs (Watenpaugh and Hargens 1996) and elevated intravascular volumes and pressures in the upper body (Diedrich et al. 2007; Watenpaugh 2001). Ultrasound measurements of the thickness of facial and tibial tissues of a cosmonaut early in flight demonstrate that fluids shift into and remain within facial tissues for the first 3 days of flight (+7 %), while the fluid shift out of the tissues located over the tibia (−17 %) lasts for the duration of the flight (Kirsch et al. 1993). Periorbital and facial edema, sinus and nasal congestion, and distention of the veins of the neck lessen after the first few days of flight, but never completely disappear until return to Earth. Crewmembers report that bicycling 30–120 min helps reduce discomfort associated with the cephalic fluid shift by transferring blood and extravascular fluids to the legs (1.25 cm increase in calf diameter) with effects lasting about 30 min after the workout (Gibson 1977). Thigh cuffs and lower body negative pressure (LBNP) using the Chibis Suit (Kozlovskaya et al. 1995) are commonly used by cosmonauts to counteract cephalic fluid shifts.

Starling pressures regulate the fluid shifts between blood and interstitial fluid (Hargens et al. 1981). Arterial pressure gradients within the body are substantial during upright posture on Earth, but are likely absent in microgravity (Fig. 1). The fluid pressure factors in the Starling–Landis equilibrium are affected by the lack of gravity, and only colloid osmotic pressure of the blood remains to oppose fluid flow into upper body tissue. In microgravity, where gravitational acceleration drops to zero, the weight of the fluid and body tissues is essentially zero, so that interstitial fluid pressure also falls (Fig. 2). We suggest that this loss of tissue weight as well as altered vascular pressures during exposure to microgravity shift the Starling–Landis Equilibrium to greater transcapillary filtration into tissues, leading to facial edema and elevated intracranial pressure (ICP) (Parazynski et al. 1991). This is consistent with the findings of increased fluid filtration in space by Leach et al. (1996).

These head-ward fluid shifts may contribute to many of the early discomforts of space travel, such as the headaches, nausea, and malaise associated with Space Adaptation Syndrome. The head-ward fluid shifts probably raise ICP as well as intraocular (IOP) and cerebrospinal (CSF) pressures. Recently, protracted head-ward fluid shifts have been suggested to contribute to loss of visual acuity (Polk 2009). Jugular vein congestion and elevated ICP may be responsible for the vision impairment during long-duration

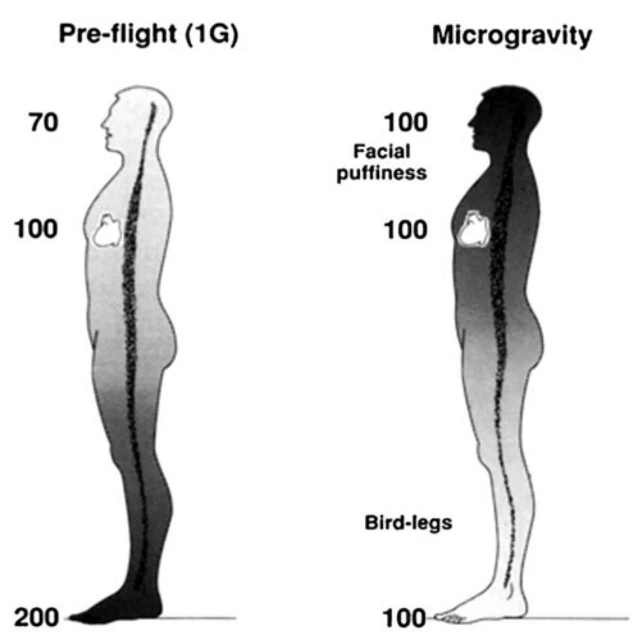

Fig. 1 Hypothetical arterial blood pressures (mmHg) while upright in 1-G and during microgravity. Modified from Hargens and Richardson (2009)

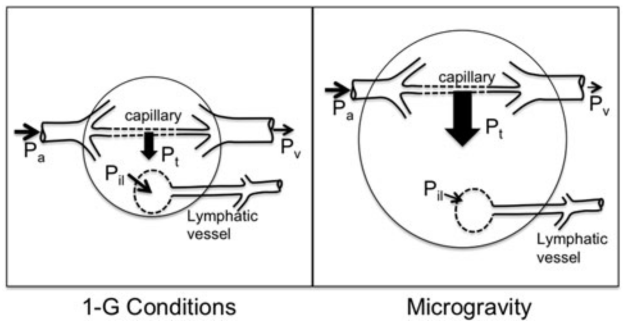

Fig. 2 Altered capillary transmural pressure (blood to tissue) due to microgravity. The arterial pressure P_a, venous pressure P_v, transmural pressure P_t, and interstitial fluid to lymph pressure gradient P_{il} are shown, with *larger arrows* indicating greater pressure gradients. One-G conditions reflect relative values on Earth. In microgravity, the loss of tissue weight reduces tissue hydrostatic pressure further, generating even higher transmural pressure. The increase in transmural pressure causes increased fluid flow into the tissue and thus, edema. Because lymph flow depends highly on tissue deformation and local hydrostatic gradients, lymphatic flow may be reduced in space. Arterial flow depends on the input arterial pressure Pa involved (see Fig. 1). However, altered Starling–Landis pressures do not directly correlate with the loss of gravity-induced hydrostatic pressure gradients because capillary hydrostatic pressures are regulated by pre-capillary sphincter activity and myogenic responses. From Hargens and Richardson (2009)

missions as evidenced by optic disc edema, globe flattening, choroidal folds, cotton wool spots, intraocular pressure, and intracranial hypertension (Mader et al. 2011). Post-flight lumbar punctures performed in four crewmembers with optic disc edema document moderate elevations of opening CSF pressure 12–60 days after returning to Earth. In addition, of about 300 astronauts questioned about vision changes during and after their missions (Fogarty et al. 2011), 29 and 60 % of astronauts experienced a degradation in distant and near visual acuity, respectively. Some of these vision changes persisted for more than 1 year after their space mission. While many explanations are possible, elevated ICP due to a head-ward fluid shift in microgravity is strongly inferred as the mechanism for vision loss because these symptoms are similarly observed in patients with idiopathic intracranial hypertension. Moreover, venous congestion in the head and neck may also contribute to ICP elevation in microgravity. We propose that thigh cuffs, LBNP alone, exercise within LBNP or some other form of artificial gravity may be used to prevent head-ward fluid shifts and thus, reduce ICP and alleviate loss of vision.

Physiological responses of the cardiovascular system

Heart muscle, similar to skeletal muscle, is responsive to changes in work. For the heart, work is partly determined by the force required to propel blood to the upper regions of the body against the hydrostatic gradient caused by gravity. Levine and associates have clearly demonstrated that changes in cardiac mass and function occur within only 2 weeks of simulated microgravity exposure when subjects do not exercise (Levine et al. 1997). Cardiac atrophy and decreased ventricular compliance cause a reduction in stroke volume for any given filling pressure. An inability to maintain stroke volume is believed to be one of the primary factors responsible for orthostatic intolerance and reduced aerobic capacity after bed rest or spaceflight. Recently, Dorfman et al. (2007) found that women have similar cardiac adaptations to simulated microgravity as men. Further, the cardiac atrophy in non-exercising women after 60 days of bed rest was prevented in another group of women who exercised (on alternate days either treadmill exercise within LBNP or high-intensity resistive exercise) only 45 min day^{-1}. A nutritional supplement consisting of 0.45 g kg^{-1} day^{-1} of protein plus 7.2 g day^{-1} of essential amino acids administered to a third group of non-exercising women in this WISE study partially prevented the cardiac atrophy. In this as well as in other bed rest studies, subjects in the control groups usually do not exercise as almost all astronauts and cosmonauts do. Thus, such bed rest studies of the efficacy of exercise countermeasures may overestimate their effects because the scientifically sound control group should rather be one that is exercising just as crew members do in actual microgravity.

Altered blood volume, red cell mass and associated changes in vascular wall sheer forces and perfusion pressures in microgravity may alter gene expression and morphology in the walls of arteries and veins of the upper and lower body (Zhang 2004). These vascular changes impair the cardiovascular reflexes that distribute blood flow among the various body regions, especially reflexes that maintain blood pressure during sudden perturbations in posture or activity. Under normal conditions, cardiovascular reflexes redirect blood flow to active muscles during exercise and limit blood flow to splanchnic and lower-body regions during orthostatic stress. Microgravity exposure may impair both dilatory and constrictor vascular responses. The evidence for this effect during simulated microgravity includes endothelial remodeling obtained from cell (Kang et al. 2011) or animal studies (Behnke et al. 2008; Colleran et al. 2000; Prisby et al. 2006; Wilkerson et al. 2005) and ultrasound structural or Doppler flow studies from humans undergoing orthostatic stress (Arbeille et al. 2005, 2008; Demiot et al. 2007; Yuan et al. 2012). For example, after 56 days of bed rest, Demiot et al. (2007) reported both impaired endothelial-dependent vasodilation, assessed by iontophoresis of acetylcholine, and impaired endothelial-independent vasodilation, assessed by iontophoresis of nitroprusside, in leg cutaneous vessels. The vascular sheer stresses that accompany fluctuations in posture and activity in a 1-G environment are believed to maintain endothelial function. In microgravity, sheer stress forces are reduced, resulting in vascular wall remodeling and increased susceptibility to flow-induced endothelial damage. In the study by Demiot et al. (2007), vascular function was maintained when female bed rest subjects performed only 45 min of aerobic exercise within LBNP or high-intensity resistive exercises each day. Finally, microgravity also reduces erythropoietin and mass of red cells which may importantly lower oxygen transport capacity in space (Rice and Alfrey 2005).

Physiological responses of the musculoskeletal system

In recent years, further understanding is available of the translational mechanisms by which gravity induces molecular responses in human tissues. Under normal gravity conditions, cellular turnover occurs continuously, maintaining tissue mass and viability. However, anabolic/catabolic balance responds immediately to altered gravity or activity. For bone, upon simulated microgravity exposure, the initial response is an increase in resorption (Baecker et al. 2003), while for muscle the immediate response is a decrease in protein synthesis (Ferrando et al. 1996). For example, Ferrando et al. (1996) found negative nitrogen balance and a 50 % reduction in skeletal muscle protein synthesis during the first 2 weeks of bed rest, despite a stable diet and no significant changes in serum cortisol, testosterone, or insulin. Within 2 days of bed rest, Lueken et al. (1993) noted increases in calcium excretion and bone resorption markers. Bone resorption markers increase as much as 60 % with little change in bone formation markers during bed rest without exercise countermeasures (Baecker et al. 2003) and during spaceflight (LeBlanc et al. 2007). The rate of bone loss during spaceflight is greater than during bed rest, and the rate of recovery after a microgravity exposure is 2–3 times slower than the rate of bone loss. Another recent finding is that previous measurements of bone loss during spaceflight may have underestimated the risk for bone fracture. LeBlanc et al. (2007) reported using high-resolution quantitative computed tomography (QCT) bone scans that the rate of trabecular bone loss from the hip of International Space Station (ISS) crewmembers was almost twice as great as total hip bone loss estimates obtained using Dual-energy X-ray absorptiometry. The selective cortical loss of bone from the endocortical side of the femoral neck, trochanter, and total hip emphasize that in addition to bone loss, changes in bone properties may make bones weaker. These bone losses occur despite the crewmembers' participation in exercise countermeasures.

The molecular responses to microgravity are believed directly sensitive to mechanical loading, but may also be induced by changes in tissue perfusion or the hormonal or neural responses caused by altered body fluids. Using microspheres to quantify changes in bone blood flow in rats during hindlimb unloading, Colleran et al. (2000) found that the changes in bone mass (increases in the upper head and decreases in the lower body) were proportional to the shifts in bone perfusion, supporting their hypothesis that altered blood perfusion provides the stimulus for bone remodeling in microgravity (Bloomfield 2006). Besides unloading and altered blood flow, other aspects of spaceflight may also contribute to atrophy of muscle and bone. Increased stress hormones (Paddon-Jones et al. 2006; Stein et al. 1999b) decreased Vitamin D levels (Smith et al. 2005), altered circadian signaling, and decreased caloric balance (Stein et al. 1999a) have varying influence on crewmembers.

While aerobic exercise is proposed as a countermeasure to maintain cardiovascular function, muscle metabolic characteristics, and neuromotor responses; it is thought that resistive exercise is the most effective mode of exercise to maintain muscle mass and strength. Ferrando et al. (1997) found that the reduction in protein synthesis in men during bed rest was prevented by moderate leg resistive exercise on alternate days. Besides this study, many other investigators report that even minimal application of high-intensity resistive exercise prevents decreases in leg muscle mass and strength (Akima et al. 2000; Alkner and Tesch 2004; Mulder et al. 2006; Trappe et al. 2001) and that higher intensity or increased frequency of resistive exercise can prevent myosin heavy chain modifications and myofibril atrophy (Akima et al. 2003; Bamman et al. 1998; Trappe et al. 2004).

In a normal-gravity environment, high-impact aerobic exercise or high-intensity resistive exercises are prescribed to maintain or increase bone mass and density. During spaceflight, however, the effectiveness of aerobic and resistive exercise countermeasures is not as clear. Crewmembers on ISS who perform approximately 5 h week^{-1} of treadmill running or cycling and moderate-intensity resistive exercises 3–6 days week^{-1}, still have significant calf atrophy, loss of strength, and muscle morphological changes (Trappe et al. 2009). Similarly, bone mass decreases consistently during spaceflight, despite participation of crewmembers in American or Russian exercise countermeasure programs (LeBlanc et al. 2007). The ineffectiveness of exercise countermeasures thus far is likely due to inadequacies of flight exercise hardware. The flight Treadmill in Vibration Isolation System (TVIS) provides only partial body-weight loading (McCrory et al. 1999), and previous resistive exercise devices (bungee cords and the interim resistive exercise device) (Trappe et al. 2009) have serious force limitations. A new Advanced Resistive Exercise Device (ARED) was delivered to ISS in November 2008. The ARED is designed to provide greater resistance 273 kg (600 lbs), as compared with the interim resistive exercise device 136 kg (300 lbs), and it can also apply resistance across a wider range of motion and provide greater eccentric-muscle loads than the interim resistive exercise device. Anecdotally, the ARED is thought to be well accepted by crewmembers, who may be showing less decrement in post-flight muscle mass and strength.

Aerobic exercise as a multi-system countermeasure

Exercise is a critical countermeasure for maintaining health and preventing deconditioning of crew members during prolonged spaceflight. However, little is known about the physiology of exercise performed in a microgravity environment. The mode, volume, and intensity of microgravity exercise necessary to maintain health and fitness in a microgravity environment have yet to be defined. This represents a whole new field of exercise physiology in altered gravity. A study during long-term space flight without any form of exercise has never been performed to our knowledge.

Aerobic exercises have been performed primarily using a cycle ergometer, a rower, a passive and more recently motorized treadmill (Moore et al. 2010). Aerobic exercise alone, without concurrent real or artificial gravity, is insufficient to maintain upright exercise capacity, orthostatic tolerance, or musculoskeletal mass and function during bed rest (Convertino 1996) or spaceflight (Trappe et al. 2009). Thus far, the cardiovascular stimulation and the impact loading during treadmill exercise are limited because of the biomechanics and the discomfort caused by the harness system used to secure the exercising crewmember to the treadmill (Genc et al. 2006; McCrory et al. 1999). Also, Genc et al. (2006) suggest that the vibration isolation system used to isolate the movement of the treadmill from the ISS structure may buffer some of the impact forces. However, from their modeling work, Genc et al. (2006) predict that if the impact forces are able to attain normal gravity levels, treadmill exercise could provide sufficient loading to protect bone mass.

The cardiovascular stimulus provided by cycle exercise in microgravity should be similar to that in a normal gravity environment. Yet, post-flight exercise responses and orthostatic tolerance remain compromised when post-flight exercise testing is performed in an upright seated position (Moore et al. 2010). Thus, presently available, moderate-intensity aerobic exercise in a microgravity environment is insufficient to maintain cardiovascular responses post-flight.

In addition to the physiological benefits, the psychological effects of exercise on mental health are evident based on anecdotal information from previous Soviet and Russian space missions. During spaceflight, the impact of confinement within the orbiter or space station and the lack of gravitational loading both reduce the metabolic cost of daily physical activity. Recently, the important role of physical activity from a genomic standpoint is also apparent. For example, the work of Booth and Lees (2007) has documented that the human genome is predisposed to health when physical activity is maintained. When physical activity is reduced, genes associated with chronic diseases such as cardiovascular disease, diabetes, bone loss, and cancer become activated. Thus, a threshold of physical activity is required to normalize gene expression to counteract disease. The amount of exercise necessary to prevent inactivity-related changes in blood lipoproteins, glucose regulation, and blood-pressure control in a normal gravity environment is estimated to require a minimum of approximately 1,000 kcal week^{-1} (Garber et al. 2011). This is in addition to the non-exercise activity thermogenesis (NEAT) associated with standing, sitting, and ambulating in a normal gravity environment. The energy expenditure associated with NEAT is considered significant for the control of muscle metabolic mechanisms (Hamilton et al. 2007). Thus, the amount of exercise required to maintain cardiovascular and metabolic health during spaceflight is unknown, but likely to be greater than that on Earth.

The negative consequences of excessive exercise and inappropriate exercise during spaceflight must be considered as well. For example, during flight many crewmembers have a negative caloric balance, and the extra caloric expenditure of a prolonged aerobic exercise program might contribute to overall musculoskeletal deconditioning (Stein et al. 1999b). Also, a high volume or intensity of exercise may add to the crewmembers' existing stress. Thus, it is critical that exercise countermeasures during spaceflight are efficient and enjoyed by crew members. One possible strategy for improving crew compliance to exercise is to provide a virtual environment within which to exercise and load/time monitoring devices to quantify exercise performed.

Resistive exercise as a multi-system countermeasure

High resistive exercises during spaceflight also have been limited. Until recently, crewmembers could only exercise with elastic bands or devices that provided limited resistance (Trappe et al. 2009). Hopefully, the new ARED will allow a more effective training response. However, as crewmembers now exercise more with the ARED, vision impairment has become a concern. There may be a connection between the higher blood pressures with maximal intensity resistive exercise (MacDougall et al. 1985) and intraocular alterations associated with venous congestion and elevated ICP (Dickerman et al. 1999).

Whole-body vibration combined with resistive exercise may be useful in enhancing the effects of resistive exercise training. In a study of changes in the distal tibia, resistive exercise combined with whole-body vibration during bed rest is an effective countermeasure against loss of cortical area and cortical thickness compared with both no exercise and resistive exercise alone (Belavy et al. 2011). Several other measurements including trabecular thickness are not preserved, which may be attributed to the small sample size or limitations of the high-resolution peripheral computed tomography device used. A similar study dealing with changes in musculature in response to bed rest found that the effect of countermeasures varies greatly between different muscle groups. Resistive exercise and whole-body vibration compared with resistive exercise alone does not show any statistical effect for gluteal and hamstring muscles (Miokovic et al. 2011). In general, both countermeasure regimens enable quicker recovery of musculature post-bed rest compared with the control group. There are also experiments performed on mice that examine the effects on the intervertebral disc of hindlimb unloading and whether vibration mitigates these changes. Hindlimb unloading caused hypotrophy of the intervertebral disc, reduced disc height, and decreased glycosaminoglycan content. Short periods of weight bearing do not prevent these changes. However, when loading is combined with low-intensity vibrations, intervertebral disc physiology is largely maintained (Holguin et al. 2011). In the mouse model, vibration with upright posture but without exercise counteracts the effects of hindlimb unloading. However, in humans, vibration alone is unreliable as a stand-alone countermeasure (Baecker et al. 2012).

Vibration and resistive exercise show effects especially in relation to motor control in the lumbo-pelvic region. Electromyography is used to measure the degree to which the central nervous system "ramps" the activity-levels of each muscle with increases in movement speed (Belavy et al. 2012). This variable is much higher in the inactive control group than in the group that performed resistive exercise with whole-body vibration, therefore affecting motor control. However, this study did not include experimental groups with resistive exercise or whole-body vibration alone, so it is unclear which of the methods plays a larger role in producing these results. Therefore, vibration with resistive exercise has potential as an effective countermeasure, possibly lowering the intensity required for a training response. On the other hand, it is necessary to first isolate the physiological effects of vibration and separately, resistive exercise to determine their respective roles as an integrated countermeasure during spaceflight.

Artificial gravity alone as a multisystem physiologic countermeasure

Artificial gravity (AG), achieved by centrifugation, was first proposed as a multisystem physiologic countermeasure by a Russian scientist Tsiolkovsky more than 100 years ago. Subsequently, small centrifuges have flown on Cosmos, Space Shuttle, and ISS to provide a normal-gravity control condition for animal studies in space. Rotation of an entire spacecraft to provide continuous AG for astronauts significantly increases cost and complicates design and safety. An alternative is to provide a small (<3 m) centrifuge within a spacecraft for intermittent, rather than continuous, gravitational exposure. Ground-based results for bone, muscle, and cardiovascular systems in humans suggest that intermittent exposure to centrifugation may prove an adequate countermeasure (Caiozzo et al. 2009; Iwase 2005; Iwase et al. 2004). AG may counteract some aspects of bed rest-induced cardiovascular deconditioning, including orthostatic intolerance and aerobic power. These improvements are mainly achieved through improved sympathetic responsiveness to orthostatic stress (Stenger et al. 2012).

Intermittent AG could be provided using a short radius possibly human-powered centrifuge mounted inside the vehicle. However, short-radius systems require significant rotation rates and necessitate adaptation to initially unpleasant vestibular and Coriolis effects. Types of exercise are limited on centrifuges as well. For example, it is unlikely that treadmill exercise can be performed on a short-arm centrifuge due to Coriolis and cross-coupling effects as well as lateral strains induced on the exercising joints.

Engineering design of exploration spacecraft for multiyear missions depends on whether AG by way of centrifugation is necessary in a multi-system countermeasure, and whether continuous large radius AG is needed or intermittent short-radius AG is adequate. AG is likely insufficient in itself, so exercise during AG should be the main focus of future exercise countermeasure research. If AG is required, human bed rest/centrifuge studies in ground labs are essential to establish dose–response relationships as well as the gravity level, gradient, RPM, duration, and frequency required to maintain Earth-like health during prolonged microgravity. Several international space agencies have active human and ground-based AG research programs in place. Centrifugation, aerobic exercises, vibration, resistive exercise, and exercise within LBNP are currently some of the methods being extensively explored individually and in combinations as such countermeasures.

The impact of centrifugation alone as an effective countermeasure for the skeletal system is unclear. Although inducing AG to combat bone loss in microgravity is successful in theory, in practice the feasibility of this method as a reliable countermeasure is limited by the side effect of motion sickness particularly with short-radius centrifugation (Arya et al. 2007) or the inability to apply a sufficient level of AG without inducing orthostatic intolerance in passive, non-exercising subjects. Stenger et al. (2012) were able to employ heel rises at will to counteract orthostatic intolerance during the centrifugation. Another important limitation of AG alone is that women do not tolerate orthostatic stress on centrifuges or LBNP as well as men which can be attributed to various factors including lesser ventricular compliance (Fong et al. 2007). It is not yet known whether the difference in body size or hormone levels plays a role in this phenomenon. Centrifugation alone can maintain normal cardiovascular control but does not restore exercise capacity (Iwasaki et al. 2001). Centrifuge-induced AG fails to maintain maximal oxygen uptake, heart rate, or pulmonary ventilation during ergometric leg exercise (Greenleaf et al. 1999). Due to these limitations, centrifugation is usually combined with exercise to increase efficacy.

It is possible that AG alone could be useful in reversing some of fluid shifts in microgravity and thus preventing the recently observed vision effects. During exposure to LBNP, for example, interstitial fluid pressure decreases in parallel with LBNP chamber pressure, foot venous pressure does not change, and leg circumference increases significantly by shifting plasma to interstitial fluids (Aratow et al. 1993). Thus, LBNP alone produces a significant movement of fluid into the lower body. LBNP alone may also be an effective method to prevent some of the head-ward fluid shifts in microgravity. These changes may be especially important in the brain and around the optic nerve, where chronic and sustained increases in intracranial, intraocular, venous, and retinal pressures may induce clinically important structural and functional abnormalities that alter visual acuity. Early development and deployment of a simple LBNP chamber with mild negative pressures in the range of about 30 mmHg may be efficacious to shift blood and body fluids to the lower body over periods of 6–8 h/day on ISS. Such a system can be used while crew members are busy at work stations so that crew operations are not interrupted. Due to the current lack of LBNP hardware on ISS, it is recommended that the Russian Chibis suit be tested initially.

Exercise with artificial gravity as a multisystem physiologic countermeasure

Combining AG with a high-impact aerobic exercise can overcome some of the shortcomings of AG alone, particularly with respect to restoring bone metabolism to retain bone density. AG with aerobic exercise also has notable effects on muscle sympathetic nerve activity and fluid shifts in addition to restoring cardiac and muscular function as seen with centrifugation alone (Iwase et al. 2004). Centrifuge-induced high G-load supplemented with low-intensity exercise counteracts orthostatic intolerance while the centrifuge-induced, low G-load and high-intensity exercise favored maintenance of cardiovascular functions. Therefore, further testing is necessary to determine the G-load and exercise intensity that will maximize results. Although centrifuge-induced AG can be effective, it is important to recognize its limitations in the development of a protocol to reduce physiological changes during spaceflight and bed rest. Short-comings of centrifuge-induced AG include motion sickness, lateral strains induced on lower body joints, and low foot-ward forces during exercise.

Another method to induce AG during exercise is to enclose the treadmill in an LBNP device. A novel physiologic countermeasure was developed and tested (at normal and higher gravity levels) for preventing the cardiovascular and musculoskeletal deconditioning associated with prolonged bed rest (Boda et al. 2000; Cao et al. 2005; Lee et al. 1997, 2007, 2009; Macias et al. 2007; Monga et al. 2006; Schneider et al. 2002, 2009; Smith et al. 2003; Watenpaugh et al. 2000, 2007; Zwart et al. 2007). The countermeasure concept of treadmill exercise within LBNP was tested during 30 days of microgravity simulated by HDT bed rest. In these studies, identical twins were recruited to improve the power of the comparisons before and after bed rest (Hargens et al. 2006; Lee et al. 2007, 2009). The efficacy of the countermeasure was evaluated by comparing test results in control twins with bed rest and no exercise to their identical siblings similarly exposed to bed rest but who performed the treadmill exercise within LBNP countermeasure for 40 min day^{-1}, 6 days week^{-1}. The treadmill within LBNP protocol maintains plasma volume and sprint speed (30 day HDT bed-rest studies of identical twins), a degree of orthostatic tolerance, upright exercise capacity, and muscle strength and endurance during 30-day (twin studies) and 60-day (WISE-2005) bed-rest simulations of microgravity. During WISE 60-day HDT studies, the treadmill exercise within LBNP was performed 3–4 days each week along with resistive exercise that was performed 2–3 days each week. Combining treadmill exercise within LBNP and resistive exercises during HDT, cardiac mass as measured by MRI decreased significantly in the non-exercise, control group but actually increased in the exercise group (Dorfman et al. 2007). Upright peak VO_2 (Schneider et al. 2009), muscle strength of the knee, and knee extensor endurance (Trappe et al. 2007, 2008) decreased significantly in control group but were preserved in the exercise group. It is important to note that in this 60-day HDT study, the treadmill LBNP countermeasure plus 10 min of static LBNP after exercise was last performed 3 days before the end of the bed rest, but orthostatic tolerance was still partially maintained in the exercise group compared with the control group at the end of bed rest (Guinet et al. 2009).

Theoretically, an integrated and physiologic countermeasure for extended exposure to microgravity should combine high loads on the musculoskeletal system with regional distributions of transmural pressure across blood vessels. In this regard, there is evidence that dynamic loads during supine treadmill exercise within LBNP provide inertial forces on the musculoskeletal and cardiovascular systems similar to those present during upright exercise on Earth. Moreover, our 30- and 60-day bed rest studies of identical twins and women document that LBNP treadmill exercise with foot-ward forces similar to Earth's gravity, protects against bone loss while maintaining muscle strength, exercise capacity, and to a lesser degree, orthostatic tolerance (Guinet et al. 2009; Hargens and Richardson 2009; Kirsch et al. 1993; Lee et al. 2007, 2009; Schneider et al. 2009; Watenpaugh et al. 2007). Similar results are reported in bed rest studies using a short-arm centrifuge (Caiozzo et al. 2009; Iwase 2005; Iwase et al. 2004). However, to maintain multiple physiologic systems prior to successful installation of centrifugation on ISS or another space craft as artificial gravity, an early, low power, low-cost countermeasure such as exercise within LBNP may provide an integrated and well-tested countermeasure for prolonged space flight.

Conclusions

Few countermeasures employed to date have been thoroughly documented as effective in preventing deconditioning during long-duration spaceflight when applied individually. Recent ground-based research suggests that to prevent deconditioning in microgravity, it is necessary to perform exercise countermeasures within artificially induced gravity to induce foot-ward loading and to restore body fluid hydrostatic gradients. Aerobic exercise within a centrifuge restores cardiovascular function and separately, aerobic exercise within LBNP restores cardiovascular function and helps protect the musculoskeletal system. Resistive exercises with vibration stimulation may increase the effectiveness of lower intensity resistive exercise to preserve muscle function. Inexpensive methods to induce AG alone (to counteract fluid shifts) and during exercise, such as a short-arm centrifuge or exercise within LBNP, should be developed and evaluated as multi-system countermeasures.

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