Plantar Stimulation as a Possible Countermeasure to Microgravity-Induced Neuromotor Degradation

Charles S. Layne and Katharine E. Forth

Layne CS, Forth KE. *Plantar stimulation as a possible countermeasure to microgravity-induced neuromotor degradation.* **Aviat Space Environ Med 2008; 79:787–94.**

Since the early days of human spaceflight it has been reported that extended exposure to gravitational unloading results in a myriad of neuromotor adaptations that, while appropriate for microgravity, are maladaptive upon return to Earth. If not countered, these adverse effects of microgravity can result in negative health consequences and place crewmembers at risk for injury. The most commonly used countermeasures in today's space programs are those requiring active participation in prescribed exercise regimes that are time intensive, not completely effective, and have led to relatively low compliance. In this paper we review evidence that suggests a "passive" countermeasure in the form of dynamic foot stimulation (DFS) to the plantar surfaces of the feet may be a useful supplement to more traditional exercise countermeasures. This includes reports from both Russian and American investigators using both human and animal models indicating the overall effectiveness of DFS, the specific stimulation parameters involved, and a physiological explanation for the outcomes associated with the exposure to microgravity. Additionally, the use of DFS has the potential to benefit those at risk for muscle atrophy, including those experiencing extended bedrest, the elderly, and those with spinal cord injuries.

Keywords: atrophy, bed rest, foot stimulation, dry immersion, spaceflight.

SCULPTED BY EVOLUTION, humans are well adapted to the Earth's environment. With gravity being a constant in the environment many human sensory systems detect gravity, directly or indirectly, for sensorimotor integration, motor control, and, ultimately, survival. The involvement of the vestibular otolith organ in directly detecting the gravity vector for spatial orientation and ocular adjustments is well accepted and has been previously reviewed (see 33,58). Other sensory systems are sensitive to the indirect effect of gravity: gravitational loading on the musculoskeletal system. Although the gravity vector is constant, the level of gravitational loading experienced by an individual is variable and dependent on the individual's anatomy, body segment configuration, and environmental context. With the development of human bipedalism came a mechanical challenge for maintaining postural stability with a large mass being above a small base of support. This small base of support makes contact with the environment at the soles of the feet. Thus, sensory information from the feet, including detection of changing gravitational load, contributes substantially to effective movement control both on Earth and in microgravity. For example, plantar contact is important for establishing a vertical reference for body orientation (57) and triggering postural responses (34–36) in microgravity. In this review we will concentrate on the deleterious neuromotor effects of microgravity, their relationship to absent plantar sensory information, and the role mechanically applied plantar sensory stimulation can have in countering these negative effects.

Short-term adaptations to the removal of the gravity vector during spaceflight can have adverse effects for returning to life on Earth. It has been well established that without gravitational loading, skeletal muscles, particularly the antigravity extensors, will atrophy in prolonged microgravity (for review see 10). Additionally, sensorimotor connections at the muscle, cellular, and neuronal levels can be disrupted and contribute to neuromotor degradation that will contribute to compromised postflight posture and movement control (3). It should be noted that maladapted functioning in other physiological systems, such as the vestibular, visual, and cardiovascular systems, also contributes to difficulties in movement control upon return from spaceflight.

To counter the muscle atrophy and sensorimotor degradation astronauts experience from extended periods in low-gravity environments, a variety of countermeasures have been developed. However, the majority of these countermeaures require "active" participation by the astronaut to perform exercise regimes. Treadmill running, ergometer cycling, and resistive exercises are among the currently used in-flight countermeasures, and to achieve positive effects from these exercises requires an extensive amount of the crewmembers' time. This time commitment is among the reasons few crewmembers exhibit full compliance to their prescribed

---

From the Laboratory of Integrated Physiology, Department of Health and Human Performance, University of Houston, Houston, TX.

This manuscript was received for review in February 2008. It was accepted for publication in May 2008.

Address reprint requests to: Charles Layne, Ph.D., 104 Garrison, 3855 Holman Street, Houston, TX 77204-6015; clayne2@uh.edu.

Reprint & Copyright © by the Aerospace Medical Association, Alexandria, VA.

DOI: 10.3357/ASEM.2293.2008

countermeasure regime (29). A new generation of passive countermeasures, pharmaceutical and mechanical, are thought to be highly advantageous because they effectively attenuate the adverse physiological consequences of microgravity while reducing the strain on crewmember time and effort (13,29). These passive countermeasures need not compete with traditional inflight exercise, but instead can be used as a supplement. The Russian crew health program has implemented passive mechanical countermeasures for some time with pressure cuffs and "penguin" suits that provide resistance to body segment motions. Similarly, NASA is currently investigating the use of Jobst compression stockings as a passive countermeasure. In 2006, the Japan Aerospace Exploration Agency (JAXA) and Asics Corporation announced an agreement to build shoes for astronauts to attenuate muscle strength losses during spaceflight. These shoes will enhance stimulation of the feet as crewmembers go about their daily activities. Evidence suggests (reviewed below) that an important component of a passive countermeasure designed to reduce neuromotor degradation, particularly degradation associated with lower limb functioning, will require that the mechanoreceptors of the feet are consistently stimulated.

Neuromotor Adaptations Resulting from Removal of Support Unloading

There were early hints from the Spacelab-1 mission that tactile information was upweighted during flight, suggesting that foot stimulation may take on increasing importance during flight (55,56). Likewise, Roll et al. (50) reported that the application of a 'gravitational' load applied to upright astronauts strongly affected the responses to muscle vibration relative to either freefloating or upright, but unloaded bipedal body configurations. This further suggests that sensory information from the soles has an important role during exposure to microgravity.

A relationship between the loss of support afferentation and neuromotor degradation was first suggested in 1961 by Graveline et al. (15). Early reports by Russian space physiologists and others emphasized this relationship based upon tests of cosmonauts experiencing weightlessness during space station flights (18,21). More recently, Kozlovskaya and her colleagues, based at the Institute for Biomedical Problems in Moscow, Russia, have postulated that the loss of support afferentation is the primary cause of the many neurodecrements observed during both spaceflight and the various ground-based models of unloading which include bed rest and dry immersion (17,25–31,42,47). They have proposed that sensory input related to gravitational loading is a prerequisite for the levels of tonic muscle activation normally observed during activities in 1 g. Conversely, the removal of support afferentation during gravitational unloading is the initiating factor that suppresses small motor unit tonic muscle activity and enhances the phasic activity of larger motor units of the lower limb musculature (24,28). This fundamental change in normal motor unit recruitment processes then triggers a cascade of neuromotor adaptations. These adaptations ultimately result in significant alterations in neuromuscular functioning, which negatively impacts posture and locomotor control, and, therefore, place crewmembers returning from spaceflight in potentially harmful circumstances unless adequately countered during flight. The strong influence of sensory input on motor unit recruitment order has also been demonstrated by Garnett and Stephens, who reported that continuous stimulations of the index finger resulted in modifying recruitment thresholds for large and small motor units of the first dorsal interosseous muscle (14).

Evidence supporting Kozlovskaya's contention was obtained during experiments conducted during both spaceflight and dry immersion protocols. Dry immersion uses an elastic waterproof cloth that prevents direct contact between the subject and the water. It is believed that this technique provides a more realistic simulation of exposure to microgravity as the subject experiences less gravitational loading along the long axis of the body relative to that experienced during bed rest (51). Results obtained from a dry immersion study revealed that within 24 h of immersion there were decreases in both surface electromyography (EMG) and muscle stiffness of the soleus and increases in these measures for the tibialis anterior (30). These data support the idea that loss of support afferentation serves as an initiating trigger for the proposed cascade of neuromotor adaptations which ultimately negatively impact whole body movement activities. It seems obvious that these responses observed upon immediate exposure to immersion are not the result of a muscle disuse phenomenon, but rather are directly related to the removal of normal levels of sensory input associated with 1-g functioning. The results of their investigations have led Kozlovskaya et al. (28) to maintain that "support unloading, accompanied by the great reduction in afferent inflow, could be considered as the main 'pathogenic' factor of all changes in movement parameters that were observed both in short-term as well as long-term exposures" to gravitational unloading (28, p. 150).

In 1982, Kozlovskaya and her colleagues first published results from an experiment designed to test the efficacy of using mechanical stimulation of the feet during spaceflight as a countermeasure to the neuromotor degradation that develops during extended missions (20). This paper reported that the Russian crewmember aboard the Salyut-6 space station who used the 'Cuban sandal' preserved lower limb strength and overground locomotion kinematics relative to the Cuban cosmonaut who had not worn the sandal during flight. The sandal provided patterned stimulation to the soles with pneumatic bladders during periods of freefloating. Since that time various investigators have explored both human and animal models to determine the effectiveness of mechanical foot stimulation as a countermeasure to neuromotor degradation resulting from gravitational unloading (6,11,23,29,30,32,38–40,42,44,47,48).

Replacing sensory input associated with support afferentation in some form seems a necessary prerequisite if dynamic foot stimulation (DFS) is to be used as a supplemental countermeasure. Mechanical stimulation of the soles during gravitational unloading may effectively provide such input and thereby attenuate the cascade of neuromotor consequences stemming from support afferentation removal. Early work by our group was intended to determine if mechanical foot stimulation resulted in enhanced neuromuscular activation of the lower-limb musculature during exposure to microgravity. Consistent with early observations that crewmembers display decreased muscle activation during spaceflight as a result of the limited use of their legs, Layne and Spooner (34) reported that the anticipatory activation of the biceps femoris observed during arm raises in 1 g was absent during freefloating arm raises performed during parabolic flight. However, further experimentation revealed that when the soles were stimulated the previously absent biceps femoris activity was restored (36). In this experiment, sole stimulation was provided using a primitive system composed of a harness and bungee cords, attached around the subject's waist, fastened to a pair of slippers. This finding suggested that providing stimulation to the soles might be useful in generating neuromuscular activity in the lower-limb musculature while in microgravity. This early work was followed by experiments conducted on the U.S. Space Shuttle and Russian Mir space station using boots containing pneumatic bladders and customized sole inserts that when inflated provided enhanced stimulation preferentially to the balls and heels. Again it was found that previously absent anticipatory biceps femoris activity was restored with the application of sole stimulation during freefloating arm raises. Additionally, enhanced activation was observed in the paraspinals, gastrocnemius, and tibialis anterior as a result of applying stimulation to the soles. This response pattern strongly suggests that foot stimulation has the potential to increase neuromuscular activation throughout the entire lower-limb musculature, thereby enhancing its utility as a possible countermeasure (37). These results are consistent with Dietz and Colombo (9), whose ground-based immersion study also demonstrated the importance of plantar and/or leg-loading afferents for postural adjustments to voluntary arm movements (7–9,43).

Habituation of Responses

For DFS to be maximally effective as a countermeasure, it is important that the response to foot stimulation be maintained throughout an extended mission, during which the human physiological system undergoes significant adaptation in response to microgravity. In 2000, Layne et al. (38) reported that the enhanced lower-limb musculature response to foot stimulation during freefloating arm movements during a Mir mission was maintained through flight day 188. In this investigation static foot stimulation was applied for approximately 3 min once every 5 wk. The important finding was that the response to foot stimulation did not degrade throughout the course of an extended mission. In other words, the response did not 'adapt out' as the time in flight increased. This important finding suggests that DFS may be an effective long-term countermeasure.

It is well known that physiological responses to a static stimulus tend to habituate within a relatively short period of time (22). Thus, a countermeasure employing stimulation of the soles needs to provide a dynamic stimulus. Current work is, therefore, aimed at identifying optimal stimulation patterns during ground-based experiments (11,12,39,40) and the effects of a dynamic pattern of stimulation on many physiological measures during dry immersion (23,42,44,47).

Responses to Variations in Stimulus Parameters

Using a pneumatic pressure pad, Layne et al. (39) explored the interaction between voluntary muscle activation and responses generated by dynamic sole stimulation of seated subjects in a laboratory setting. The pneumatic system enabled a stimulus to be applied intermittently and to a specific area of the sole, unlike the static stimulation boots used during the above experiments conducted during spaceflight. Thus, the potential for response habituation was eliminated. Subjects were asked to perform plantar or dorsiflexions of the ankle while foot stimulation was applied at one of three time periods relative to the onset of voluntary neuromuscular activation: Early (−150–50 ms prior to activation, Coincident (49 ms prior to activation to 49 ms after activation), and Late (50 ms to 150 ms after activation). Stimulation was applied to either the ball or the heel of the foot depending upon the experimental condition. Baseline trials consisting of only voluntary muscle activation or only foot stimulation were also included for comparison purposes. The dependent measure was the integrated area obtained from surface EMG of the plantar or dorsiflexors. It was hypothesized that pairing foot stimulation with voluntary contraction would increase the overall neuromuscular response and that the site and the timing of stimulation would influence the response. Indeed, it was found that enhanced neuromuscular activation occurred, relative to baseline, when the stimulation was delivered either Early or Coincident relative to voluntary activation onset. The greatest enhancement, however, occurred in the Early condition. This response pattern was true whether the stimulation was delivered to either the ball or the heel of the foot and held for both the plantar flexor (i.e., soleus) and dorsiflexor (i.e., tibialis anterior). These findings were interpreted to suggest that afferent information resulting from sole stimulation modifies motoneuronal thresholds such that a descending command for voluntary activation results in a greater number of motoneurons being activated, and thus, producing greater neuromuscular activity relative to contractions not paired with sole stimulation. Regardless of the physiological mechanisms involved, this experiment provided useful information about the interaction between voluntary muscle activation and that generated as a result of foot stimulation.

Evidence from studies employing electrical stimulation of the sole suggested that the site of stimulation could also influence the subsequent response (1,2,52,53). Knowledge that certain stimulation sites on the sole produced greater or less muscle activation would be an important consideration in DFS countermeasure design. Therefore, Layne et al. (40) investigated the neuromuscular responses to spatially localized sole stimulation in a ground-based protocol using seated subjects. The dynamic foot stimulator used in this investigation employed electrically activated solenoids with a hemispherical plastic cap that applied 13.8 N · cm^{-2} of pressure over a 1.77-cm^2 surface area. This device provided significantly improved spatial resolution of the stimulation site and improved frequency characteristics relative to the previous system, which used relatively large pneumatic pads with a relatively slow inflation/deflation rate. Stimulation was provided to the heel, first (medial) metatarsal head, and fifth (lateral) metatarsal head, depending upon the experimental condition. Surface EMG was obtained from the soleus, lateral gastrocnemius, and tibialis anterior of the lower limb experiencing the stimulation. For all three monitored muscles, stimulation of the sole at the fifth metatarsal head produced the greatest neuromuscular activation, with the heel producing a non-significant increase relative to quiet baseline EMG. Stimulation under the first metatarsal head produced a significant response relative to baseline, but significantly less than that observed as a result of fifth metatarsal head stimulation. It is important to note that the increases in neuromuscular activation were achieved in electrically 'quiet' muscles. This is in contrast to results using electrical stimulation which require some level of voluntary activation to produce a response to a non-noxious stimulus (5,54).

This same study investigated the effect of temporally pairing two stimuli from different sites. The subjects experienced six different stimulation patterns, where a pattern was defined as the stimulation of one site on the sole followed 250 ms later by stimulation of another site. For instance, one pattern consisted of stimulation under the fifth metatarsal head followed by stimulation under the first metatarsal head. A second pattern consisted of stimulation of the heel followed by stimulation under the fifth metatarsal head. Using the three stimulation sites mentioned above, all combinations of stimulation sites resulted in six different stimulation patterns (see 40, Table 2). The dependent measure was surface EMG amplitude obtained in experimental trials and compared with responses obtained in baseline trials using only a single stimulus per trial. The data from this protocol indicated that in all muscles, responses to fifth and first metatarsal head stimulation resulted in decreased neuromuscular activity if the stimulation was preceded by stimulation at any other site. For example, the response of the soleus to first metatarsal head stimulation was decreased relative to a baseline response when paired with a prior stimulation of the fifth metatarsal head (see 40, Fig. 6 and 7). Interestingly, the soleus and lateral gastrocnemius significantly increased their responses to heel stimulation when paired with first metatarsal head stimulation. Although statistically significant, the increase observed in this condition was substantially less than the magnitude of inhibition observed in response to the other patterns of stimulation. The findings from this protocol suggest that when using patterned stimulation to generate lower-limb neuromuscular contraction, it is very important to apply patterns of stimulation that account for both stimulation site and the fact that closely temporally paired stimulation may result in neuromuscular inhibition rather than increased activation.

A subsequent experiment was completed that assessed the phenomenon of neuromuscular inhibition that results in the second response to two stimuli paired closely in time (41). This protocol involved seated subjects who received mechanical stimulation under the fifth metatarsal head while surface EMG was collected from the lateral gastrocnemius, soleus, and tibialis anterior. The stimuli were delivered as a 'couplet,' with a second stimuli being delivered following the first stimuli at different interstimulus intervals (ISI). The purpose of this protocol was to begin to identify the ISI time frame that resulted in neuromuscular inhibition to the second stimuli and conversely, identify the ISI at which the response to the second stimuli was no longer inhibited. The ISIs were 100, 140, 180, 220, 260, or 300 ms. The amplitudes of the second responses associated with the various ISIs were compared to baseline responses obtained in response to single stimuli. The results indicated that for all three muscles, the neuromuscular responses to a second stimulus within a couplet were inhibited for ISIs of at least 260 ms. Additionally, there was a linear response recovery curve with shorter ISIs resulting in nearly complete inhibition with the neuromuscular activity gradually increasing as the ISI increased. At an ISI of 300 ms all muscles displayed a complete recovery in response amplitude to that recorded during baseline trials. These data are consistent with the findings of Layne et al. (40), who reported inhibited responses to the second of two mechanical stimuli and suggest that when developing a countermeasure using patterned stimuli to the sole, it will be important to assess the impact of interstimulus intervals on neuromuscular response parameters. Griffin et al. (16) have also shown that the force output of whole muscles can be modified depending upon the pattern of stimulation.

Currently, our group has been focused on identifying neuromuscular response parameters to varying stimulus features. Little work designed to identify the exact neural pathways involved in the response has been completed. However, during laboratory experiments we have been careful to control for any movement of the ankle joint in response to the mechanical stimulation. The tibialis anterior also responds to the stimuli and if the ankle joint was flexing during the experimental protocols, this muscle would be shortening. Thus, we are confident that the observed responses are not simple stretch reflexes. However, based upon the onset latencies, it is logical to conclude the responses are polysynaptic reflexes with cutaneous and foot muscle afferents playing an important role (11,12).

Effectiveness of Dynamic Stimulation—Human Model

More direct tests of the potential effectiveness of providing DFS to attenuate neuromotor degradation associated with unloading have been conducted by Kozlovskaya's research team employing the unloading technique of dry immersion. During recent dry immersion investigations (29,30), 18 healthy men were exposed to 7 d of dry immersion. Resting surface EMG and transverse stiffness of the soleus and tibialis anterior was obtained prior to, during, and after immersion. During another session of 7 d dry immersion these subjects received DFS for 20 min $\cdot$ h^{-1} for 6 h throughout the day (i.e., for a total of 120 min $\cdot$ d^{-1}). The device used was a custom-made shoe employing pneumatic bladders that provided 0.5 kg $\cdot$ cm^{-2} of pressure using 10 min of stimulation matching a cadence of 75 steps per minute alternated with 10 min of a cadence of 120 steps per minute. It was reported that without DFS, soleus EMG activation significantly decreased while tibialis anterior activation increased during immersion. However, the use of DFS greatly attenuated the decrease in soleus activity and the increase in tibialis anterior such that the results obtained during dry immersion with DFS and those of baseline were not significantly different. During the early stages of dry immersion, the use of DFS greatly inhibited the large decreases in transverse stiffness observed during dry immersion without DFS, but by the sixth day of immersion the decreases in soleus stiffness between the with and without DFS measures were equal. Conversely, dry immersion resulted in significant increases in tibialis anterior stiffness, which was significantly inhibited as a result of DFS. This inhibitory effect was still present on day 6 of immersion.

During this same investigation, the functional properties of the lower-limb musculature were assessed by concentric isokinetic dynamometry throughout a range of speeds. Locomotor testing was also performed. During locomotor testing, the subjects walked at 90 steps per minute while surface EMG was obtained from the medial gastrocnemius, soleus, and tibialis anterior. After dry immersion, without DFS, both ankle flexion and extension force-velocity curves were significantly reduced at all speeds relative to baseline records. The use of DFS during immersion significantly increased both the flexion and extension curves such that there were no significant changes between pre- and post-immersion testing. This result was consistent with that of Khusnutdinova et al. (23), who used a similar dry immersion and DFS protocol. The EMG obtained during walking after dry immersion revealed significant increases in both the soleus and gastrocnemius neuromuscular activity with the increase in the gastrocnemius being significantly greater than that of the soleus. The differential increases of these two muscles resulted in a significant change in the ratio of soleus to gastrocnemius activity during walking. The use of DFS resulted in reduction of the observed increase in the gastrocnemius, but a further increase of the activation of the soleus such that the ratio of soleus to gastrocnemius activity was restored to baseline levels. In the tibialis anterior EMG activity increased relative to baseline without DFS, but was restored to baseline levels with the use of DFS.

An investigation of force-velocity characteristics of the knee flexor and extensors after 7 d dry immersion revealed that during isokinetic testing there is a significant decrease in voluntary force in both flexion and extension after immersion (47). The use of DFS greatly attenuated these declines in strength. During isotonic testing there were significant decreases in knee extensor strength, but less so for knee flexion. These decreases were also eliminated with the use of DFS.

Effectiveness of Dynamic Stimulation—Animal Models

Overall the evidence obtained during functionally related tests of strength and performance seems to suggest that the use of DFS to reduce the deleterious impact of gravitational unloading on humans holds promise for the development of a spaceflight countermeasure. Additional work using animal models and humans has focused on attempting to identify physiological responses to DFS. One investigation that demonstrated the role that plantar stimulation could play in producing significant physiological results on disordered neuromuscular systems was conducted by Muir and Steeves (45). In this study, hatchling chicks with hemisectioned thoracic cords were provided plantar stimulation while swimming during the surgery recovery period. Lower-limb kinematics obtained during overground walking and swimming served as the dependent variables. Chicks that did not receive plantar stimulation after thoracic hemisection never demonstrated a full recovery of normal lower-limb motion. However, those receiving plantar stimulation did recover normal patterns of motion that were retained even after removal of the stimulation. This evidence is a powerful demonstration of the impact that plantar stimulation can have on even severely disordered physiological systems. It is also important to note the positive effects of plantar stimulation in this report occurred in the absence of limb loading and suggest that plantar stimulation during spaceflight may also be effective.

One of the first reports designed to explore the impact of plantar stimulation on muscle fiber characteristics of hindlimb suspended rats was by that of Nemirovskaya and Shenkman (46). Their protocol involved a freely moving control group, and several hindlimb suspended conditions. These conditions all included a free hanging left hindlimb combined with either 1) a free hanging right limb; 2) a right hindlimb supported by a small platform; 3) an immobilized ankle of a free-hanging right limb which prevented soleus contraction; or 4) a right limb that was both supported and immobilized. This design enabled the investigators to isolate the effects of muscle contraction and plantar stimulation (i.e., supported platform condition) versus that of plantar stimulation without contraction (i.e., immobilization plus platform support). Dependent measures following this 14-d protocol included soleus muscle mass, cross-sectional area (CSA) of slow and fast twitch fibers, and enzymatic activity. The predominate findings indicated that total muscle mass and CSA of both slow-twitch and fast-twitch in the left limb decreased relative to the control group and that atrophy was totally prevented only in the right limb supported condition. This was interpreted to suggest that only in conditions enabling both plantar stimulation and muscle contraction would the beneficial effect of plantar stimulation be observed. Despite the size similarity between the control and supported right soleus, there were decreases in enzymatic activity between the control and supported right soleus. This decrease in enzymatic activity in the supported right soleus is in contrast to the significant increase found in the freely hanging left soleus.

Consistent with the above work is that of Kyparos et al. (32), who reported that stimulation of the plantar surface of hindlimb suspended rats resulted in no differences in soleus CSA being observed between those rats receiving DFS and the ambulatory controls (32). These authors employed a pneumatic cuff that rapidly inflated and deflated to provide dynamic stimulation to the soles. The protocol used DFS for only 160 $\text{min} \cdot \text{d}^{-1}$ over the 10-d suspension protocol. Thus, the rats in the experimental group received DFS for only 5.6% of the entire period they were suspended. This is in great contrast to the protocol of Nemirovskaya and Shenkman (46), whose rats received plantar stimulation continuously throughout the entire suspension protocol. In the protocol of Kyparos et al. (32), one group of suspended rats had the pneumatic cuff attached to their foot the same period of time as those rats experiencing DFS, but the cuff was not activated (i.e., inflated and deflated). Interestingly, just the application of the cuff was enough to prevent muscle atrophy of the soleus and attenuate that of the medial gastrocnemius. That is, the application of mechanical stimulation of the plantar surface was effective whether the pneumatic cuff was active or not. This finding is consistent with that of Nemirovskaya and Shenkman (46), in that both studies strongly suggest that the ankle musculature must be free to contract if mechanical stimulation of the soleus is to be an effective counter to muscle atrophy. It is suggested that in the condition involving the intact but unactivated cuff, that during the course of ankle movement the rats gained dynamic stimulation of the plantar surface, making that condition very similar in terms of stimulation to that of the experimental condition involving activation of the inflatable bladder. Supporting this idea is the fact when the cuff was applied to the ankle but the inflatable bladder was removed (i.e., no plantar stimulation), the soleus atrophied to the same degree as that in rats experiencing only hindlimb suspension. This finding reinforces the contention that plantar stimulation is essential for protection against muscle atrophy induced by unloading.

Additional work in this area has been conducted by DeDonker et al. (6). These investigators stimulated the plantar surface of the hindlimb suspended rats using an inflatable balloon, which, when inflated, made contact with the restrained feet. The inflation/ deflation cycle was only employed for 10 min per day throughout the 14-d suspension period. Results indicated that the application of DFS attenuated soleus atrophy by approximately 40% depending upon the fiber type assessed. Additionally peak twitch tension was also greater than that of hindlimb suspended rats that did not experience DFS. They concluded that "modifications in the stimulation of cutaneous receptors of rat foot soles (increases in time and number of applications) would provide a more effective means of preventing muscular atrophy and the associated postflight motor control deficits experienced by astronauts" (6, p. 2350).

Physiological Mechanisms of Response to Plantar Stimulation

Little work with humans has been completed to elucidate the mechanisms by which plantar stimulation attenuates neuromotor degradation. However, two preliminary studies have been conducted with humans that have employed dry immersion and DFS. Moukhina et al. (44) reported that after 7 d of dry immersion the percentage of type I soleus fibers significantly decreased. However, with the use of DFS (23,29,30), there was no change in the percentage of type I fibers. Cross-sectional area of type I fibers in the soleus decreased by 24% during immersion relative to baseline without DFS. However, when DFS was used during immersion there was no significant change in cross-sectional area. This finding is very consistent with that observed in studies using hindlimb suspended rats and DFS. The total protein concentration increased in both subject groups, suggesting a loss of cross-sectional area that could be credited to the loss of the non-protein elements of the fibers. Measures of NO-synthase I, which provide an index of muscle cell signaling activity, were also obtained. In the dry immersion only group, NO-synthase I significantly decreased while it remained essentially unchanged from baseline level in subjects experiencing DFS. This was interpreted to suggest that the soleus muscle maintained a greater level of contractile activity throughout the immersion period relative to those subjects not receiving DFS. This finding can also be interpreted to suggest DFS is generating muscle activation consistent with the increased EMG observed by DeDonker et al. (6).

An additional study by Litvinova et al. (42) using the identical dry immersion protocol as that above measured peak maximal tension of single soleus fibers, single fiber diameter, and titin/myosin heavy chains (MHC) and nebulin/MHC ratios were computed. These ratios provide information about proteins which are important for the assembly and function of muscle sarcomeres. It was reported that without the protective use of DFS, fiber diameter was significantly reduced, as was maximal peak tension. The use of DFS prevented these declines. Nebulin/MHC and titin/MHC ratios decreased by more than 30% in the immersion only group, but only by 14% in the immersion with DFS group. These data and that of Moukhina et al. (44) suggest that DFS during periods of unloading functions to maintain both muscle fiber integrity and function.

In an effort to determine if muscle spindle afferents from the plantar and/or dorsiflexors influenced the response to mechanical stimulation of the sole, Layne et al. (40) conducted an experiment that varied ankle angle prior to a series of trials containing a single stimuli. Using seated subjects, ankle angle was fixed at either 70°, 90°, or 110° and the responses of the soleus, lateral gastrocnemius, and tibialis anterior were collected with surface EMG. For the soleus and gastrocnemius, trials with decreased ankle angle (i.e., stretch of the plantar flexors) resulted in larger amplitude responses than those with increased ankle angle. The exact opposite response pattern was observed in the tibialis anterior, where the greatest responses were observed during trials with increased ankle angle (40, Fig. 8 and 9). These findings strongly suggest that muscle spindle afferents from the shank musculature do influence the neuromuscular response to foot stimulation. Further confirmation that shank musculature afference can modify the reflexive response was obtained during an experimental condition which held the ankle angle constant at 90°, but used Achilles tendon vibration while the stimuli was delivered. This protocol revealed that the responses to sole stimulation were greatly inhibited with the use of vibration. Since it has long been known that tendon vibration preferentially affects muscle spindle responses (4,19,49), we interpreted these findings as confirmatory evidence that shank musculature afference does influence reflexive responses to foot stimulation. As with the results obtained from the protocols reviewed above, these results may be important for the development of a countermeasure designed to provide optimal responses to mechanical foot stimulation.

Summary

In this review we have discussed the negative impacts microgravity exposure can have on the human neuromuscular system and stressed the need to ameliorate those effects with the possible use of passive countermeasures. It has been argued that the removal of the support-loading afferentation can trigger a cascade of neuromotor adaptations beginning with a reversal of motor unit recruitment order in the extensor muscles used for bipedal postural control and ultimately resulting in compromised whole-body movement activities. We have suggested that providing a dynamic mechanical stimulus to the soles can partially restore support-loading afferentation in a manner that can prevent the initiation of the negative cascade and thereby counter the neuromotor degradation associated with exposure to microgravity during spaceflight. Both human and animal model evidence strongly suggests that DFS is effective in attenuating the negative effects of unloading. Additionally, for the application DFS as a countermeasure, stimulus parameters and their resulting responses need to be understood. The research efforts aimed at identifying stimulus parameters designed to maximize the positive impacts of DFS and possibly elucidate the neurophysiological mechanisms underlying the response to DFS have been also discussed.

ACKNOWLEDGMENTS

Authors and affiliations: Charles S. Layne, Ph.D., and Katherine E. Forth, Ph.D., Laboratory of Integrated Physiology, Department of Health and Human Performance, University of Houston, Houston, TX.

REFERENCES

1. Andersen OK, Sonnenborg FA, Arendt-Nielsen L. Modular organization of human leg withdrawal reflexes elicited by electrical stimulation of the foot sole. Muscle Nerve 1999; 22:1520–30.
2. Andersen OK, Sonnenborg FA, Arendt-Nielsen L. Reflex receptive fields for human withdrawal reflexes elicited by non-painful and painful electrical stimulation of the foot sole. Clin Neurophysiol 2001; 112:641–9.
3. Arrott AP, Young LR. M.I.T./Canadian vestibular experiments on the Spacelab-1 mission: 6. Vestibular reactions to lateral acceleration following ten days of weightlessness. Exp Brain Res 1986; 64:347–57.
4. Burke D, Hagbarth KE, Lofstedt L, Wallin BG. The responses of human muscle spindle endings to vibration of non-contracting muscles. J Physiol 1976; 261:673–93.
5. Burke D, Dickson HG, Skuse NF. Task-dependent changes in the responses to low-threshold cutaneous afferent volleys in the human lower limb. J Physiol 1991; 432:445–58.
6. De-Doncker L, Picquet F, Falempin M. Effects of cutaneous receptor stimulation on muscular atrophy developed in hindlimb unloading condition. J Appl Physiol 2000; 89:2344–51.
7. Dietz V, Horstmann GA, Trippel M, Gollhofer A. Human postural reflexes and gravity–an under water simulation. Neurosci Lett 1989; 106:350–5.
8. Dietz V, Gollhofer A, Kleiber M, Trippel M. Regulation of bipedal stance: dependency on “load” receptors. Exp Brain Res 1992; 89:229–31.
9. Dietz V, Colombo G. Effects of body immersion on postural adjustments to voluntary arm movements in humans: role of load receptor input. J Physiol 1996; 497(Pt 3):849–56.
10. Fitts RH, Riley DR, Widrick JJ. Physiology of a microgravity environment invited review: microgravity and skeletal muscle. J Appl Physiol 2000; 89:823–39.
11. Forth KE, Layne CS. Background muscle activity enhances the neuromuscular response to mechanical foot stimulation. Am J Phys Med Rehabil 2007; 86:50–6.
12. Forth KE, Layne CS. Neuromuscular responses to mechanical foot stimulation: the influence of loading and postural context. Aviat Space Environ Med (in press).
13. Gallasch E, Kozlovskaya I. Functional testing of space flight induced changes in tonic motor control by using limb-attached excitation and load devices. Acta Astronaut 2007; 60:295–300.
14. Garnett R, Stephens JA. Changes in the recruitment threshold of motor units produced by cutaneous stimulation in man. J Physiol 1981; 311:463–73.
15. Graveline DE, Balke B, Mc KR, Hartman B. Psychobiologic effects of water-immersion-induced hypodynamics. Aerosp Med 1961; 32:387–400.
16. Griffin L, Godfrey S, Thomas CK. Stimulation pattern that maximizes force in paralyzed and control whole thenar muscles. J Neurophysiol 2002; 87:2271–8.
17. Grigor’ev AI, Kozlovskaia IB, Shenkman BS. [The role of support afferents in organisation of the tonic muscle system] (Article in Russian). Ross Fiziol Zh Im I M Sechenova 2004; 90:508–21.
18. Gurovskii NN, Eremin AV, Gazenko OG, Egorov AD, Brianov II. Medical studies during flights of “Soiuz-12”, “Soiuz-13”, “Soiuz-14” space ships and “Saliut-3” orbital station. Kosm Biol Aviakosm Med 1975; 9:48–54.

19. Hagbarth K, Burke D, Wallin G, Lofstedt L. Single unit spindle responses to muscle vibration in man. Prog Brain Res 1976; 44:281–9.
20. Hernandez-Corvo R, Kozlovskaia IB, Kreidich IuV, Martinez-Fernandez S, Rakhamanov AS. Effect of a 7-day space flight on the structure and function of the human locomotor apparatus. Kosm Biol Aviakosm Med 1983; 17(2):37–44.
21. Kakurin LI, Cherepakhin MA, Pervushin VI. Space flight effects on man's muscle tone. Kosm Biol Aviakosm Med 1971; 2:63–8.
22. Kandel E, Jessell TM. Touch. In: Kandel E, Schwartz JH, Jessell TM, eds. Principles of neuroscience. New York: Elsevier; 1991.
23. Khusnutdinova D, Netreba A, Kozlovskaya I. Mechanic stimulation of the soles support zones as a countermeasure of the contractile properties decline under microgravity conditions. J Gravit Physiol 2004; 11:P141–2.
24. Kirenskaya AV, Kozlovskaya IB, Sirota LI. Effects of immersion hypokinesia on characteristics of rhythmic activity of m. soleus motor units. Physiology of Man 1986; 12:617–32 (in Russian).
25. Koryak YA. Surface action potential and contractile properties of the human triceps surae muscle: effect of "dry" water immersion. Exp Physiol 2002; 87:101–11.
26. Kozlovskaya IB, Kreidich Yu V, Oganov VS, Koserenko OP. Pathophysiology of motor functions in prolonged manned space flights. Acta Astronaut 1981; 8:1059–72.
27. Kozlovskaya IB, Kreidich YV, Rakhmanov AS. Mechanisms of the effects of weightlessness on the motor system of man. Physiologist 1981; 24:559–64.
28. Kozlovskaya IB, Aslanova IF, Kirenskaya AV. The effect of support unloading in characteristics of motor control systems activity. In: Motor control. New York: Pergamon Press; 1986.
29. Kozlovskaya IB, Sayenko IV, Vinogradova OL, Miller TF, Khusnutdinova DR, Melnik KA, Yarmanova EN. New approaches to countermeasures of the negative effects of microgravity in long-term space flights. Acta Astronaut 2006; 59:13–9.
30. Kozlovskaya IB, Sayenko IV, Sayenko DG, Miller TF, Khusnutdinova DR, Melnik KA. Role of support afferentation in control of the tonic muscle activity. Acta Astronaut 2007; 60:285–94.
31. Kreidich IuV, Repin AA, Barmin VA, Kozlovskaia IB. [Effect of immersion hypokinesia on the characteristics of eye and head movement during the human gaze fixation reaction.] (Article in Russian.) Kosm Biol Aviakosm Med 1982; 16:41–5.
32. Kyparos A, Feeback DL, Layne CS, Martinez DA, Clarke MS. Mechanical stimulation of the plantar foot surface attenuates soleus muscle atrophy induced by hindlimb unloading in rats. J Appl Physiol 2005; 99:739–46.
33. Lackner JR, DiZio P. Vestibular, proprioceptive, and haptic contributions to spatial orientation. Annu Rev Psychol 2005; 56:115–47.
34. Layne CS, Spooner BS. EMG analysis of human postural responses during parabolic flight microgravity episodes. Aviat Space Environ Med 1990; 61:994–8.
35. Layne CS, Spooner BS. Effects of postural set on anticipatory muscle activation prior to rapid arm flexion. Res Q Exerc Sport 1992; 63:196–9.
36. Layne CS, Spooner BS. Microgravity effects on "postural" muscle activity patterns. Adv Space Res 1994; 14:381–4.
37. Layne CS, Mulavara AP, Pruett CJ, McDonald PV, Kozlovskaya IB, Bloomberg JJ. The use of in-flight foot pressure as a countermeasure to neuromuscular degradation. Acta Astronaut 1998; 42(1-8):231–46.
38. Layne CS, Mulavara AP, Pruett CJ, McDonald PV, Kozlovskaya IB, Bloomberg JJ. Using foot pressure to maintain neuromuscular function during long duration spaceflight. In: El-Genk MS, ed. Space Technology and Applications International Forum. College Park, MD: American Institute of Physics; 2000:226–31.
39. Layne CS, Forth KE, Baxter MF, Houser JJ. Voluntary neuromuscular activation is enhanced when paired with a mechanical stimulus to human plantar soles. Neurosci Lett 2002; 334:75–8.
40. Layne CS, Forth KE, Abercromby AF. Spatial factors and muscle spindle input influence the generation of neuromuscular responses to stimulation of the human foot. Acta Astronaut 2005; 56:809–19.
41. Layne CS, Nguyen K, Forth KE. Muscle contractions in response to foot stimulation as an inflight countermeasure. Acta Astronaut 2008; (in press).
42. Litvinova KS, Vikhlyantsev IM, Kozlovskaya IB, Podlubnaya ZA, Shenkman BS. Effects of artificial support stimulation on fiber and molecular characteristics of soleus muscle in men exposed to 7-day dry immersion. J Gravit Physiol 2004; 11:P131–2.
43. Massion J, Fabre JC, Mouchnino L, Obadia A. Body orientation and regulation of the center of gravity during movement under water. J Vestib Res 1995; 5:211–21.
44. Moukhina A, Shenkman B, Blottner D, Nemirovskaya T, Lemesheva Y, Puttman B, Kozlovskaya I. Effects of support stimulation on human soleus fiber characteristics during exposure to "dry" immersion. J Gravit Physiol 2004; 11:P137–8.
45. Muir GD, Steeves JD. Sensorimotor stimulation to improve locomotor recovery after spinal cord injury. Trends Neurosci 1997; 20:72–7.
46. Nemirovskaya TL, Shenkman BS. Effect of support stimulation on unloaded soleus in rat. Eur J Appl Physiol 2002; 87:120–6.
47. Netreba AI, Khusnutdinova DR, Vinogradova OL, Kozlovskaya IB. Effect of dry immersion in combination with stimulation of foot support zones upon muscle force-velocity characteristics. J Gravit Physiol 2004; 11:P129–30.
48. Popov DV, Saenko IV, Vinogradova OL, Kozlovskaya IB. Mechanical stimulation of foot support zones for preventing unfavorable effects of gravitational unloading. J Gravit Physiol 2003; 10:59–60.
49. Roll JP, Vedel JP, Ribot E. Alteration of proprioceptive messages induced by tendon vibration in man: a microneurographic study. Exp Brain Res 1989; 76:213–22.
50. Roll R, Gilhodes JC, Roll JP, Popov K, Charade O, Gurfinkel V. Proprioceptive information processing in weightlessness. Exp Brain Res 1998; 122:393–402.
51. Shul'zenko EB, Will-Williams IF. [Possibility of carrying out prolonged water immersion by the method of "dry" submersion. Kosm Biol Aviakosm Med 1976; 10:82–4.
52. Sonnenborg FA, Andersen OK, Arendt-Nielsen L. Modular organisation of excitatory and inhibitory reflex receptive fields elicited by electrical stimulation of the foot sole in man. Clin Neurophysiol 2000; 111:2160–9.
53. Sonnenborg FA, Andersen OK, Arendt-Nielsen L, Treede RD. Withdrawal reflex organisation to electrical stimulation of the dorsal foot in humans. Exp Brain Res 2001; 136:303–12.
54. Stein RB, Bawa P. Reflex responses of human soleus muscle to small perturbations. J Neurophysiol 1976; 39:1105–16.
55. Young LR, Shelhamer M, Modestino S. M.I.T./Canadian vestibular experiments on the Spacelab-1 mission: 2. Visual vestibular tilt interaction in weightlessness. Exp Brain Res 1986; 64:299–307.
56. Young LR, Shelhamer M. Microgravity enhances the relative contribution of visually-induced motion sensation. Aviat Space Environ Med 1990; 61:525–30.
57. Young LR, Mendoza JC, Groleau N, Wojcik PW. Tactile influences on astronaut visual spatial orientation: human neurovestibular studies on SLS-2. J Appl Physiol 1996; 81:44–9.
58. Young LR. Vestibular reactions to spaceflight: human factors issues. Aviat Space Environ Med 2000; 71(9, Suppl.):A100–4.