Review

Potential exercise countermeasures to attenuate skeletal muscle deterioration in space

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Exposure to a zero gravity (g) environment has led to atrophy of both whole muscle and single muscle fibers. Previous research suggests that this is due to inadequate levels of exercise intensity and that greater loading is needed to counteract the deleterious effects of microgravity on skeletal muscle.

Objectives: The purpose of this paper is to analyze both structural and functional microgravity related alternations in skeletal muscle tissue, and the mechanisms which underlie these effects. Most importantly however we review a novel countermeasure which may attenuate skeletal muscle deconditioning in space.

Design and Methods: Non systematic review.

Results: Recent research with blood flow restriction (BFR) training suggests that BFR in combination with equipment already used in zero g may result in more favorable skeletal muscle outcomes than the methods currently used. BFR exercise is potentially beneficial because the muscular adaptations occur in the absence of higher loads.

Conclusion: For any long duration flight in space to be successful, more effective exercise countermeasures will need to be developed and implemented. Based on research completed on Earth, it may be possible for BFR exercise to attenuate muscle function declines in a zero g environment because BFR exercise is not dependent upon higher exercise loads.
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Key words: KAATSU ■ NASA ■ strength ■ muscle hypertrophy

Sputnik-1, the first satellite to orbit earth was put into motion by the Russians in 1957. By 1969 the United States led by President John F. Kennedy's initiative, placed Neil Armstrong as the first man on the moon. During historic missions such as Gemini and Apollo, notable deconditioning effects were observed in astronauts and cosmonauts as a result of the zero gravity (g) environment.[1] A major area of both structural and functional deconditioning occurs in skeletal muscle tissue[2] leading NASA to have concerns regarding a: (I) loss of ability to make emergency exits when landing in partial gravity; (II) the inability to properly perform activities of daily living in a microgravity environment; (III) and a loss in the capacity to sustain demanding mission specific tasks which vary in magnitude of intensity.[3] Previous reviews on exercise countermeasures have been outlined in Table 1. The purpose of this paper is to analyze both structural and functional microgravity related alternations in skeletal muscle tissue, and the mechanisms which underlie these effects. Most importantly however we review a novel countermeasure which may attenuate skeletal muscle deconditioning in space.

Effects of zero gravity on skeletal muscle tissue structure

Exposure to a zero g environment has been demonstrated to have drastic effects on skeletal muscle tissue in both human and animal models. A classic study by Martin et al.[4] found a 36 % reduction in isolated rat muscle fibers of the soleus after a 7-day NASA spaceflight mission. In humans, whole limb girth measurements, taken following Skylab and Apollo missions recorded a 4 to 10 % decrease in magnetic resonance imaging (MRI) determined muscle volume across 5 muscle groups.[5] Moreover, individual muscle fiber analysis has led to as high as a 26% decrease in cross sectional area of slow twitch soleus muscle fibers following 2 and a half weeks of zero g exposure.[6]

The extent to which muscle tissue is lost as a function of time is difficult to fully elucidate due to a general lack of data from long duration space flights. However, a number of simulated weightlessness models have led research to suggest muscle tissue loss is asymptotic, reaching a constant of two-thirds of the initial pre values at approximately 270 days of simulated microgravity.[7] During space flight, antigravity muscles incur a greater atrophic response than non-antigravity muscles. For example, seven days of zero g exposure aboard the Discovery space shuttle resulted in a 36 % decrease in soleus muscle mass. In contrast, non-weight bearing muscle groups such as the tibialis anterior and extensor digitorum longus did not change.[4]

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Table 1. The main conclusions from previous reviews discussing exercise countermeasures in space.

Author(s)	Conclusions
Narici & Boer (2011)[37]	Resistance exercise is presently the method of choice for mitigating or even preventing the negative effects of unloading on skeletal muscle. However, the application of artificial gravity with intensive (90% of maximum heart rate) aerobic training have been found to maintain muscle size during simulated microgravity (bed rest).
Smith & Zwart (2008)[38]	The exercise protocols used to date have not succeeded in maintain muscle mass or strength during spaceflight. This may be related to the time available for exercise and/or hardware availability.
Bajotto & Shimomura (2006)[39]	Even short duration spaceflight can result in significant muscle atrophy and changes in myosin heavy chain isoform expression. Prevention involves countermeasure actions such as periodic loading (flywheel-based resistance exercise) and dietary supplementation.
Macias et al. (2005)[40]	Lower body negative pressure may provide astronauts with a countermeasure to maintain physiologic structure and function during long term space flight.
Fitts, Riley, & Widrick (2000)[2]	The ideal program should include isometric and istotonic exercise. Human and rat data indicate high-intensity exercise as the modality of choice for the protection of limb muscle structure and function.
Booth & Criswell (1999)[41]	Resistance exercise together with growth hormone and insulin-like growth factor-1 are effective countermeasures to unloading, however more research is needed; specifically in the absence of gravity.
Baldwin (1996)[42]	The combination of aerobic and heavy resistance activity will be necessary for supporting different protein fractions in the muscle cell.
Edgerton & Roy (1994)[43]	A combination of exercise modes is likely to be most effective in space, with each type of exercise inducing specific effects on specific muscle groups and even types of muscle fibers within a muscle or muscle group.
Keller, Strauss, & Szpalski (1992)[44]	To minimize musculoskeletal deconditioning associated with space, it is suggested that very intensive exercise, which impose high loads on the musculoskeletal system for brief periods, may be more efficient in preserving bone and muscle conditioning than low intensity activities.
Hargens et al. (1989)[45]	The eccentric muscle action is important for muscle adaptation and the almost complete absence of eccentric exercise in space may be an important contributor to muscle atrophy. Equipment should be designed to integrate eccentric actions into exercise protocols for space.

Effects of zero gravity on functional measures of skeletal muscle tissue

Peak force has been demonstrated to decline across a range of space flight lengths. Zange and colleagues[8] found that 6 months in space decreased peak force to 48 % in the soleus, with parallel changes in volume as high as 20%. Lambertz et al.[9] investigated the effects of long term space flight (90-180 days) on functional measures of the human plantarflexor muscles in 14 cosmonauts before and 2-3 days after landing. Despite in-flight countermeasures, the flight resulted in an average 17 % decline in maximal isometric torque production. Intriguingly enough these changes were accompanied by decreases in muscle activation (-39 %) and whole joint stiffness under passive conditions (21%). Widrick et al.[6] provided additional data through the examination of the effects of 17 days of space flight on various functional and structural measures of single chemically skinned muscle fibers. Pre and immediate post flight biopsy samples of the soleus provided individual fibers, which were stimulated to contract via exposure to Ca^{2+}. Results found a 21 % decline in average peak Ca^{2+} activated force.

Interestingly, power has previously been shown to decrease to a greater extent than muscle mass losses can account for. Specifically, Antonutto et al.[10] found a decrease in maximal explosive jump power (45-67 %) and maximal cycling power (67 %) following 31-180 days of space flights in 4 astronauts. However, because muscle mass only lost 9-13%, the authors suggested that changes in neural activity explained part of the variance in the findings. This was further supported by the rapid recovery of power to pre-flight values 2 weeks after return to a 1-g environment.

While atrophy and functional changes are serious cause for concern, the effects of these changes on muscle tissue integrity upon return to a 1-g environment are also critical to astronauts and cosmonauts. Important data from Riley et al.[11] in the 8-11 hours following space flight revealed substantial eccentric contraction-like damage of muscle fibers in antigravity muscles which included hyperextension of sarcomeres with A-band filaments pulled apart and fragmented. These results have been replicated in a number of microgravity and simulated microgravity conditions (for a review see Riley et al.[12]) and suggest that the deconditioning effects seen in the microgravity environment increase the risk of damage upon return to a 1-g environment.

Mechanisms of microgravity-induced muscle atrophy

Recently a number of interesting new developments have occurred in the analysis of possible proteolytic pathways that zero g environments may affect. The Ubiquitin-proteasome-proteolytic (Ub) pathway is generally accepted to be the primary mechanism responsible for specific intracellular protein degradation.[13] The Ub- pathway involves the covalent attachment of multiple ubiquitin molecules to the protein substrate to be degraded. Once 'tagged', the substrate is recognized and subsequently degraded by the 26S proteasome complex.[14] Increased activity and expression of the Ub-pathway appears to be a common finding in conditions which elicit increased muscular proteolysis[15,16] including simulated antigravity models[17] and a general lowering of physical activity[14]. The similarity of these conditions indicates that the Ub-pathway may be activated during space flight as well.

Landmark research on the effects of various proteolytic pathways on muscle tissue in space was conducted by Ikemoto and colleagues.[18] These investigators analyzed the expression of key enzymes or components in the three major proteolytic pathways (Ca^{2+}-dependent, lysosomal, and Ub-pathways) in skeletal muscle of young rats flown in the STS-90 space flight mission. The mission lasted 16 days and rats were then analyzed after returning to the Kennedy Space Center. Sixteen days of flight resulted in enhanced levels of myosin heavy chain (MHC) degradation fragments ranging across 6 differing molecular weights (120-180 kDa). Concomitantly there were also increases in mRNA expression of Ubiquitin, the E2 conjugating enzyme, and the 20S proteasome responsible for degrading tagged proteins. In contrast, space flight did not affect either the lysosomal or calpain-dependent pathways. These results suggest that the Ub-pathway is at least partly responsible for the accelerated degradation of muscle tissue within a zero g environment.

Exercise as a countermeasure

Early space exploration via the Mercury program consisted of vehicles with little physical space which restricted cosmonauts to non-machine based isometric contractions in an attempt to maintain physical conditioning.[1] However with the introduction of Sky Lab in the 1970s, rope pull apparatuses capable of developing 365 N of force were instituted, along with space based passive treadmill devices and cycle ergometers.[1] In 2001 the International Space station entered into existence leading to the introduction of advanced treadmills capable of delivering 1-g of force to astronauts, as well as an interim resistive exercise device (iRED), which is able to simulate 16 earth based exercises. These advances in the international space station have seen exercise requirements increase from 30 minutes per day 3 times per week to two and a half hours per day 6 days a week.[1] Fitts et al.[19] found that treadmill exercise in excess of 200 min/week can provide partial protection from muscle atrophy, however they concluded that an in-flight high resistance training device would be able to better maintain muscle mass and strength.

Effect of interim resistance exercise device

The iRED was developed by NASA for use in the space station, to provide greater resistance in a microgravity environment. This was developed since previous strength-type exercises utilizing bungee-supported resistance exercise, did not attenuate losses of muscle strength or muscle mass. The iRED is an elastometer-based resistance device, which is a mode of exercise commonly used for rehabilitation.[20] Multiple exercises and muscle groups for both the upper and lower body can be trained with this device (e.g. squats, deadlifts, upright rows, shoulder press, etc.). However, a few major concerns with this device included a limited loading range,[21] the complexity involved with switching from exercise to exercise,[21] and the force curve produced[20]. The loading range is of concern because the lowest resistance that can be used is 9kg and the highest is 136 kg. Therefore, depending on the exercise the load may be too high or too light. In addition, time spent on reconfiguring the device for a different exercise reduces the amount of scheduled time (60 min) for resistance exercise.[21] Furthermore, the force curve produced by this type of device is not ideal because the peak resistance is at the end of the range of motion, which is problematic when performing many exercises. Also, with this device, the resistance decreases during the eccentric portion of the lift which may decrease the overall effectiveness of the stimulus.[22]

Schneider et al.[20] evaluated the musculoskeletal responses to 16 weeks of training with the iRED compared to regular free weights in a 1-g environment. They found that iRED training resulted in increases in muscle strength and mass, but no changes in bone mineral density. The free weight group saw similar increases in muscle strength and mass, but also saw increase in whole body lean mass and lumbar spine bone mineral density. Also, this study found an unusually high rate of injury, which they speculate was due to an overly aggressive training program, or possibly the non-ideal biomechanics of the iRED. This observation was also observed in a report by NASA who found that some subjects experienced an apparent over-use injury induced by bicep curling with the iRED long bar attachment.

Trappe et al.[23] investigated the effectiveness of the iRED device in astronauts aboard the space station for 6 months. They observed substantial decreases in calf muscle mass and performance, despite the use of the iRED, and concluded that the exercise intensity needed to be increased.

Effect of blood flow restricted exercise

Blood flow restriction (BFR) in combination with low-load exercise (~20% concentric 1RM) may be of benefit to astronauts seeking to maintain skeletal muscle size and strength. BFR training involves restricting blood flow at the most proximal portion of the arm or leg.[24] Interestingly, although the BFR is limited to the limbs, favorable adaptations have also been observed the trunk, which is proximal to the

BFR stimulus.[25] A variety of devices have been used to restrict blood flow during exercise including elastic knee wraps,[26] elastic belts with a pneumatic bag inside,[27] nylon pneumatic cuffs,[28] or a traditional nylon blood pressure cuff[29].

A recent Meta-Analysis of BFR training suggests that this type of training produces skeletal muscle adaptation similar to that observed with higher load (>60% concentric 1RM) resistance exercise,[30] however the exact mechanisms behind the benefits observed with this mode of training are largely unknown[31]. One potential hypothesis involves fluid shift induced muscle cell swelling as the primary mechanism for adaptation.[32] In addition, Manini et al.[28] recently found that BFR resistance training reduces the expression of ligases that regulate the Ub-pathway, which is the pathway postulated for many of the detrimental muscular effects observed with zero g conditions.

As previously mentioned, exercise in excess of 200 min/week can in part compensate for the lack of an effective high intensity exercise device.[19] However, despite the partial protection, the current exercise interventions during space flight have been ineffective in preventing skeletal muscle atrophy. The application of BFR in combination with the current low intensity modalities already available in space may be a viable option for combatting the muscle atrophy induced by microgravity.

Numerous studies have demonstrated the efficacy of this training in full gravity settings with moderate blood flow restriction. To illustrate, Abe and colleagues have observed increases in muscle size and strength with BFR treadmill walking[33] and cycling[34]. These adaptations were observed with low-intensity treadmill walking for 20 minutes at low speeds (67 m/min; 5 days a week) and low intensity cycling (40% VO_{2max}) for only 15 minutes a day, 3 days a week. Furthermore, these benefits have also been observed with low intensity (~20-30% concentric 1RM) resistance training combined with BFR.[25,35,36] Interestingly, recent findings from Yasuda et al.[25] indicate that these benefits may not be exclusive to the BFR limbs. For example, restricting the upper arm during chest press resulted in significant muscle hypertrophy and strength gains in the pectoralis. It should be noted that incongruence may exist between BFR findings performed in full gravity settings from those performed in zero g conditions, however, the combination of BFR with any of the aforementioned pieces of equipment already on board the space station could potentially help attenuate whole body skeletal muscle (upper/lower body and trunk) and strength losses observed with space flight.

Conclusions

Zero g conditions result in deleterious structural and functional changes to skeletal muscle. The Ub-pathway appears to mediate many of the negative cellular responses observed in muscle tissue. Although current exercise protocols have been largely ineffective due to the inability to train at a high enough intensity, it is possible that BFR in combination with those methods (e.g. iRED, treadmill walking, cycling) could result in more favorable skeletal muscle outcomes. For any long duration flight in space to be successful, such as a manned mission to Mars, more effective exercise countermeasures will need to be developed and implemented.

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