Microgravity-Induced Fiber Type Shift in Human Skeletal Muscle

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ABSTRACT

Prolonged microgravity exposure alters human skeletal muscle by markedly reducing size, function, and metabolic capacity. Preserving skeletal muscle health presents a major challenge to space exploration beyond low Earth orbit. Humans express three distinct pure myosin heavy chain (MHC) muscle fiber types (slow → fast: MHC I, IIa, and IIx), along with hybrids (MHC I/IIa, IIa/IIx, and I/IIa/IIx). After reviewing current research, this paper presents evidence for a "slow to fast" microgravity-induced skeletal muscle fiber type shift in humans. Spaceflight and bed rest induce decreased MHC I fiber proportion while increasing fast hybrid types (particularly MHC IIa/IIx fibers). This alteration in muscle cell phenotype negatively impacts performance and induces undesirable metabolic adaptations. While exercise has been postulated to minimize the negative effects of microgravity on human muscle, past spaceflight countermeasures have insufficiently prevented fiber type shifts in humans. However, a new high-intensity, low volume resistance and aerobic exercise regimen has recently been implemented aboard the International Space Station (ISS). This paper aims to reveal that 1) a slow to fast microgravity-induced fiber type shift occurs in humans and 2) the new high-intensity, low volume exercise countermeasures program onboard the ISS has promise to mitigate this fiber type transition and preserve skeletal muscle health.

Key words: Myosin Heavy Chain; Exercise Countermeasures; Unloading; Bed Rest; Spaceflight

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INTRODUCTION

Consistent residency aboard the International Space Station (ISS) places humans in position to explore the Moon, Mars, and beyond. Human physiological limitations present clear obstacles to long-duration space missions as microgravity exposure deleteriously affects many organ systems, including skeletal muscle. Spaceflight induces quantitative and qualitative modifications to skeletal muscle by markedly decreasing size, strength, and endurance (Fitts et al., 2000). Despite exercise countermeasures, muscle mass has been shown to decrease from -13% to -17% during long-duration spaceflight (Gopalakrishnan et al., 2010; LeBlanc et al., 2000; Trappe et al., 2009). Significant decrements in muscle size can impair substrate utilization and insulin sensitivity, as the largest metabolic reservoir in the human body is skeletal muscle. Furthermore, long-mission studies conducted aboard the ISS, Skylab, and Mir have shown significant decreases (-20-35%) in muscle performance (Lambertz et al., 2001; Rummel et al., 1975; Trappe et al., 2009). This magnitude of reduction in muscle size and performance not only impairs astronauts upon return to Earth, but may also inhibit their ability to complete essential mission tasks, extravehicular activities (EVA), and emergency egress.

Researchers suggest chronic unloading (i.e. spaceflight and bed rest) alters mammalian muscle fiber phenotype (Fitts et al., 2000; Pette, 2002). A slow- to fast-twitch transition characterizes this “microgravity-induced fiber type shift.” Given that muscle fiber types exhibit a wide range of functional and metabolic characteristics (Pette and Staron, 1997), this shift likely contributes to reduced muscle performance and undesirable metabolic adaptations during spaceflight. This paper aims to outline newly compiled evidence supporting the microgravity-induced fiber type shift in humans and overview the new high-intensity, low volume resistance and aerobic exercise countermeasures program recently implemented aboard the ISS. This new exercise prescription is based upon 15 years of ground-based research that titrated the optimal dose, intensity, and balance of aerobic and resistance exercise to protect skeletal muscle health (Bell et al., 2000; Putman et al., 2004; Schulze et al., 2002; Trappe et al., 2007).

MICROGRAVITY-INDUCED FIBER TYPE SHIFT

Myosin heavy chain (MHC) protein composition determines mammalian skeletal muscle fiber classifications. Humans express three distinct fiber types (MHC I, IIa, and IIx) along with hybrids containing more than one phenotype (MHC I/IIa, IIa/IIx, and I/IIa/IIx). MHC I are slow-oxidative fibers (slow isoform contractile proteins, high mitochondrial density), MHC IIa are fast-oxidative fibers (fast contractile velocity, relatively fatigue resistance), and MHC IIx are fast-glycolytic fibers (fastest contractile proteins, low mitochondrial volume) (Spangenburg and Booth, 2003). Figure 1 shows the human skeletal muscle fiber type continuum measured via sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), the current fiber typing “gold standard” (Pandorf et al., 2010). The MHC type and proportion expressed in skeletal muscle affects whole muscle performance (strength and endurance) and metabolic efficiency (ability to store and utilize energy).

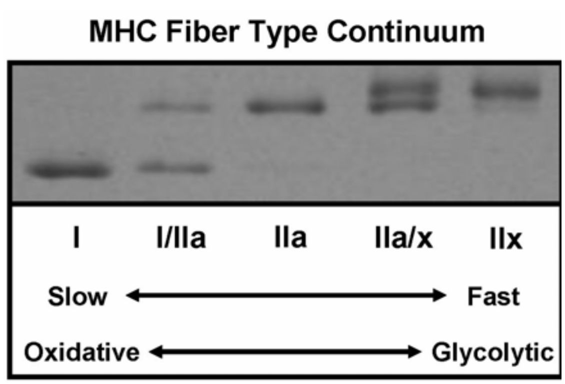

Figure 1. Visual representation of the fiber type continuum, including myosin heavy chain (MHC) isoform, twitch speed, and metabolic properties. Each lane shows MHC protein of a single muscle fiber categorized by migration distance through polyacrylamide gel. Note, MHC I/IIa/IIx fiber type is not shown.

Skeletal muscle is a dynamic tissue, continually adjusting to current conditions. Living and being active in a 1 *g* environment provides the “ideal phenotype” for human skeletal muscle, while removing gravity rapidly disrupts muscle homeostasis. Evidence suggests muscle fibers shift phenotype when exposed to certain chronic stimuli (Pette and Staron, 1997). To date, the most extreme example of a fiber type shift in humans was observed in spinal cord injured (SCI) patients that had been wheelchair bound for 3-15 years. The SCI patients expressed significantly less MHC I (-23%) and IIa (-20%) fibers and more IIx (+33%) fibers than ambulatory control subjects (Malisoux et al., 2007).

Research supporting a MHC fiber type shift during spaceflight in humans has been increasing since the mid-1990s (Edgerton and Roy, 1996; Zhou et al., 1995). Undoubtedly, rodent models show modifications in muscle phenotype following periods of unloading (i.e. hindlimb suspension), expressing a slow to fast fiber shift along with increased hybrid types (Fitts et al., 2000). These hybrid fibers are likely in transition from one phenotype to another (e.g., MHC I → I/IIa → IIa) (Pette, 2002). After several ISS missions and long-term bed rest experiments in the last decade, enough data now exists to draw conclusions on the presence of spaceflight related fiber type shifts in humans.

Figure 2 contains compiled data from our laboratory and others, lending support to the microgravity-induced fiber type shift paradigm in humans (Borina et al., 2010; Gallagher et al., 2005; Trappe et al., 2009; Trappe et al., 2007; Widrick et al., 1999; Zhou et al., 1995). Each of the studies report changes in fiber type from pre-

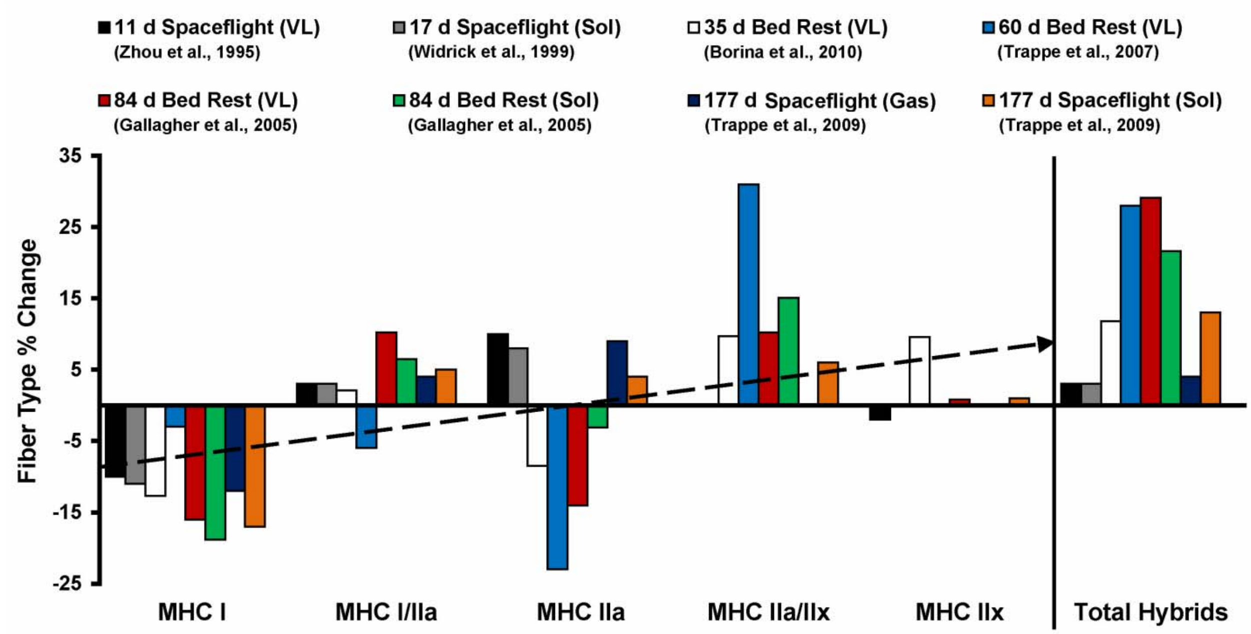

Figure 2. Changes in myosin heavy chain (MHC) fiber type during unloading (spaceflight or bed rest). The linear trend-line is based on mean fiber type % change from all studies and illustrates a slow to fast fiber type shift (Plotted using Microsoft Excel 2010, trend-line equation: y = 3.51x - 10.408). All studies fiber typed using SDS-PAGE. Bed rest data is from control subjects. Total Hybrids represent fibers with multiple MHC isoforms. VL, vastus lateralis. Sol, soleus. Gas, gastrocnemius.

to post-spaceflight (or bed rest) in men and women measured via SDS-PAGE. Unloading duration ranged from 11 to 177 days, with an average of ~81 days. The studies investigated one of three lower limb muscles: the vastus lateralis (VL), soleus (Sol), or gastrocnemius (Gas). MHC I (slow) fiber composition decreased and total hybrid fiber proportion increased in all studies by an average of -13% and +14%, respectively. While unloading duration probably dictates the transition magnitude, trends were similar regardless of duration, unloading mode, or the muscle studied. Furthermore, the trend-line compiled from mean percent changes of all studies clearly illustrates a slow to fast shift across the MHC fiber type continuum. Consistency in these human data supports previous speculations of a fiber type shift caused by unloading.

Skeletal muscle phenotype transitions likely stem from changes in transcriptional processes associated with MHC expression. Recent investigations from Dr. Kenneth Baldwin's laboratory show MHC promoter elements regulate expression of MHC genes undergoing phenotypic remodeling in response to inactivity (Huey et al., 2003; McCall et al., 2009). While specific mechanisms responsible for MHC regulation during unloading remain under investigation, it is evident that the magnitude of fiber type shift affects astronaut physical performance (Trappe et al., 2009). The slow to fast shift explains, in part, the decrease in muscular endurance seen following spaceflight. To counteract microgravity-induced loss of slow fibers while maintaining muscular integrity across the fiber type spectrum, a new training protocol is underway onboard the ISS.

LONG-DURATION SPACEFLIGHT EXERCISE COUNTERMEASURES

Long-duration manned missions beyond low Earth orbit (LEO) remain a primary goal of the international space community. However, maintaining skeletal muscle health continues to be a major obstacle in human space exploration. Past exercise regimens onboard the ISS were varied among crewmembers, but generally included moderate intensity aerobic (~5 days/wk) and resistance exercise (3-6 days/wk) (Trappe et al., 2009). The guidelines prescribed exercise for up to 2.5 h/day for 6-7 days/wk (time included hardware setup, stowage, and personal hygiene) utilizing a running treadmill, cycle ergometer, and resistance exercise device (Trappe et al., 2009). These previous exercise countermeasures failed to completely preserve skeletal muscle size and function, warranting modifications to long-duration mission exercise prescription and/or hardware.

For decades, ground-based exercise physiology studies have shown chronic high-intensity exercise promotes positive skeletal muscle adaptations (i.e. increases strength and endurance) and alters fiber type composition (Andersen and Henriksson, 1977; Baumann et al., 1987; Harridge et al., 1998; Parcell et al., 2005; Simoneau et al., 1985). Figure 3 illustrates fiber type changes (maintained MHC I, increased MHC IIa, decreased MHC IIx) following high-intensity and sprint cycle training in men and women ranging from 42 to 105 days in duration. These studies measured fiber type by SDS-PAGE or histochemical staining (standard technique of the 1970s and '80s). Hybrid fibers were not reported in these investigations. MHC I fiber percentage varied but was generally maintained (+1%), while MHC IIa composition increased (+6%) and MHC IIx composition decreased (-5%) on average. As opposed to spaceflight and bed rest, the trend-line compiled from these high-intensity/sprint cycling studies demonstrates a fast to relatively slower fiber type shift. Notably, Simoneau et al. (1985) showed MHC I fibers significantly increased (+6%), MHC IIa fibers were maintained, and MHC IIb (IIx) fibers significantly decreased (-6%) after 105 days of sprint cycling, suggesting lengthier training durations might induce increases in MHC I proportions as their transition may take longer to manifest. Additionally, resistance training has been shown to elicit overall fast to slow fiber type shifts (maintenance of MHC I, increase in MHC IIa, and decrease in MHC IIx) while decreasing hybrid types (Liu et al., 2003; Williamson et al., 2001). Data from Figures 2 and 3 suggest mitigation of the microgravity-induced slow to fast shift is possible by employing high-intensity exercise during spaceflight. The idea of high-intensity exercise preventing a shift in MHC phenotype during long-

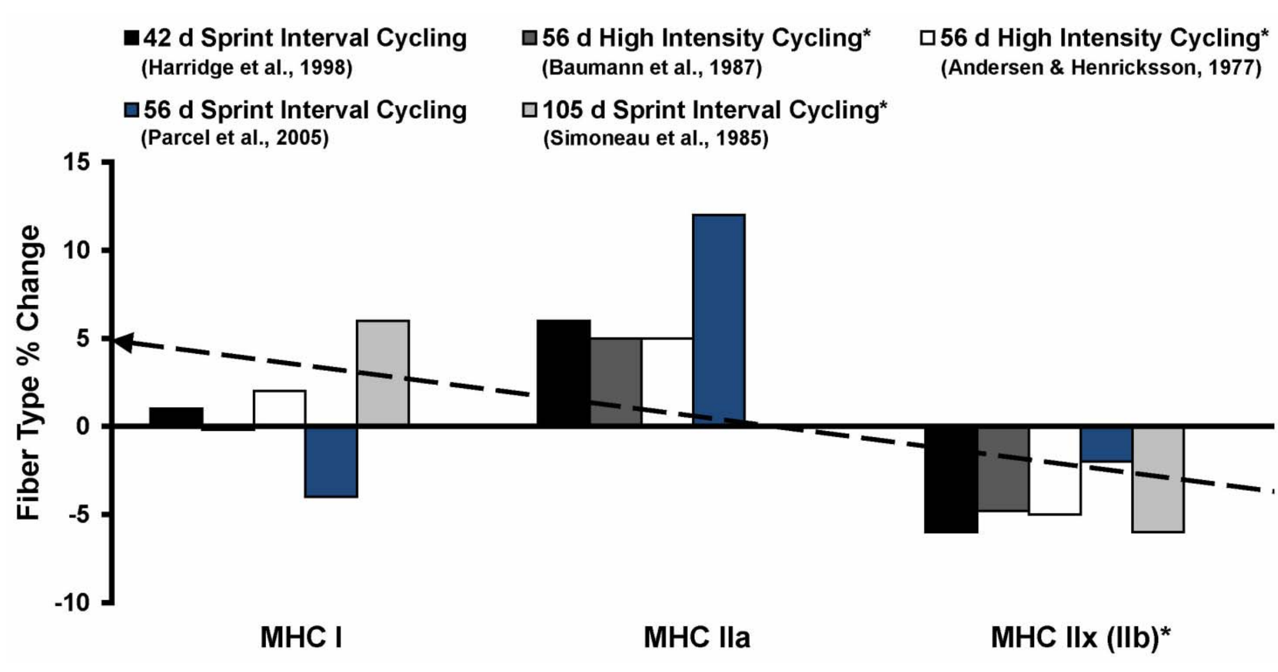

Figure 3. Changes in myosin heavy chain (MHC) fiber type during high intensity exercise training. The linear trend-line is based on mean fiber type % change from all studies and illustrates a fast to slow fiber type shift (Plotted using Microsoft Excel 2010, trend-line equation: y = -2.86x + 6.32). *Fiber typing via ATPase histochemistry (IIb equivalent to IIx). VL, vastus lateralis.

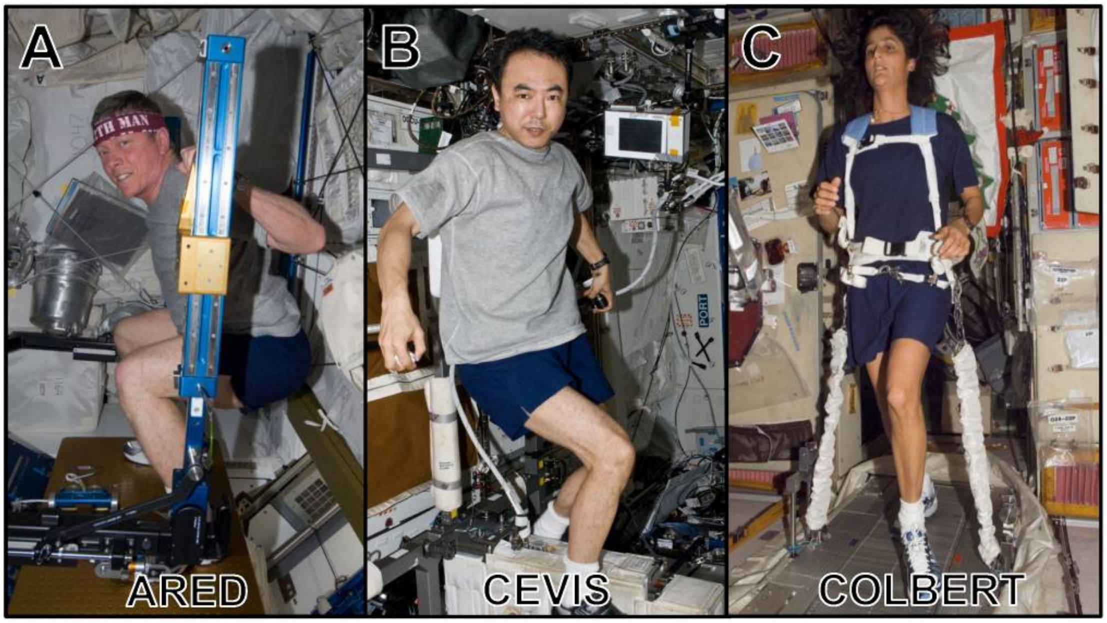

Figure 4. Images of astronauts exercising on equipment currently used aboard the ISS. A: Advanced Resistance Exercise Device (ARED), B: Cycle Ergometer with Vibration Isolation and Stabilization System (CEVIS), and C: Combined Operational Load Bearing External Resistance Treadmill (COLBERT). Images retrieved from http://www.nasa.gov/.

duration unloading was recently shown with bed rest (60 day), which has served as a guide for moving the exercise countermeasure program forward (Trappe et al., 2007).

Past exercise countermeasures onboard the ISS have insufficiently prevented fiber type shifts in humans (as seen in Figure 2). Moving forward, two key changes to the exercise program for spaceflight have occurred. The first was placement of new hardware on the ISS that allows for greater loading and comfort for performing more robust exercise. Figure 4 shows images of these devices, which include the Advanced Resistance Exercise Device (ARED), Cycle Ergometer with Vibration Isolation and Stabilization System (CEVIS), and Combined Operational Load Bearing External Resistance Treadmill (COLBERT). Second, was the implementation of a new high-intensity, low volume resistance and aerobic exercise prescription for astronauts. The new regimen alternates days of high-intensity interval training with continuous aerobic exercise (opposed to predominately continuous aerobic exercise) and 3 days/wk of high-intensity resistance training (opposed to 3-6 days/wk at lower intensity) (NASA, 2011). Ongoing research is underway to investigate the validity of the new exercise program for protecting crewmembers' skeletal muscle health after long duration stays on the ISS.

CONCLUSION

A substantial microgravity-induced fiber type shift would be detrimental to human health during long-duration spaceflight, increasing risk of crewmember injury and rendering essential mission tasks difficult to complete. Slow to fast fiber shifts alter skeletal muscle quality, affecting the entire body by decreasing physical performance (increasing fatigability) and negatively influencing muscle metabolism by modifying substrate utilization, insulin sensitivity, and myokine production (e.g., IL-6 and IL-18) (NASA, 2010; Plomgaard et al., 2005). Ground-based studies support newly employed high-intensity exercise countermeasures onboard the ISS, which aim to improve skeletal muscle health. Based on current data, we conclude that high-intensity, lower volume exercise will aid in maintaining MHC I, increasing MHC IIa, and decreasing fast MHC hybrid proportions during long-duration spaceflight. Both current astronauts and future space explorers will benefit from the ongoing exercise countermeasures research conducted aboard the ISS. A greater understanding of optimal exercise paradigms for spaceflight can also be translated to the human based challenges of inactivity, aging, and disease on Earth.

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