Optimization of Exercise Countermeasures to Spaceflight Using Blood Flow Restriction

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INTRODUCTION: During spaceflight missions, astronauts work in an extreme environment with several hazards to physical health and performance. Exposure to microgravity results in remarkable deconditioning of several physiological systems, leading to impaired physical condition and human performance, posing a major risk to overall mission success and crew safety. Physical exercise is the cornerstone of strategies to mitigate physical deconditioning during spaceflight. Decades of research have enabled development of more optimal exercise strategies and equipment onboard the International Space Station. However, the effects of microgravity cannot be completely ameliorated with current exercise countermeasures. Moreover, future spaceflight missions deeper into space require a new generation of spacecraft, which will place yet more constraints on the use of exercise by limiting the amount, size, and weight of exercise equipment and the time available for exercise. Space agencies are exploring ways to optimize exercise countermeasures for spaceflight, specifically exercise strategies that are more efficient, require less equipment, and are less time-consuming. Blood flow restriction exercise is a low intensity exercise strategy that requires minimal equipment and can elicit positive training benefits across multiple physiological systems. This method of exercise training has potential as a strategy to optimize exercise countermeasures during spaceflight and reconditioning in terrestrial and partial gravity environments. The possible applications of blood flow restriction exercise during spaceflight are discussed herein.

KEYWORDS: spaceflight, health, exercise countermeasure, blood flow restriction exercise.

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Human spaceflight is entering a new era with plans to extend exploration beyond low Earth orbit to interplanetary travel. Astronauts work in an extreme microgravity (μG) environment posing several hazards to human health and performance, including deconditioning of several physiological systems.[35,65] Impairment of an astronaut's physical condition increases the difficulty of performing routine everyday tasks and extravehicular spacewalks.[88] It increases the risk of training-related injuries, which are the most common source of injury to astronauts on mission.[158] Furthermore, impaired physical condition and performance could be detrimental for mission critical tasks such as exiting a spacecraft.[188] Astronauts will need to maintain physical fitness during nonterrestial living to enable successful exploration and transit back to Earth. Physical deconditioning during transit may, therefore, affect overall mission success and crew safety.

Exercise is a key countermeasure to mitigate deconditioning caused by μG.[110,159] The refinement of exercise protocols throughout years of spaceflight and analogous research has reduced the magnitude of deconditioning, but it cannot be completely counteracted with current countermeasures. Postflight reconditioning is required to return astronauts to their preflight physical condition.[141] Interplanetary exploration will place further operational, technical, and logistical constraints upon the use of exercise, e.g., less space for exercise equipment in the Orion spacecraft.[102] Longer duration missions (i.e., up to 3 yr for a Martian mission) will also impose a more difficult reconditioning process. Space agencies aim to optimize exercise countermeasures to facilitate longer duration and interplanetary missions.[141,159]

Blood flow restriction (BFR) exercise may enable optimization of exercise countermeasures.[12,65] Using a tourniquet cuff to

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restrict blood flow in the exercising limb during exercise elicits several positive training adaptations in the physiological systems affected by μG.[84,132,139] It requires minimal equipment and is low-intensity, which compliments the anticipated operational, technical, and logistical constraints of future spaceflight.[102] Previous reviews have discussed the potential for BFR as an exercise countermeasure during spaceflight,[12,64,187] with several limitations. Firstly, the use of BFR exercise for post-spaceflight reconditioning has not been explored. Secondly, while these reviews have focused on resistance and aerobic exercise with BFR, evidence suggests that BFR can be combined with novel training techniques, including whole body vibration[5,28] and neuromuscular electrical stimulation.[58,128,163] Finally, to our knowledge, the specific means by which BFR could be used to optimize current exercise countermeasures[159] has not been explored in depth. Therefore, this review aims to discuss how BFR training may be used to optimize exercise countermeasures during and post-spaceflight, the optimal method of application, and potential safety issues.

Physiological Effects of Exposure to μG

The absence of 1 G triggers remodeling of the cardiovascular, neuromuscular, and musculoskeletal systems. The first challenge from Earth to space involves a cephalad shift of blood from the lower extremities, causing central blood volume expansion and increased cardiac preload, stroke volume, and cardiac output.[134,135] Blood pressure, however, is maintained,[135] either by adapted fluid loss through urine (e.g., natriuresis or diuresis) or an unknown mechanism of peripheral vasodilation.[134] This cephalad fluid shift is associated with nausea, headaches, and facial edema and may occur chronically,[134] possibly contributing to ophthalmic changes given increases in intracranial pressure.[118]

Concurrently, neural and downstream skeletal muscle connections begin to adapt to new sensory stimuli and reduced use. Spatial orientation impairment,[195] increased difficulty comparing the mass of objects, and increased reaction time have been reported during and post-spaceflight.[17,91,153] Magnetic resonance imaging (MRI) of International Space Station (ISS) crewmembers postflight have found brain structural gray matter decreases, including large areas in the temporal and frontal poles.[91] Bilateral focal gray matter has also been observed within the medial primary somatosensory and motor cortex.[91] In parallel, reductions in mechanical loading and reduced neuromuscular use lowers the rates of basal and stimuli-induced muscle protein synthesis (MPS).[57,169] Combined with standard or accelerated muscle protein breakdown (MPB) rates, this shifts protein balance to a negative state.[57,170] Consequently, muscle fiber cross-sectional area (CSA) is decreased[50] and muscle fiber composition shifts toward faster myosin heavy chain expression.[50,95] Type I fibers appear to be the most influenced by altered gravity, with in-flight research demonstrating a shift to Type IIx with spaceflight.[179] However, most of the muscles of the lower extremities atrophy during spaceflight,[104] even with mandated exercise and other countermeasures (e.g., nutritional, pharmaceutical).

Concomitantly, bone mineral is released from skeletal stores and is a major concern for astronaut health.[161] During 4–6 mo on the ISS, rates of bone loss were 0.9% per month in the spine [areal bone mineral density (BMD)] and 1.4–1.5% per month at the hip.[97] Moreover, in the hip, integral, cortical, and trabecular volumetric BMD were lost at rates of 1.2–1.5% per month, 0.4–0.5% per month, and 2.2–2.7% per month, respectively.[97] The loss in BMD may lead to increased osteoporosis and fracture risk in astronauts.[160] Complicating bone loss is the potential for changes in acid-base balance from the diet via consumption of sulfur containing amino acids.[63] This concept is based on the acid-ash hypothesis,[180] whereby in-flight higher partial pressure of carbon dioxide (CO_2) and endogenous acid production from the diet (amino acids, phosphorus, chlorine) may alter acid buffering, leading to bicarbonate being sequestered from bone to compensate.[199] The CO_2 concentration is ~10 fold higher on the ISS compared to Earth as a result of metabolically produced CO_2 and the processes required for its removal and/or recycling.[101,155] Chronic exposure to such CO_2 levels can lead to headaches, nausea, altered sensorimotor and vestibular function,[118,155] and may be associated with spaceflight associated neurooccular syndrome.[105]

For human spaceflight, the translational challenge of this deconditioning is human safety and the negative impact on astronaut task performance.[4,158] Future missions will require landing on unknown surfaces and long-term habitation. Extensive physical work will be performed for survival and mission success while in a physiologically deconditioned state. Decrements in maximal oxygen consumption ($\dot{V}O_{2max}$),[124] neurological reorganization during task performance,[91] weakened skeletal muscle morphology,[44] and elevated risk of bone injury[160] represent significant factors to be mitigated by the international spaceflight community.

Current Exercise Countermeasures and Challenges for Longer Duration Spaceflight

The exercise hardware onboard the ISS allows for both high intensity resistance and aerobic exercise informed by our understanding of the requirements for keeping humans healthy during longer duration missions.[65] For detailed reviews on the evolution of exercise hardware and countermeasures for spaceflight, the reader is directed to previously published works.[92,159] Target intensities are 70–80% of one repetition maximum and 60–90% $\dot{V}O_{2max}$ for aerobic exercise. Astronauts are allocated approximately 2.5 h/d for exercise and accompanying procedures, 6 d/wk, where each day includes a resistance and aerobic exercise session, typically 45 min in duration each, with a minimal break in between.[110,159] Upon returning to Earth after long duration missions, astronauts undergo a postflight reconditioning program to return them to their preflight physical condition and prevent long term health issues.[96,141] This begins with treatment of any injuries followed by functional, endurance, and strength exercises which are gradually progressed in intensity for several weeks until the astronaut returns to work.

Future missions place several technical and physiological constraints on exercise countermeasures. The new generation of spacecraft (e.g., the Orion Multipurpose Crew Vehicle) cannot accommodate the size and weight of current exercise equipment used on the ISS.[22] It is anticipated that astronauts will have less available time for exercise and device maintenance and repair.[102] Mars missions are expected to cause greater physiological deconditioning during transit, which requires development of 'preconditioning' exercise programs.[171] These will be implemented toward the end of transit to prepare astronauts for re-exposure to nonterrestrial gravity. Upon arrival, reconditioning programs will be required to address physical health issues and prepare astronauts for work, and training programs will be needed to maintain physical fitness during nonterrestrial habitation, which will be constrained by limited exercise equipment and specialist assistance.

Blood Flow Restriction Exercise

Application. BFR is most commonly combined with low intensity (i.e., 20–40% of maximal strength or 45–50% of maximal aerobic capacity) resistance and aerobic exercise.[139] **Fig. 1** outlines how to apply BFR through the following steps: 1) the cuff is applied proximally to the limb to be exercised; 2) the cuff is connected to an inflation device; 3) 'limb occlusion pressure' (LOP) is measured to individualize pressure prescription; 4) the cuff is inflated to compress the underlying vasculature; and 5) the individual performs exercise with BFR.

The goal is to partially restrict arterial inflow to tissues distal to the tourniquet cuff while completely restricting venous outflow.[139] The optimal method of determining BFR pressure is to measure the individual's LOP, which is defined as the minimum pressure required for complete restriction of arterial blood flow in that limb, and prescribe pressure relative to this.[139] For more detail on optimal BFR exercise parameters, the reader is directed to a recent consensus paper.[139] Current best practice is to use an automatic system consisting of a wide pneumatic cuff connected to an inflation device that automatically measures LOP and calculates the required pressure for BFR exercise.[68] As blood pressure and flow behave differently in space, in-flight measurement of LOP would be required.[12] While these automatic devices have been validated on Earth,[68] it is currently unknown if μG would affect LOP measurement and regulation of BFR pressure during dynamic exercise in space. Therefore, future research should seek to determine the validity of BFR pressure prescription and regulation during spaceflight analogs, e.g., parabolic flight.

Physiology of BFR exercise. Exercise causes increased deoxyhemoglobin (HHb) and reduced oxyhemoglobin (O_2Hb). These changes are reversed during recovery by a hyperemic supraexercise increase in O_2Hb and tissue oxygenation saturation (stO_2) due to vasodilation and increased demand for blood flow. A greater decrease in stO_2 is observed during BFR exercise compared to matched volume exercise without BFR (−50% vs. −35%, respectively).[116] Collectively, decreases of 29–50% for O_2Hb and and 27–50% for stO_2 have been reported with BFR exercise, concomitant with a 200–250% and 31–60% increase in HHb and total hemoglobin, respectively.[56,75,79] Importantly, when BFR is applied through exercise and rest periods, there is

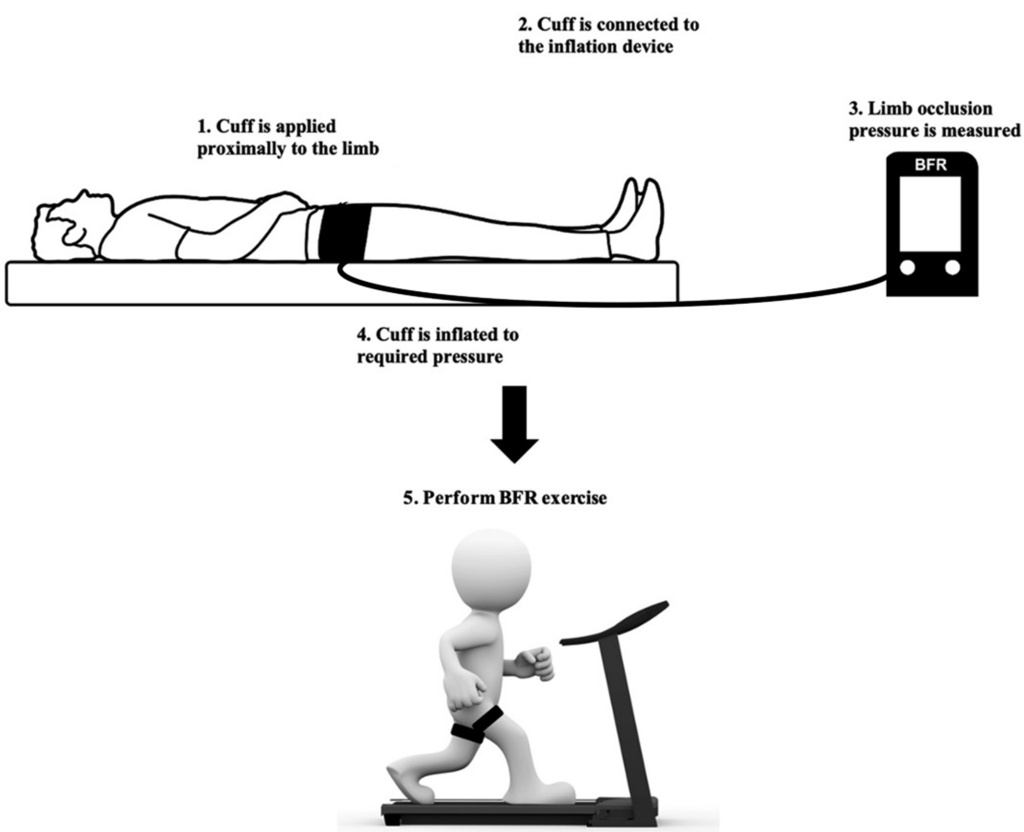

Fig. 1. Application of blood flow restriction exercise.

significantly lower stO_2 recovery compared to exercise without BFR.[56,116] The decrease in O_2Hb and increase in HHb indicate local hypoxia, which rapidly resolves upon BFR cuff deflation.[75]

Local hypoxia during BFR exercise causes a reliance on anaerobic energy pathways with several notable physiological changes. Franz et al.[53] demonstrated that BFR exercise leads to greater reductions in venous pH, partial pressure of O_2 (Po_2) (~40% reduction), and O_2 content, alongside a greater increase in venous Pco_2 (~50% vs. ~25%) compared to matched load exercise without BFR. Furthermore, a greater increase in venous lactate level was observed with BFR exercise (from ~2.0 to 7.5 mmol · L^{-1}), alongside a greater reduction in HCO_3^- (~24 to 20 mmol · L^{-1}). Collectively, these changes suggest that arterial oxygenated blood does not reach the capillary bed of the working limb and BFR causes metabolic acidosis in the venous portion of the working limb. Similarly, Yasuda et al.[189] observed lower levels of venous Po_2 (28 mmHg vs. 33 mmHg), O_2 content (34% vs. 52% mmHg), and pH (7.19 vs. 7.27), alongside high levels of venous Pco_2 (72 vs. 60 mmHg) and lactate concentration (5.4 vs. 3.0 mmol · L^{-1}), during BFR exercise compared to matched load exercise without BFR.

The physiological changes observed by Franz et al.[53] returned to pre-exercise levels by 5 min postexercise, indicating rapid recovery. This study involved individuals with no prior BFR training experience, and there is evidence to suggest that aspects of this response may be attenuated with chronic BFR training.[29] Yasuda et al.[189] demonstrated that high intensity exercise resulted in greater changes in venous pH (7.14), Pco_2 (91 mmHg), and lactate concentration (7.0 mmol · L^{-1}) compared to BFR exercise. Nevertheless, the augmented physiological response to BFR exercise is hypothesized to be a primary driver of training adaptation via activation of several secondary mechansims[76] (**Fig. 2**), which will be discussed throughout this review.

BFR Exercise as a Countermeasure to the Physiological Effects of Spaceflight

Fluid shifts and orthostatic intolerance: spaceflight and analogous data. Cephalad fluid redistribution and altered cardiovascular function in μG can cause orthostatic intolerance upon return to 1 G. The concept of applying restrictive pressure cuffs to the limbs to mitigate these changes has been explored previously. In the 1990s Russia developed inflatable "Bracelet" cuffs designed for lower extremity fluid sequestration and prevention of fluid shifts. These cuffs were able to maintain fluid volume and preflight cardiac status in a cosmonaut during Mir flights,[7] and alleviate discomfort associated with cephalad fluid shift.[51] On the ISS, the Bracelet cuffs have shown commensurate effects on cardiac performance and mitigation of postflight orthostatic intolerance.[51]

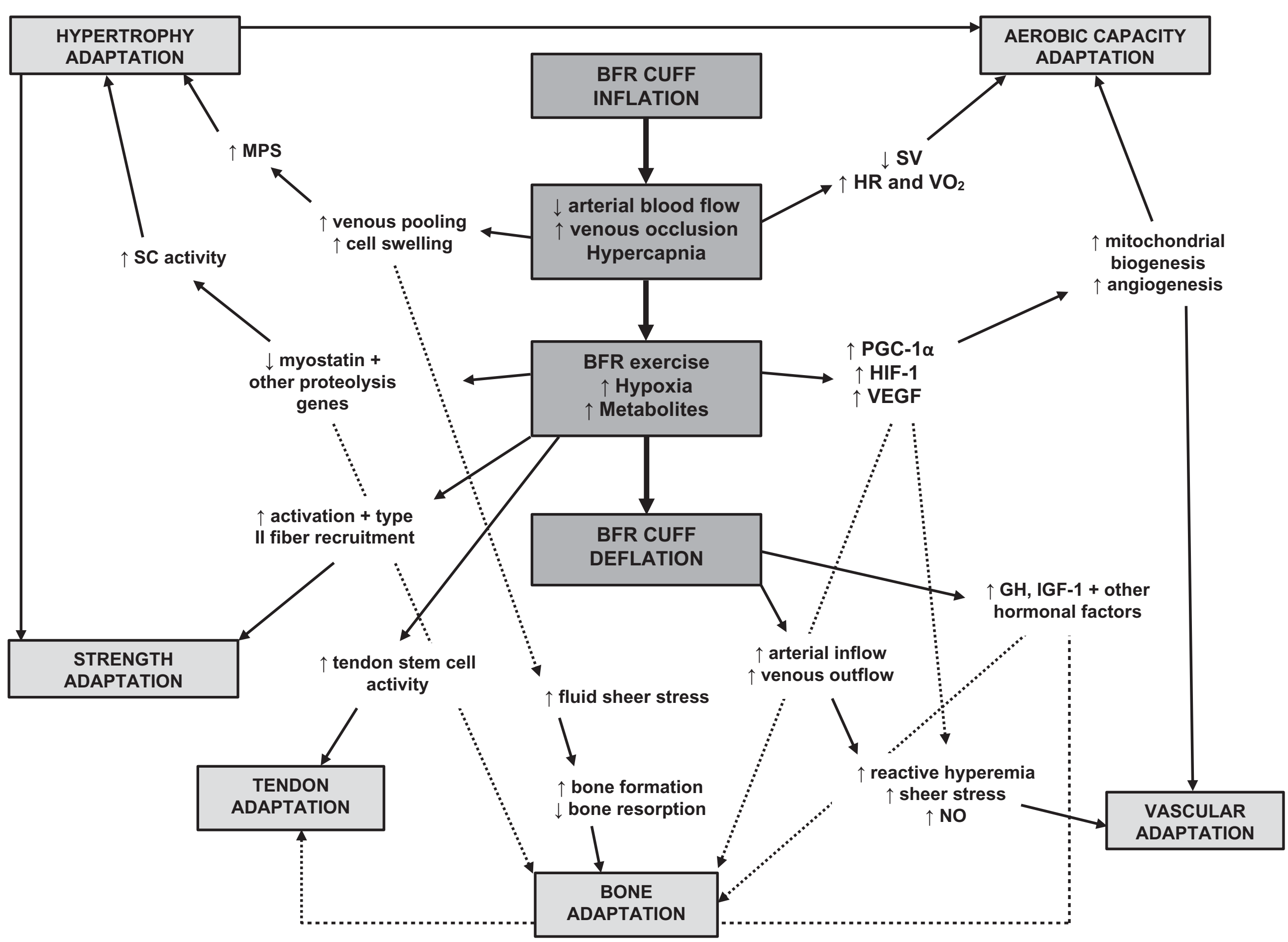

Fig. 2. The physiological effects of BFR exercise and possible mechanisms of adaptation.

A gravity-like stimulus, such as lower body negative pressure, would likely be the most effective in-flight countermeasure for this orthostatic challenge.[64] The application of BFR passively[126] and with resistance exercise[94] during head-down tilt studies elicits similar hemodynamic and neurohumoral responses as gravity-induced stress. As highlighted by Hackney et al.,[64] BFR exercise results in several physiological changes similar to the effects of lower body negative pressure, including lower limb blood pooling, decreased venous return, and augmented autonomic activation. Therefore, repeated application of BFR toward the end of spaceflight may induce gravity-like stress on the cardiovascular system and help reduce postflight orthostatic intolerance. BFR exercise could be used to improve blood flow[73,138] to mitigate the decrease in lower limb blood flow observed after long duration spaceflight.[81] To date, BFR has only been tested in environments that simulate weightlessness (i.e., head-down tilt), with no in-flight data available.

Muscle atrophy and associated mechanisms. The available BFR evidence elucidates how it could be used to counteract remodeling of several physiological systems during spaceflight. The most apparent application is to mitigate muscle atrophy[104] that is driven by lower rates of basal[169] and stimuli-induced MPS[57] and accelerated MPB rates[170] during spaceflight. Low intensity resistance exercise [i.e., 20% 1 repetition maximum (RM)] with BFR increases MPS by 46–69% in the 24 h following exercise compared to equivalent exercise without BFR through increased activation of the mTOR-p70S6K pathway, increased MAPK-mediated anabolic signaling, and reduced proteolysis-related gene expression.[54,55,62,117] BFR resistance exercise was recently shown to increase cumulative myofibrillar protein synthesis similarly to high intensity exercise over 6 wk of training.[162] These anabolic effects may contribute to muscle hypertrophy with BFR training,[2] an idea which is supported by BFR studies reporting increases in muscle CSA at a similar rate (0.11–0.22% per day)[100,175] as heavy load resistance training at the same frequency.[186]

The reduction in muscle satellite cell (SC) content and myonuclear number following spaceflight[36,176] provides a mechanistic explanation for reduced MPS and muscle atrophy.[50] SCs play an indispensable role in muscle tissue maintenance and regeneration[143,193] and are activated by several factors, including mechanical load.[24] Maintenance of SC and myonuclear number during spaceflight is a potentially valuable method of mitigating atrophy and preserving regenerative capacity.[146] Wernbom et al.[185] demonstrated that BFR resistance exercise acutely increased the number of SCs per muscle fiber for up to 48 h postexercise, alongside phosphorylation of the mTOR-p70S6K pathway. Short duration (< 3 wk) high frequency (i.e., daily) BFR resistance exercise training can increase the number of SCs and myonuclei per muscle fiber alongside substantial muscle hypertrophy and strength improvement[15,131] (Fig. 2). Interestingly, these responses peaked between 10–20 d after cessation of training, suggesting delayed myoblast fusion into existing muscle fibers. The available data indicates that the increase in SC content and myonuclear number is greater than typical changes observed with high intensity resistance training.[142,143] At present, there is no data available concerning the effect of longer duration or less frequent BFR training on SCs.

Increased SC activity is driven by temporal expression of several myogenic regulatory factors which are upregulated with BFR exercise.[40,103] The myostatin signaling pathway is a key negative regulator of muscle mass which affects SC proliferation and differentiation[43] and has been targeted to protect against skeletal muscle atrophy during spaceflight.[106] In rodent models, inhibition of myostatin using a neutralizing antibody has a protective effect against loss of skeletal muscle mass and strength during spaceflight.[106,164] Myostatin is downregulated endogenously with exercise; for example, Cotter et al.[34] showed that concurrent high intensity interval aerobic exercise and maximal exertion strength training could mitigate the increase in myostatin during simulated μG with limb suspension. Laurentino et al.[100] demonstrated that 8 wk of BFR resistance training (20% 1 RM) decreased myostatin mRNA expression similarly to high intensity (80% 1 RM) training (45% vs. 41%) alongside comparable increases in muscle mass and strength. They also reported increased expression of several regulatory genes that act as intracellular myostatin inhibitors.[100] When high intensity training is not feasible during spaceflight, low intensity BFR training could be used to positively affect protein turnover, increase SC activity, and reduce expression of myostatin and several other genes involved in proteolysis. This may mitigate skeletal muscle loss and preserve muscle regenerative capacity in preparation for reloading (**Fig. 3**).

Bone, tendon and associated mechanisms. μG leads to elevated bone resorption and reduced bone formation, causing an imbalance in bone metabolism,[60,97] driven via effects on the Wnt/-catenin signaling pathway[82] and several cytokines, growth factors,[60] and bone morphogenetic proteins.[6] Bone remodeling is initiated when osteocytes perceive mechanical stress via the action of integrins[194] and interstitial fluid movement.[152] Despite using a lower mechanical load, evidence suggests BFR exercise may benefit bone. BFR exercise acutely decreases blood markers of bone resorption[13] and chronically elevates markers of bone formation[11] compared to equivalent exercise without BFR. In older adults, Karabulut et al.[85] found 6 wk of BFR resistance exercise training (20% 1 RM) increased blood markers of bone formation similarly to high intensity (80% 1 RM) exercise (21% vs. 23%, respectively).

Due to a lack of data on BMD, it is difficult to draw definite conclusions concerning the effect of BFR on bone. While the mechanism by which BFR exercise may improve bone parameters is not established, several possibilities have been explored. BFR exercise may trigger molecular processes for bone remodeling via fluid shear stress within the osteocyte membrane caused by venous blood pooling and cell swelling.[111] Furthermore, BFR training has been shown to activate vascular endothelial growth factor (VEGF)[174] via the hypoxia inducible transcription factor pathway and improve blood flow,[46,73] which may enhance delivery of factors necessary for bone remodeling. Finally, downregulation of myostatin with BFR exercise may positively impact bone metabolism[42,90] (Fig. 2).

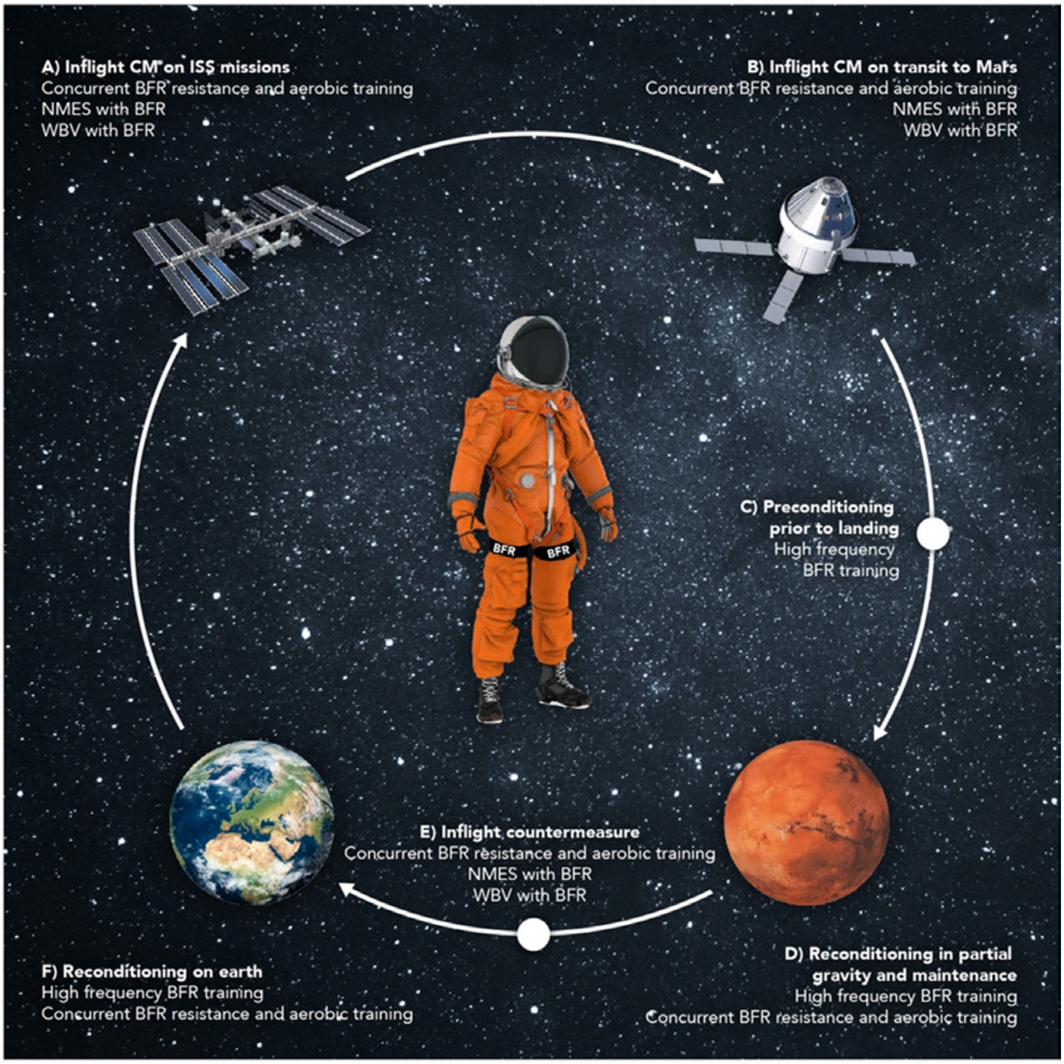

Fig. 3. The potential applications of blood flow restriction during spaceflight. CM, countermeasure; ISS, International Space Station; BFR, blood flow restriction; NMES, neuromuscular electrical stimulation; WBV, whole body vibration.

There is some evidence of a possible effect of BFR on tendons. Kubo et al.[93] found no change in stiffness of the tendon-aponeurosis complex following 12 wk of low intensity BFR resistance training, which concurs with the literature advocating training loads of a minimum 70% 1RM for optimal adaptive responses in tendon properties.[18] However, Centner et al.[27] reported 12 wk of BFR resistance training elicited similar increases in tendon stiffness (36%) and CSA (8%) as heavy load training. Hypoxia can stimulate the proliferation of human tendon stem cells[107,196] and is critical for bone-tendon junction healing;[197] therefore, the ischemic and hypoxic environment with BFR exercise may stimulate tendon adaptation (Fig. 2). Furthermore, upregulation of several growth factors and improved blood flow may facilitate collagen synthesis.[156] Therefore, BFR may provide a means of targeting tendon-bone junction atrophy during spaceflight.[83] However, these are the only two studies concerning the chronic effect of BFR on tendon properties with conflicting findings. Further investigation is needed for more definitive conclusions.

***Aerobic capacity, vascular remodeling, and associated mechanisms*.** A major challenge is to mitigate the decrease in $\dot{V}O_{2max}$ that occurs during spaceflight.[124] Combining low intensity (i.e., < 50% $\dot{V}O_{2max}$) cycling or walking exercise with BFR improves aerobic capacity compared to equivalent exercise without BFR.[14] This may be driven by changes to central hemodynamics and adaptations throughout the vascular tree. Studies show a higher $\dot{V}O_2$ at a given low intensity workload and a disproportionate increase in $\dot{V}O_2$ with increased workload when aerobic exercise is performed with BFR.[178] Due to venous occlusion, stroke volume decreases and heart rate increases during BFR exercise.[174] The metabolic, hemodynamic, and intensity demands appear augmented when low intensity aerobic exercise is performed with BFR.

μG is a potent stimulus for vascular remodeling. Spaceflight and bedrest analog studies report decreased arterial diameter,[16,41] increased arterial stiffness,[10,72,181] increased venous diameter,[8] altered venous compliance, and decreased emptying rates[52] in the lower limbs. Altered vascular wall pressure without gravity may drive vascular remodeling via several similar mechanisms causing altered arterial and venous morphology on Earth.[198] Peripheral arterial adaptations to BFR resistance training include increased conduit artery flow mediated dilation, and resting and maximal diameters.[29,73] Increased reactive hyperemic blood flow,[47,73,138] vascular conductance,[125] capillary filtration,[46,73] and number of capillaries per myofiber[132] with BFR resistance training reflect decreased peripheral resistance of the microvasculature. Resistance and aerobic training with BFR may increase venous compliance;[78,125] however, this evidence is limited and equivocal, with one study reporting no change in venous compliance with BFR resistance training.[48] There are several mechanistic explanations for these adaptations, including upregulation of endothelial nitric oxide synthase, hypoxia-inducible factor 1-α, PGC-1α, and VEGF,[31,49,98] which are driven by hypoxia and increased vascular shear stress from blood pooling and reactive hyperemia.[30] Furthermore, increased blood CO_2 concentration with BFR exercise[53,189] may contribute to vascular adapation. Literature suggests that local tissue acidosis from elevated CO_2 concentration causes induction of regional VEGF synthesis and an NO-dependent increase in collateral blood perfusion. While existing evidence demonstrates elevations in VEGF and CO_2 with BFR exercise, there is currently no evidence directly linking the elevation in CO_2 with BFR exercise to adaptation.

Hematopoietic homeostasis and associated mechanisms. Following spaceflight many astronauts have hematopoietic disorders[61] and altered responses such as decreased plasma and blood cell mass and modified blood flow.[59] These changes may be driven by altered activity of hematopoietic stem progenitor cells (HSPC), also known as endothelial progenitor cells.[183] Plett et al.[144] demonstrated that μG inhibited cell migration, cycle progression, and differentiation in $CD34^+$ HSPCs. Wang et al.[183] showed that spaceflight and simulated μG decrease the number and proliferative capacity of HSPCs in vitro. Exercise can stimulate HSPCs[154] when performed at higher intensities for longer durations.[99,177] The role of hypoxia in upregulation of these cells is shown by concomitant elevations in several angiogenic factors, e.g., VEGF.[154] BFR exercise was found to acutely upregulate $CD34^+$ HSPCs in circulation, alongside increased vasoprotective enzyme angiotensin-converting enzyme 2, due to regional hypoxia induced by BFR.[84] This promotes skeletal muscle angiogenesis and vascular regeneration, which likely contribute to increased myogenesis. Elevation in CO_2 concentration can mobilize endothelial progenitor cells;[80] however, there is currently no evidence concerning the effect of increased CO_2 concentration with BFR exercise on endothelial progenitor cell activity. Montgomery et al.[123] previously reported no changes in circulating HSPCs at 30 min following acute BFR resistance exercise.[123] The authors observed a delayed angiogenic gene expression response to BFR exercise.[123] As HSPCs were unchanged in the immediate postexercise period and upregulated at 2+ h postexercise,[154] future research should examine the time-course response and potential impact of CO_2.

BFR during preconditioning and postflight reconditioning. Data suggests it is more challenging to return to gravity than to adapt to μG[136,140] and reapplying mechanical load is the most effective method to restore muscle mass and increase myonuclear and SC number.[24] BFR exercise has several implications for: 1) in-flight preconditioning in preparation for landing; and 2) postflight reconditioning (Fig. 3). The most evident benefit for postflight reconditioning is the low intensity nature and potent rehabilitation capacity. Returning astronauts are load compromised and perform initial reconditioning exercises at a low intensity to minimize the risk of injury.[96] BFR exercise is an effective rehabilitation tool for muscular, aerobic, and functional adaptations in load compromised populations with minimized risk of injury.[69–71] It could be used to maximize adaptations to low intensity exercise, minimize risk of injury, and treat transit-induced injuries during postflight reconditioning of astronauts on Earth and another planet (Fig. 3).

Muscle hypertrophy and strength improvements are seen with 1–3 wk of daily and twice daily BFR training.[131,139] A short training block of high-frequency BFR training may rapidly improve strength to prepare astronauts for safe landing and exiting of the spacecraft (Fig. 3). Delayed myonuclear addition to existing fibers[15,131] may improve regenerative capacity during reconditioning, as impairment to SCs blunts the hypertrophy response to exercise.[45] This approach increases myocellular stress and inflammation without apparent structural muscle damage.[25] No evidence is presently available concerning high frequency aerobic exercise with BFR and the effect on other tissues. Some BFR evidence shows muscle hypertrophy and strength improvements in muscles proximal to the cuff,[20,21] including trunk muscles.[1,191] This may help target trunk muscles to improve postural control during astronaut reconditioning.[96] It is hypothesized that downstream fatigue increases fiber recruitment in proximal muscles to maintain force output during multijoint BFR exercise.[190] However, there is a paucity of research with inconsistent results and the adaptive mechanisms remain unclear.[157,191,192]

Optimization of Exercise Countermeasures with BFR

Efficient, concurrent, and combined training. Due to exercise time and equipment constraints for future missions, combining exercise methods to facilitate rapid adaptations is vital.[159,187] Resistance exercise elicits specific muscular adaptations with little improvement in cardiovascular fitness,[74] with the opposite true for aerobic training.[184] Concurrent training could optimize exercise countermeasures with simultaneous aerobic and muscular adaptations.[159,165] A high exercise intensity is recommended to maximize adaptations to resistance and aerobic training.[3] This may impair training adaptations, particularly muscle strength gains. This is termed the 'interference effect'[39] and is governed by training intensity, load, and volume.[165] This presents a paradox, whereby reducing the intensity of one exercise type may benefit the other but dampen its own effect.[165] BFR exercise may minimize the interference effect without reducing the efficacy of concurrent training. Libardi et al.[108] compared concurrent high intensity resistance and aerobic exercise (70–80% 1RM and 50–80% $\dot{V}O_{2max}$) to concurrent training with aerobic exercise at 50–80% $\dot{V}O_{2max}$, and resistance exercise at 20–30% 1RM with BFR. Comparable increases in muscle CSA, 1RM strength, and $\dot{V}O_{2max}$ were observed. BFR training can also benefit multiple physiological systems with one type of exercise. Several studies show combining either resistance or aerobic exercise with BFR leads to muscular and cardiovascular adaptations simultaneously.[1,89,137] BFR could be used for 'combined training' to optimize exercise countermeasures during spaceflight[159] (Fig. 3).

'Efficient' training describes the process of reducing training volume while maintaining effectiveness, identified as a strategy for optimizing exercise countermeasures.[159] Abe et al.[1] compared the effect of two aerobic exercise protocols on muscle volume, CSA, strength, and $\dot{V}O_{2max}$ over 8 wk of training. Both protocols involved cycling at 40% $\dot{V}O_{2max}$, with one group cycling for 45 min per session while the other group cycled for only 15 mins with BFR. Increases in muscle CSA (3–5%), strength (8%), $\dot{V}O_{2max}$ (6%), and exercise time until exhaustion (15%) were observed with BFR training only, despite a lower training volume. de Oliveira et al.[137] compared low intensity interval training with BFR to high intensity interval training. They reported similar improvements in $\dot{V}O_{2max}$ and maximal power output with both types of training, while muscle strength increased (11%) only after training with BFR, despite a 340% greater training volume with high intensity interval training. A low volume of BFR training appears sufficient for muscular and aerobic adaptations and may provide a more efficient exercise countermeasure. However, the minimal effective dose is currently unknown.

BFR as a complementary strategy. Novel countermeasures that enhance the effects of exercise or reduce reliance on it are paramount for future spaceflight missions.[159] Neuromuscular electrical stimulation (NMES) is targeted to compliment pre-existing exercise countermeasures.[115] This technique involves application of preprogramed electrical stimuli to superficial muscles to generate muscle contractions. It can mitigate muscle atrophy during periods of unloading[37] by increasing MPS[182] and decreasing MPB.[38] Despite promising spaceflight and analogous studies, a major limitation is the discomfort caused by the high currents required to maximize effectiveness.[114] Performing BFR during lower intensity NMES can increase muscle hypertrophy and strength compared to NMES alone,[58,128] possibly via increased mTOR and MAPK signaling.[129] NMES with BFR was found to attenuate muscle mass loss during 14 d of limb immobilization,[163] but was not protective against loss of muscle strength or structural and functional deconditioning of the femoral artery.[33] Addition of BFR to NMES during spaceflight may effectively mitigate muscle atrophy while minimizing discomfort, and astronauts could perform other tasks concomitantly (Fig. 3). Future research should compare this to high intensity NMES and aim to identify optimal parameters of application.[67]

Whole body vibration (WBV) can mitigate muscle atrophy, bone loss, and conduit artery remodeling during bed rest.[16,122,149] It passively contracts muscles through high frequency stimulation of spinal neuronal networks, increasing lower limb muscle tissue oxygenation, blood flow, and activation.[32,112,150] Higher vibration frequencies elicit greater muscle activation,[66,147] but may cause severe muscle soreness, hematoma, and may even reduce muscle activation due to a complex interaction of mechanical and reflex inhibitory factors.[147,151] Performing BFR during WBV was found to increase muscle mass, strength, and endurance compared to WBV alone,[26] possibly via greater acute neuromuscular, metabolic, and hemodynamic changes,[28,86] and increased activation and proliferation of SCs.[5] Performing BFR with WBV during spaceflight may, therefore, increase its effectiveness at mitigating physiological deconditioning, particularly muscle atrophy via increased SC activity (Fig. 3). However, one study reported no additional benefit of performing BFR during WBV,[121] highlighting the need for more research.

Operational benefits of BFR exercise. BFR exercise may provide additional benefits for future missions. Logistically, BFR exercise requires minimal equipment and less space and loading capacity than current exercise protocols.[110,159] This may reduce exercise-specific and, potentially overall, mission costs and reduce vibration transmission to the spacecraft. Operationally, more efficient training with BFR exercise would allow more time for nonexercise related missions tasks. The low intensity nature of BFR exercise could reduce the incidence of strain-related injuries from in-flight training.[158] Furthermore, BFR exercise would provide a potent rehabilitation tool for any injuries.[69]

Safety of BFR

The majority of peer-reviewed evidence supports the safety of BFR exercise in supervised settings.[25,139] As with any type of exercise there remains a possibility of adverse outcomes, which mostly manifest as disturbed hemodynamics, blood clotting, excessive discomfort, and muscle damage.[139] This section will discuss the safety and feasibility of BFR exercise and considerations for future spaceflight research.

Clotting and disturbed hemodynamics. Coagulation of blood and thrombus formation is recurrently identified as a potential risk factor for BFR exercise.[23] However, acute and chronic studies have reported no detrimental effect of BFR exercise on markers of venous thromboembolism (VTE).[139] Two studies suggest that, similarly to normal resistance exercise, BFR exercise may stimulate the fibrinolytic system, evidenced by increased concentration of the thrombus-degrading tissue plasminogen activator.[113,127] Astronauts may be at heightened risk for a thrombus formation during spaceflight,[119] particularly in the internal jugular vein, due to the blood stasis, hypercoagulability, and endothelial dysfunction that occurs in μG.[109] The first case of thrombus formation in an astronaut that required anticoagulant medication was recently reported,[9] with one case of thrombus formation reported previously.[119] A previous study found no change in several markers of blood coagulation with BFR application during analogous 6° head-down tilt.[127] Considering this and the rigorous medical examinations and supervision that astronauts undergo, it would be reasonable to assume that BFR exercise would not exacerbate the risk of VTE during spaceflight. However, this should be examined using ground-based analogs (e.g., bed rest) to provide more conclusive evidence.

Another concern is that BFR exercise may generate abnormal reflex-mediated cardiovascular responses through ischemia and metabolite-mediated stimulation of the muscle metaboreflex arm of the exercise pressor reflex.[168] As ischemic BFR exercise leads to considerable metabolite accumulation in the muscle,[172,173] it is hypothesized that this may stimulate the sympathoexcitatory pressor reflex, causing an augmented hemodynamic response.[19,168] BFR exercise does elicit a greater hemodynamic response compared to equivalent exercise without BFR.[139] However, the changes are within normal ranges[130] and are less than or equivalent to high intensity exercise.[130,139] The hemodynamic response can be minimized via application of BFR according to optimal guidelines for tourniquet cuff width and pressure.[139] Spranger[167] argues that greater caution is warranted when BFR is prescribed to populations with a compromised vascular system. Research suggests that the muscle metaboreflex is enhanced during spaceflight,[77,87] in particular the metaboreflex inputs from weight-bearing muscles.[87] Stimulation of group III and IV afferents with BFR exercise can increase cerebral blood flow, but only when a hyperventilation-related decrease in P_{CO_2} is prevented by CO_2 clamping.[145] Considering this and the fact that blood pressure acts differently in μG,[133] future research should first examine the impact of BFR on the metaboreflex and hemodynamic response and cerebral blood flow during exercise in simulated microgravity (e.g., parabolic flight).

There may also be a risk associated with CO_2. Chronic exposure to elevated CO_2 concentrations on the ISS and hypercapnia cause several adverse effects for astronauts.[118,155] Obstruction and accumulation of CO_2 rich blood during BFR exercise and subsequent bolus-like release may have both favorable and unfavorable effects such as increased intracranial pressure, arrhythmogenic effects, and exacerbated Spaceflight Associated Neuro-ocular Syndrome (SANS). As discussed previously, the magnitude of CO_2 increase with BFR exercise is less than high intensity exercise,[189] which is currently performed onboard the ISS, and systemic concentrations of CO_2 appear to return to baseline by 5 min post-BFR exercise.[53] However, these data arise from ground-based studies and, as yet, the impact of BFR exercise on CO_2 levels in astronauts who are exposed to rising CO_2 levels throughout the working day is not known.

Discomfort and muscle damage. Other factors may determine the feasibility of using BFR exercise in spaceflight, such as the associated discomfort. BFR training causes more discomfort than the same exercise without BFR.[166] The level of discomfort can be attenuated by application of lower pressures prescribed to LOP, and BFR has been well tolerated in postsurgical populations using this method.[70] Furthermore, chronic use of BFR reduces the level of discomfort and increases tolerability.[120] Despite some concerns of an increased risk of muscle damage with BFR exercise, the majority of available evidence suggests that BFR does not appear to induce a muscle damage response to low intensity exercise.[139] Furthermore, there is a lack of objective risk-specific evidence available to support these concerns.[25] Astronauts undergo thorough and extensive medical screening prior to flight, therefore it is highly unlikely that they are predisposed to a heightened risk of muscle damage. However, astronauts may be more susceptible to muscle damage when performing postflight reconditioning exercises if they are unaccustomed to the exercise load.[148] Therefore, it is important that thorough medical screening is combined with use of optimal BFR exercise parameters, monitoring of the individual's response, and gradual progression of training.[139]

Conclusion

BFR could offer several operational and physiological benefits during different phases of spaceflight missions as a standalone and complimentary therapy. Substantial terrestrial findings support the efficacy of BFR training for improving the structure and function of the muscular and cardiovascular systems. Emerging data suggests that BFR exercise may have beneficial effects on other tissues such as bone, tendon, and hematopoietic cells; however, these effects are largely unknown and require further investigation. At present there is no rigorous evaluation of BFR during spaceflight or ground-based analogs. Further research in the use of BFR as an exercise countermeasure to spaceflight is warranted.

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REFERENCES

1. Abe T, Fujita S, Nakajima T, Sakamaki M, Ozaki H, et al. Effects of low-intensity cycle training with restricted leg blood flow on thigh muscle volume and $\dot{V}O_{2max}$ in young men. J Sports Sci Med. 2010; 9(3):452–458.
2. Abe T, Yasuda T, Midorikawa T, Sato Y, Kearns CF, et al. Skeletal muscle size and circulating IGF-1 are increased after two weeks of twice daily "KAATSU" resistance training. Int J KAATSU Train Res. 2005; 1(1):6–12.
3. Garber CE*, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, et al. American College of Sports Medicine Position Stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011; 43(7):1334–1359.
4. Ade CJ, Broxterman RM, Craig JC, Schlup SJ, Wilcox SL, et al. Prediction of lunar- and Martian-based intra- and site-to-site task performance. Aerosp Med Hum Perform. 2016; 87(4):367–374.
5. Aguayo D, Mueller SM, Boutellier U, Auer M, Jung HH, et al. One bout of vibration exercise with vascular occlusion activates satellite cells. Exp Physiol. 2016; 101(2):295–307.

*Refs. 3, 41, and 137 are out of alphabetical order due to either the author list being corrected or the first author being alphabetized by last name rather than particle.

6. Aleshcheva G, Wehland M, Sahana J, Bauer J, Corydon TJ, et al. Moderate alterations of the cytoskeleton in human chondrocytes after short-term microgravity produced by parabolic flight maneuvers could be prevented by up-regulation of BMP-2 and SOX-9. FASEB J. 2015; 29(6):2303–2314.
7. Arbeille P, Fomina G, Achaibou F, Pottier J, Kotovskaya A. Cardiac and vascular adaptation to 0g with and without thigh cuffs (Antares 14 and Altair 21 day Mir spaceflights). Acta Astronaut. 1995; 36(8–12):753–762.
8. Arbeille P, Provost R, Zuj K, Vincent N. Measurements of jugular, portal, femoral, and calf vein cross-sectional area for the assessment of venous blood redistribution with long duration spaceflight (Vessel Imaging Experiment). Eur J Appl Physiol. 2015; 115(10):2099–2106.
9. Auñón-Chancellor SM, Pattarini JM, Moll S, Sargsyan A. Venous thrombosis during spaceflight. N Engl J Med. 2020; 382(1):89–90.
10. Baevsky RM, Baranov VM, Funtova II, Diedrich A, Pashenko AV, et al. Autonomic cardiovascular and respiratory control during prolonged spaceflights aboard the International Space Station. J Appl Physiol. 2007; 103(1):156–161.
11. Beekley MD, Sato Y, Abe T. KAATSU-walk training increases serum bone-specific alkaline phosphatase in young men. Int J KAATSU Train Res. 2005; 1(2):77–81.
12. Behringer M, Willberg C. Application of blood flow restriction to optimize exercise countermeasures for human space flight. Front Physiol. 2019; 10:33. Erratum in: Front Physiol. 2019; 10:276.
13. Bemben DA, Palmer IJ, Abe T, Sato Y, Bemben MG. Effects of a single bout of low intensity KAATSU resistance training on markers of bone turnover in young men. Int J KAATSU Train Res. 2007; 3(2):21–26.
14. Bennett H, Slattery F. Effects of blood flow restriction training on aerobic capacity and performance: a systematic review. J Strength Cond Res. 2019; 33(2):572–583.
15. Bjørnsen T, Wernbom M, Løvstad A, Paulsen G, D'Souza RF, et al. Delayed myonuclear addition, myofiber hypertrophy, and increases in strength with high-frequency low-load blood flow restricted training to volitional failure. J Appl Physiol (1985). 2019; 126(3):578–592.
16. Bleeker MWP, De Groot PCE, Rongen GA, Rittweger J, Felsenberg D, et al. Vascular adaptation to deconditioning and the effect of an exercise countermeasure: results of the Berlin Bed Rest study. J Appl Physiol. 2005; 99(4):1293–1300.
17. Bock O, Weigelt C, Bloomberg JJ. Cognitive demand of human sensorimotor performance during an extended space mission: a dual-task study. Aviat Space Environ Med. 2010; 81(9):819–824.
18. Bohm S, Mersmann F, Arampatzis A. Human tendon adaptation in response to mechanical loading: a systematic review and meta-analysis of exercise intervention studies on healthy adults. Sports Med Open. 2015; 1(1):7.
19. Boushel R. Muscle metaboreflex control of the circulation during exercise. Acta Physiol (Oxf). 2010; 199(4):367–383.
20. Bowman EN, Elshaar R, Milligan H, Jue G, Mohr K, et al. Proximal, distal, and contralateral effects of blood flow restriction training on the lower extremities: a randomized controlled trial. Sports Health. 2019; 11(2):149–156.
21. Bowman EN, Elshaar R, Milligan H, Jue G, Mohr K, et al. Upper-extremity blood flow restriction: the proximal, distal, and contralateral effects—a randomized controlled trial. J Shoulder Elbow Surg. 2020; 29(6):1267–1274.
22. Braddock M. Exercise and ergonomics on the International Space Station and Orion spacecraft. Journal of Ergonomics Research. 2018; 1(2):2.
23. Brandner CR, May AK, Clarkson MJ, Warmington SA. Reported side-effects and safety considerations for the use of blood flow restriction during exercise in practice and research. Tech Orthop. 2018; 33(2):114–121.
24. Brooks NE, Myburgh KH. Skeletal muscle wasting with disuse atrophy is multi-dimensional: the response and interaction of myonuclei, satellite cells and signaling pathways. Front Physiol. 2014; 5:99.
25. Burr JF, Hughes L, Warmington S, Scott BR, Owens J, et al. Response: commentary: can blood flow restricted exercise cause muscle damage? Commentary on blood flow restriction exercise: considerations of methodology, application, and safety. Front Physiol. 2020; 11:574633.
26. Cai ZY, Wang W-Y, Lin J-D, Wu C-M. Effects of whole body vibration training combined with blood flow restriction on muscle adaptation. Eur J Sport Sci. 2021; 21(2):204–212.
27. Centner C, Lauber B, Seynnes OR, Jerger S, Sohnius T, et al. Low-load blood flow restriction training induces similar morphological and mechanical Achilles tendon adaptations compared with high-load resistance training. J Appl Physiol. 2019; 127(6):1660–1667.
28. Centner C, Ritzmann R, Schur S, Gollhofer A, König D. Blood flow restriction increases myoelectric activity and metabolic accumulation during whole-body vibration. Eur J Appl Physiol. 2019; 119(6):1439–1449.
29. Christiansen D, Eibye K, Hostrup M, Bangsbo J. Training with blood flow restriction increases femoral artery diameter and thigh oxygen delivery during knee-extensor exercise in recreationally trained men. J Physiol. 2020; 598(12):2337–2353.
30. Christiansen D, Eibye KH, Rasmussen V, Voldbye HM, Thomassen M, et al. Cycling with blood flow restriction improves performance and muscle K+ regulation and alters the effect of anti-oxidant infusion in humans. J Physiol. 2019; 597(9):2421–2444.
31. Christiansen D, Murphy RM, Bangsbo J, Stathis CG, Bishop DJ. Increased FXYD1 and PGC-1α mRNA after blood flow-restricted running is related to fibre type-specific AMPK signalling and oxidative stress in human muscle. Acta Physiol (Oxf). 2018; 223(2):e13045.
32. Cochrane DJ, Loram ID, Stannard SR, Rittweger J. Changes in joint angle, muscle-tendon complex length, muscle contractile tissue displacement, and modulation of EMG activity during acute whole-body vibration. Muscle Nerve. 2009; 40(3):420–429.
33. Cohen JN, Slysz JT, King TJ, Coates AM, King RT, Burr JF. Blood flow restriction and electric muscle stimulation during 14-day unilateral limb immobilization does not protect against macrovascular structural and functional changes. Proc Can Soc Exerc Physiol Annu Gen Meet. 2020; 45(11):S294.
34. Cotter JA, Yu A, Haddad F, Kreitenberg A, Baker MJ, et al. Concurrent exercise on a gravity-independent device during simulated microgravity. Med Sci Sports Exerc. 2015; 47(5):990–1000.
35. Criscuolo F, Sueur C, Bergouignan A. Human adaptation to deep space environment: an evolutionary perspective of the foreseen interplanetary exploration. Front Public Health. 2020; 8:119.
36. Day MK, Allen DL, Mohajerani L, Greenisen MC, Roy RR, Edgerton VR. Adaptations of human skeletal muscle fibers to spaceflight. J Gravit Physiol. 1995; 2(1):47–50.
37. Dirks ML, Hansen D, Van Assche A, Dendale P, Van Loon LJC. Neuromuscular electrical stimulation prevents muscle wasting in critically ill comatose patients. Clin Sci (Lond). 2015; 128(6):357–365.
38. Dirks ML, Wall BT, Snijders T, Ottenbros CLP, Verdijk LB, Van Loon LJC. Neuromuscular electrical stimulation prevents muscle disuse atrophy during leg immobilization in humans. Acta Physiol (Oxf). 2014; 210(3):628–641.
39. Docherty D, Sporer B. A proposed model for examining the interference phenomenon between concurrent aerobic and strength training. Sports Med. 2000; 30(6):385–394.
40. Drummond MJ, Fujita S, Abe T, Dreyer HC, Volpi E, Rasmussen BB. Human muscle gene expression following resistance exercise and blood flow restriction. Med Sci Sports Exerc. 2008; 40(4):691–698. Erratum in: Med Sci Sports Exerc. 2008; 40(6):1191.
41. van Duijnhoven NTL*, Thijssen DHJ, Green DJ, Felsenberg D, Belavý DL, Hopman MTE. Resistive exercise versus resistive vibration exercise to counteract vascular adaptations to bed rest. J Appl Physiol. 2010; 108(1):28–33.
42. Elksrawy MN, Hamrick MW. Myostatin as a key factor linking muscle mass and skeletal form. J Musculoskelet Neuronal Interact. 2010;10(1):56–63.
43. Elliott B, Renshaw D, Getting S, Mackenzie R. The central role of myostatin in skeletal muscle and whole body homeostasis. Acta Physiol (Oxf). 2012; 205(3):324–340.
44. English KL, Lee SMC, Loehr JA, Ploutz-Snyder RJ, Ploutz-Snyder LL, Reeves JM. Isokinetic strength changes following long-duration spaceflight on the ISS. Aerosp Med Hum Perform. 2015; 86(12, Suppl.):A68–A77.

45. Englund DA, Figueiredo VC, Dungan CM, Murach KA, Peck BD, et al. Satellite cell depletion disrupts transcriptional coordination and muscle adaptation to exercise. Function (Oxf). 2020; 2(1):zqaa033.
46. Evans C, Vance S, Brown M. Short-term resistance training with blood flow restriction enhances microvascular filtration capacity of human calf muscles. J Sports Sci. 2010; 28(9):999–1007.
47. Fahs CA, Rossow LM, Seo D-I, Loenneke JP, Sherk VD, et al. Effect of different types of resistance exercise on arterial compliance and calf blood flow. Eur J Appl Physiol. 2011; 111(12):2969–2975.
48. Fahs CA, Rossow LM, Thiebaud RS, Loenneke JP, Kim D, et al. Vascular adaptations to low-load resistance training with and without blood flow restriction. Eur J Appl Physiol. 2014; 114(4):715–724.
49. Ferguson RA, Hunt JEA, Lewis MP, Martin NRW, Player DJ, et al. The acute angiogenic signalling response to low-load resistance exercise with blood flow restriction. Eur J Sport Sci. 2018; 18(3):397–406.
50. Fitts RH, Trappe SW, Costill DL, Gallagher PM, Creer AC, et al. Prolonged space flight-induced alterations in the structure and function of human skeletal muscle fibres. J Physiol. 2010; 588(Pt. 18):3567–3592.
51. Fomina G, Kotovskaya A, Arbeille F, Pochuev V, Zhernavkov A, Ivanovskaya T. Changes in hemodynamic and post-flights orthostatic tolerance of cosmonauts under application of the preventive device–thigh cuffs bracelets in short-term flights. J Gravit Physiol. 2004; 11(2):229–230.
52. Fortrat JO, de Holanda A, Zuj K, Gauquelin-Koch G, Gharib C. Altered venous function during long-duration spaceflights. Front Physiol. 2017; 8:694.
53. Franz A, Berndt F, Raabe J, Harmsen JF, Zilkens C, Behringer M. Invasive assessment of hemodynamic, metabolic and ionic consequences during blood flow restriction training. Front Physiol. 2020; 11:617668.
54. Fry CS, Glynn EL, Drummond MJ, Timmerman KL, Fujita S, et al. Blood flow restriction exercise stimulates mTORC1 signaling and muscle protein synthesis in older men. J Appl Physiol. 2010; 108(5):1199–1209.
55. Fujita S, Abe T, Drummond MJ, Cadenas JG, Dreyer HC, et al. Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. J Appl Physiol. 2007; 103(3):903–910.
56. Ganesan G, Cotter JA, Reuland W, Cerussi AE, Tromberg BJ, Galassetti P. Effect of blood flow restriction on tissue oxygenation during knee extension. Med Sci Sports Exerc. 2015; 47(1):185–193.
57. Glover EI, Phillips SM, Oates BR, Tang JE, Tarnopolsky MA, et al. Immobilization induces anabolic resistance in human myofibrillar protein synthesis with low and high dose amino acid infusion. J Physiol. 2008; 586(24):6049–6061.
58. Gorgey AS, Timmons MK, Dolbow DR, Bengel J, Fugate-Laus KC, et al. Electrical stimulation and blood flow restriction increase wrist extensor cross-sectional area and flow meditated dilatation following spinal cord injury. Eur J Appl Physiol. 2016; 116(6):1231–1244.
59. Graebe A, Schuck EL, Lensing P, Putcha L, Derendorf H. Physiological, pharmacokinetic, and pharmacodynamic changes in space. J Clin Pharmacol. 2004; 44(8):837–853.
60. Grimm D, Grosse J, Wehland M, Mann V, Reseland JE, et al. The impact of microgravity on bone in humans. Bone. 2016; 87:44–56.
61. Guéguinou N, Huin-Schohn C, Bascove M, Bueb J-L, Tschirhart E, et al. Could spaceflight-associated immune system weakening preclude the expansion of human presence beyond Earth's orbit? J Leukoc Biol. 2009; 86(5):1027–1038.
62. Gundermann DM, Walker DK, Reidy PT, Borack MS, Dickinson JM, et al. Activation of mTORC1 signaling and protein synthesis in human muscle following blood flow restriction exercise is inhibited by rapamycin. Am J Physiol Endocrinol Metab. 2014; 306(10):E1198–E1204.
63. Hackney KJ, English KL. Protein and essential amino acids to protect musculoskeletal health during spaceflight: evidence of a paradox? Life (Basel). 2014; 4(3):295–317.
64. Hackney KJ, Everett M, Scott JM, Ploutz-Snyder L. Blood flow-restricted exercise in space. Extrem Physiol Med. 2012; 1(1):12.
65. Hackney KJ, Scott JM, Hanson AM, English KL, Downs ME, Ploutz-Snyder LL. The astronaut-athlete: optimizing human performance in space. J Strength Cond Res. 2015; 29(12):3531–3545.
66. Hazell TJ, Jakobi JM, Kenno KA. The effects of whole-body vibration on upper- and lower-body EMG during static and dynamic contractions. Appl Physiol Nutr Metab. 2007; 32(6):1156–1163.
67. Head P, Waldron M, Theis N, Patterson SD. Acute neuromuscular electrical stimulation (NMES) with blood flow restriction: the effect of restriction pressures. J Sport Rehabil. 2020; 30(3):375–383.
68. Hughes L, McEwen J. Investigation of clinically acceptable agreement between two methods of automatic measurement of limb occlusion pressure: a randomised trial. BMC Biomed Eng. 2021; 3(1):8.
69. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: A systematic review and meta-analysis. Br J Sports Med. 2017; 51(13): 1003–1011.
70. Hughes L, Patterson SD, Haddad F, Rosenblatt B, Gissane C, et al. Examination of the comfort and pain experienced with blood flow restriction training during post-surgery rehabilitation of anterior cruciate ligament reconstruction patients: a UK National Health Service trial. Phys Ther Sport. 2019; 39:90–98.
71. Hughes L, Rosenblatt B, Haddad F, Gissane C, McCarthy D, et al. Comparing the effectiveness of blood flow restriction and traditional heavy load resistance training in the post-surgery rehabilitation of anterior cruciate ligament reconstruction patients: a UK National Health Service randomised controlled trial. Sports Med. 2019; 49(11):1787–1805.
72. Hughson RL, Robertson AD, Arbeille P, Shoemaker JK, Rush JWE, et al. Increased postflight carotid artery stiffness and inflight insulin resistance resulting from 6-mo spaceflight in male and female astronauts. Am J Physiol Heart Circ Physiol. 2016; 310(5):H628–H638.
73. Hunt JEA, Galea D, Tufft G, Bunce D, Ferguson RA. Time course of regional vascular adaptations to low load resistance training with blood flow restriction. J Appl Physiol. 2013; 115(3):403–411.
74. Hurley BF, Seals DR, Ehsani A, Cartier LJ, Dalsky GP, et al. Effects of high-intensity strength training on cardiovascular function. Med Sci Sports Exerc. 1984; 16(5):483–488.
75. Hwang H, Mizuno S, Kasai N, Kojima C, Sumi D, et al. Muscle oxygenation, endocrine and metabolic regulation during low-intensity endurance exercise with blood flow restriction. Phys Act Nutr. 2020; 24(2):30–37.
76. Hwang PS, Willoughby DS. Mechanisms behind blood flow-restricted training and its effect toward muscle growth. J Strength Cond Res. 2019; 33(Suppl. 1):S167–S179.
77. Iellamo F, Di Rienzo M, Lucini D, Legramante JM, Pizzinelli P, et al. Muscle metaboreflex contribution to cardiovascular regulation during dynamic exercise in microgravity: Insights from mission STS-107 of the space shuttle Columbia. J Physiol. 2006; 572(Pt. 3):829–838.
78. Iida H, Nakajima T, Kurano M, Yasuda T, Sakamaki M, et al. Effects of walking with blood flow restriction on limb venous compliance in elderly subjects. Clin Physiol Funct Imaging. 2011; 31(6):472–476.
79. Ilett MJ, Rantalainen T, Keske MA, May AK, Warmington SA. The effects of restriction pressures on the acute responses to blood flow restriction exercise. Front Physiol. 2019; 10:1018.
80. Irie H, Tatsumi T, Takamiya M, Zen K, Takahashi T, et al. Carbon dioxide-rich water bathing enhances collateral blood flow in ischemic hindlimb via mobilization of endothelial progenitor cells and activation of NO-cGMP system. Circulation. 2005; 111(12):1523–1529.
81. Ishihara A, Terada M, Kouzaki M, Hagio S, Higashibata A, et al. Blood flow in astronauts on Earth after long space stay. Acta Astronaut. 2020; 175:462–464.
82. Jackson A, Vayssière B, Garcia T, Newell W, Baron R, et al. Gene array analysis of Wnt-regulated genes in C3H10T1/2 cells. Bone. 2005; 36(4):585–598.
83. Johnson RB, Tsao AK, St. John KR, Betcher RA, Tucci MA, Benghuzzi HA. Effects of spaceflight on the attachment of tendons to bone in the hindlimb of the pregnant rat. Anat Rec A Discov Mol Cell Evol Biol. 2005; 282A(2):147–156.
84. Joshi S, Mahoney S, Jahan J, Pitts L, Hackney KJ, Jarajapu YP. Blood flow restriction exercise stimulates mobilization of hematopoietic stem/progenitor cells and increases the circulating ACE2 levels in healthy adults. J Appl Physiol. 2020; 128(5):1423–1431.

85. Karabulut M, Bemben DA, Sherk VD, Anderson MA, Abe T, Michael GB. Effects of high-intensity resistance training and low-intensity resistance training with vascular restriction on bone markers in older men. Eur J Appl Physiol. 2011; 111(8):1659–1667.
86. Karabulut U, Karabulut M, James EG. Small arteries stay stiff for a longer period following vibration exercises in combination with blood flow restriction. Clin Physiol Funct Imaging. 2018; 38(6):1000–1007.
87. Karlsson LL, Montmerle S, Rohdin M, Linnarsson D. Central command and metaboreflex cardiovascular responses to sustained handgrip during microgravity. Respir Physiol Neurobiol. 2009; 169(Suppl. 1):S46–S49.
88. Katuntsev VP, Osipov YY, Barer AS, Gnoevaya NK, Tarasenkov GG. The main results of EVA medical support on the Mir Space Station. Acta Astronaut. 2004; 54(8):577–583.
89. Kim D, Singh H, Loenneke JP, Thiebaud RS, Fahs CA, et al. Comparative effects of vigorous-intensity and low-intensity blood flow restricted cycle training and detraining on muscle mass, strength, and aerobic capacity. J Strength Cond Res. 2016; 30(5):1453–1461.
90. Koncarevic A, Cornwall-Brady M, Pullen A, Davies M, Sako D, et al. A soluble activin receptor type IIB prevents the effects of androgen deprivation on body composition and bone health. Endocrinology. 2010; 151(9):4289–4300.
91. Koppelmans V, Bloomberg JJ, Mulavara AP, Seidler RD. Brain structural plasticity with spaceflight. NPJ Microgravity. 2016; 2:2.
92. Korth DW, Reeves JM. Exercise countermeasure hardware evolution on ISS: the first decade. Aerosp Med Hum Perform. 2015; 86(12, Suppl.):A7–A13.
93. Kubo K, Komuro T, Ishiguro N, Tsunoda N, Sato Y, et al. Effects of low-load resistance training with vascular occlusion on the mechanical properties of muscle and tendon. J Appl Biomech. 2006; 22(2):112–119.
94. Kubota N, Takano H, Tsutsumi T, Kurano M, Iida H, et al. Resistance exercise combined with KAATSU during simulated weightlessness. Int J KAATSU Train Res. 2008; 4(1):9–15.
95. Lambertz D, Pérot C, Kaspranski R, Goubel F. Effects of long-term spaceflight on mechanical properties of muscles in humans. J Appl Physiol. 2001; 90(1):179–188.
96. Lambrecht G, Petersen N, Weerts G, Pruett C, Evetts S, et al. The role of physiotherapy in the European Space Agency strategy for preparation and reconditioning of astronauts before and after long duration space flight. Musculoskelet Sci Pract. 2017; 27(Suppl. 1):S15–S22.
97. Lang T, LeBlanc A, Evans H, Lu Y, Genant H, Yu A. Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. J Bone Miner Res. 2004; 19(6):1006–1012 .
98. Larkin KA, MacNeil RG, Dirain M, Sandesara B, Manini TM, Buford TW. Blood flow restriction enhances post-resistance exercise angiogenic gene expression. Med Sci Sports Exerc. 2012; 44(11):2077–2083.
99. Laufs U, Urhausen A, Werner N, Scharhag J, Heitz A, et al. Running exercise of different duration and intensity: effect on endothelial progenitor cells in healthy subjects. Eur J Cardiovasc Prev Rehabil. 2005; 12(4):407–414.
100. Laurentino GC, Ugrinowitsch C, Roschel H, Aoki MS, Soares AG, et al. Strength training with blood flow restriction diminishes myostatin gene expression. Med Sci Sports Exerc. 2012; 44(3):406–412.
101. Law J, Van Baalen M, Foy M, Mason SS, Mendez C, et al. Relationship between carbon dioxide levels and reported headaches on the International Space Station. J Occup Environ Med. 2014; 56(5):477–483.
102. Laws JM, Caplan N, Bruce C, McGrogan C, Lindsay K, et al. Systematic review of the technical and physiological constraints of the Orion Multi-Purpose Crew Vehicle that affect the capability of astronauts to exercise effectively during spaceflight. Acta Astronaut. 2020; 170:665–677.
103. Layne AS, Larkin-Kaiser K, MacNeil GG, Dirain M, Sandesara B, et al. Effects of blood-flow restriction on biomarkers of myogenesis in response to resistance exercise. Appl Physiol Nutr Metab. 2017; 42(1):89–92.
104. LeBlanc A, Rowe R, Schneider V, Evans H, Hedrick T. Regional muscle loss after short duration spaceflight. Aviat Space Environ Med. 1995; 66(12):1151–1154.
105. Lee JK, De Dios Y, Kofman I, Mulavara AP, Bloomberg JJ, Seidler RD. Head down tilt bed rest plus elevated CO2 as a spaceflight analog: effects on cognitive and sensorimotor performance. Front Hum Neurosci. 2019; 13:355.
106. Lee S, Lehar A, Meir JU, Koch C, Morgan A, et al. Targeting myostatin/activin A protects against skeletal muscle and bone loss during spaceflight. Proc Natl Acad Sci U S A. 2020; 117(38):23942–23951.
107. Lee WYW, Lui PPY, Rui YF. Hypoxia-mediated efficient expansion of human tendon-derived stem cells in vitro. Tissue Eng Part A. 2012; 18(5–6):484–498.
108. Libardi CA, Chacon-Mikahil MPT, Cavaglieri CR, Tricoli V, Roschel H, et al. Effect of concurrent training with blood flow restriction in the elderly. Int J Sports Med. 2015; 36(5):395–399.
109. Limper U, Tank J, Ahnert T, Maegele M, Grottke O, et al. The thrombotic risk of spaceflight: has a serious problem been overlooked for more than half of a century? Eur Heart J. 2021; 42(1):97–100.
110. Loehr JA, Guilliams ME, Petersen N, Hirsch N, Kawashima S, et al. Physical training for long-duration spaceflight. Aerosp Med Hum Perform. 2015; 86(12, Suppl.):A14–A23.
111. Loenneke JP, Young KC, Fahs CA, Rossow LM, Bemben DA, Bemben MG. Blood flow restriction: rationale for improving bone. Med Hypotheses. 2012; 78(4):523–527.
112. Lythgo N, Eser P, De Groot P, Galea M. Whole-body vibration dosage alters leg blood flow. Clin Physiol Funct Imaging. 2009; 29(1):53–59.
113. Madarame H, Kurano M, Takano H, Iida H, Sato Y, et al. Effects of low-intensity resistance exercise with blood flow restriction on coagulation system in healthy subjects. Clin Physiol Funct Imaging. 2010; 30(3):210–213.
114. Maffiuletti NA, Gondin J, Place N, Stevens-Lapsley J, Vivodtzev I, Minetto MA. Clinical use of neuromuscular electrical stimulation for neuromuscular rehabilitation: what are we overlooking? Arch Phys Med Rehabil. 2018; 99(4):806–812.
115. Maffiuletti NA, Green DA, Vaz MA, Dirks ML. Neuromuscular electrical stimulation as a potential countermeasure for skeletal muscle atrophy and weakness during human spaceflight. Front Physiol. 2019; 10:1031.
116. Manini TM, Clark BC. Blood flow restricted exercise and skeletal muscle health. Exerc Sport Sci Rev. 2009; 37(2):78–85.
117. Manini TM, Vincent KR, Leeuwenburgh CL, Lees HA, Kavazis AN, et al. Myogenic and proteolytic mRNA expression following blood flow restricted exercise. Acta Physiol (Oxf). 2011; 201(2):255–263.
118. Marshall-Bowman K, Barratt MR, Gibson CR. Ophthalmic changes and increased intracranial pressure associated with long duration spaceflight: An emerging understanding. Acta Astronaut. 2013; 87:77–87.
119. Marshall-Goebel K, Laurie SS, Alferova IV, Arbeille P, Auñón-Chancellor SM, et al. Assessment of jugular venous blood flow stasis and thrombosis during spaceflight. JAMA Network Open. 2019; 2(11):e1915011.
120. Martín-Hernández J, Ruiz-Aguado J, Herrero AJ, Loenneke JP, Aagaard P, et al. Adaptation of perceptual responses to low-load blood flow restriction training. J Strength Cond Res. 2017; 31(3):765–772.
121. Miller RM, Keeter VM, Freitas EDS, Heishman AD, Knehans AW, et al. Effects of blood-flow restriction combined with postactivation potentiation stimuli on jump performance in recreationally active men. J Strength Cond Res. 2018; 32(7):1869–1874.
122. Miokovic T, Armbrecht G, Gast U, Rawer R, Roth HJ, et al. Muscle atrophy, pain, and damage in bed rest reduced by resistive (Vibration) exercise. Med Sci Sports Exerc. 2014; 46(8):1506–1516.
123. Montgomery R, Paterson A, Williamson C, Florida-James G, Ross MD. Blood flow restriction exercise attenuates the exercise-induced endothelial progenitor cell response in healthy, young men. Front Physiol. 2019; 10:447.
124. Moore AD, Downs ME, Lee SMC, Feiveson AH, Knudsen P, Ploutz-Snyder L. Peak exercise oxygen uptake during and following long-duration spaceflight. J Appl Physiol. 2014; 117(3):231–238.
125. Mouser JG, Mattocks KT, Buckner SL, Dankel SJ, Jessee MB, et al. High-pressure blood flow restriction with very low load resistance training results in peripheral vascular adaptations similar to heavy resistance training. Physiol Meas. 2019; 40(3):035003.

126. Nakajima T, Iida H, Kurano M, Takano H, Morita T, et al. Hemodynamic responses to simulated weightlessness of 24-h head-down bed rest and KAATSU blood flow restriction. Eur J Appl Physiol. 2008; 104(4):727–737.
127. Nakajima T, Takano H, Kurano M, Iida H, Kubota N, et al. Effects of KAATSU training on haemostasis in healthy subjects. Int J KAATSU Train Res. 2007; 3(1):11–20.
128. Natsume T, Ozaki H, Saito AI, Abe T, Naito H. Effects of electrostimulation with blood flow restriction on muscle size and strength. Med Sci Sports Exerc. 2015; 47(12):2621–2627.
129. Natsume T, Yoshihara T, Naito H. Electromyostimulation with blood flow restriction enhances activation of mtor and MAPK signaling pathways in rat gastrocnemius muscles. Appl Physiol Nutr Metab. 2019; 44(6):637–644.
130. Neto GR, Novaes JS, Dias I, Brown A, Vianna J, Cirilo-Sousa MS. Effects of resistance training with blood flow restriction on haemodynamics: a systematic review. Clin Physiol Funct Imaging. 2017; 37(6):567–574.
131. Nielsen JL, Aagaard P, Bech RD, Nygaard T, Hvid LG, et al. Proliferation of myogenic stem cells in human skeletal muscle in response to low-load resistance training with blood flow restriction. J Physiol. 2012; 590(17): 4351–4361.
132. Nielsen JL, Frandsen U, Jensen KY, Prokhorova TA, Dalgaard LB, et al. Skeletal muscle microvascular changes in response to short-term blood flow restricted training—exercise-induced adaptations and signs of perivascular stress. Front Physiol. 2020; 11:556.
133. Norsk P. Blood pressure regulation IV: adaptive responses to weightlessness. Eur J Appl Physiol. 2014; 114(3):481–497.
134. Norsk P, Asmar A, Damgaard M, Christensen NJ. Fluid shifts, vasodilatation and ambulatory blood pressure reduction during long duration spaceflight. J Physiol. 2015; 593(3):573–584.
135. Norsk P, Damgaard M, Petersen L, Gybel M, Pump B, et al. Vasorelaxation in space. Hypertension. 2006; 47(1):69–73.
136. Ohshima H. [Secondary osteoporosis UPDATE. Bone loss due to bed rest and human space flight study]. Clin Calcium. 2010; 20(5):709–716.
137. de Oliveira MFM*, Caputo F, Corvino RB, Denadai BS. Short-term low-intensity blood flow restricted interval training improves both aerobic fitness and muscle strength. Scand J Med Sci Sports. 2016; 26(9):1017–1025.
138. Patterson SD, Ferguson RA. Increase in calf post-occlusive blood flow and strength following short-term resistance exercise training with blood flow restriction in young women. Eur J Appl Physiol. 2010; 108(5): 1025–1033.
139. Patterson SD, Hughes L, Warmington S, Burr J, Scott BR, et al. Blood flow restriction exercise: Considerations of Methodology, Application, and Safety. Front Physiol. 2019; 10:533.
140. Payne MWC, Williams DR, Trudel G. Space flight rehabilitation. Am J Phys Med Rehabil. 2007; 86(7):583–591.
141. Petersen N, Lambrecht G, Scott J, Hirsch N, Stokes M, Mester J. Postflight reconditioning for European astronauts – a case report of recovery after six months in space. Musculoskelet Sci Pract. 2017; 27:S23–S31.
142. Petrella JK, Kim JS, Cross JM, Kosek DJ, Bamman MM. Efficacy of myonuclear addition may explain differential myofiber growth among resistance-trained young and older men and women. Am J Physiol Endocrinol Metab. 2006; 291(5):E937–E946.
143. Petrella JK, Kim JS, Mayhew DL, Cross JM, Bamman MM. Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonuclear addition: a cluster analysis. J Appl Physiol. 2008; 104(6):1736–1742.
144. Plett PA, Abonour R, Frankovitz SM, Orschell CM. Impact of modeled microgravity on migration, differentiation, and cell cycle control of primitive human hematopoietic progenitor cells. Exp Hematol. 2004; 32(8):773–781.
145. Prodel E, Balanos GM, Braz ID, Nobrega ACL, Vianna LC, Fisher JP. Muscle metaboreflex and cerebral blood flow regulation in humans: implications for exercise with blood flow restriction. Am J Physiol Heart Circ Physiol. 2016; 310(9):H1201–H1209.
146. Qaisar R, Karim A, Elmoselhi AB. Muscle unloading: a comparison between spaceflight and ground-based models. Acta Physiol (Oxf). 2020; 228(3):e13431.
147. Rittweger J. Vibration as an exercise modality: How it may work, and what its potential might be. Eur J Appl Physiol. 2010; 108(5):877–904.
148. Rittweger J, Albracht K, Flück M, Ruoss S, Brocca L, et al. Sarcolab pilot study into skeletal muscle's adaptation to long-term spaceflight. NPJ Microgravity. 2018; 4:18. Erratum in: NPJ Microgravity. 2018; 4:23.
149. Rittweger J, Beller G, Armbrecht G, Mulder E, Buehring B, et al. Prevention of bone loss during 56 days of strict bed rest by side-alternating resistive vibration exercise. Bone. 2010; 46(1):137–147.
150. Rittweger J, Moss AD, Colier W, Stewart C, Degens H. Muscle tissue oxygenation and VEGF in $\dot{V}o_2$-matched vibration and squatting exercise. Clin Physiol Funct Imaging. 2010; 30(4):269–278.
151. Rittweger J, Mutschelknauss M, Felsenberg D. Acute changes in neuromuscular excitability after exhaustive whole body vibration exercise as compared to exhaustion by squatting exercise. Clin Physiol Funct Imaging. 2003; 23(2):81–86.
152. Rochefort GY, Benhamou C-L. Osteocytes are not only mechanoreceptive cells. Int J Numer Method Biomed Eng. 2013; 29(10):1082–1088.
153. Ross H, Brodie E, Benson A. Mass discrimination during prolonged weightlessness. Science. 1984; 225(4658):219–221.
154. Ross MD, Wekesa AL, Phelan JP, Harrison M. Resistance exercise increases endothelial progenitor cells and angiogenic factors. Med Sci Sports Exerc. 2014; 46(1):16–23.
155. Roy-O'Reilly M, Mulavara A, Williams T. A review of alterations to the brain during spaceflight and the potential relevance to crew in long-duration space exploration. NPJ Microgravity. 2021; 7(1):5.
156. Saatmann N, Zaharia OP, Loenneke JP, Roden M, Pesta DH. Effects of blood flow restriction exercise and possible applications in type 2 diabetes. Trends Endocrinol Metab. 2021; 32(2):106–117.
157. Sakamaki M, Bemben MG, Abe T. Legs and trunk muscle hypertrophy following walk training with restricted leg muscle blood flow. J Sports Sci Med. 2011; 10(2):338–340.
158. Scheuring RA, Mathers CH, Jones JA, Wear ML. Musculoskeletal injuries and minor trauma in space: incidence and injury mechanisms in U.S. astronauts. Aviat Space Environ Med. 2009; 80(2):117–124.
159. Scott JPR, Weber T, Green DA. Introduction to the frontiers research topic: optimization of exercise countermeasures for human space flight – lessons from terrestrial physiology and operational considerations. Front Physiol. 2019; 10:173.
160. Sibonga JD. Spaceflight-induced bone loss: is there an osteoporosis risk? Curr Osteoporos Rep. 2013; 11(2):92–98.
161. Sibonga JD, Spector ER, Johnston SL, Tarver WJ, Reeves JM. Evaluating bone loss in ISS astronauts. Aerosp Med Hum Perform. 2015; 86(12, Suppl.):A38–A44.
162. Sieljacks P, Wang J, Groennebaek T, Rindom E, Jakobsgaard JE, et al. Six weeks of low-load blood flow restricted and high-load resistance exercise training produce similar increases in cumulative myofibrillar protein synthesis and ribosomal biogenesis in healthy males. Front Physiol. 2019; 10:649.
163. Slysz JT, Boston M, King R, Pignanelli C, Power GA, Burr JF. Blood flow restriction combined with electrical stimulation attenuates thigh muscle disuse atrophy. Med Sci Sports Exerc. 2021; 53(5):1033–1040.
164. Smith RC, Cramer MS, Mitchell PJ, Lucchesi J, Ortega A, et al. Inhibition of myostatin prevents microgravity-induced loss of skeletal muscle mass and strength. PLoS One. 2020; 15(4):e0230818.
165. Sousa AC, Neiva HP, Izquierdo M, Cadore EL, Alves AR, Marinho DA. Concurrent training and detraining: brief review on the effect of exercise intensities. Int J Sports Med. 2019; 40(12):747–755.
166. Spitz RW, Wong V, Bell ZW, Viana RB, Chatakondi RN, et al. Blood flow restricted exercise and discomfort: a review. J Strength Cond Res. 2020. Online ahead of print.
167. Spranger MD. Commentary: blood flow restriction exercise position stand: considerations of methodology, application, and safety. Front Physiol. 2020; 11:599592.
168. Spranger MD, Krishnan AC, Levy PD, O'Leary DS, Smith SA. Blood flow restriction training and the exercise pressor reflex: a call for concern. Am J Physiol Heart Circ Physiol. 2015; 309(9):H1440–H1452.

169. Stein TP, Leskiw MJ, Schluter MD, Donaldson MR, Larina I. Protein kinetics during and after long-duration spaceflight on MIR. Am J Physiol. 1999; 276(6, Pt. 1):E1014–E1021.
170. Stein TP, Leskiw MJ, Schluter MD, Hoyt RW, Lane HW, et al. Energy expenditure and balance during spaceflight on the space shuttle. Am J Physiol. 1999; 276(6, Pt. 2):R1739–R1748.
171. Stokes M, Evetts S, Hides J. Terrestrial neuro-musculoskeletal rehabilitation and astronaut reconditioning: reciprocal knowledge transfer. Musculoskelet Sci Pract. 2017; 27(Suppl. 1):S1–S4.
172. Suga T, Okita K, Takada S, Omokawa M, Kadoguchi T, et al. Effect of multiple set on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. Eur J Appl Physiol. 2012; 112(11):3915–3920.
173. Takada S, Okita K, Suga T, Omokawa M, Kadoguchi T, et al. Low-intensity exercise can increase muscle mass and strength proportionally to enhanced metabolic stress under ischemic conditions. J Appl Physiol. 2012; 113(2):199–205.
174. Takano H, Morita T, Iida H, Asada K, Kato M, et al. Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. Eur J Appl Physiol. 2005; 95(1):65–73.
175. Takarada Y, Tsuruta T, Ishii N. Cooperative effects of exercise and occlusive stimuli on muscular function in low-intensity resistance exercise with moderate vascular occlusion. Jpn J Physiol. 2004; 54(6):585–592.
176. Tarantino U, Cariati I, Marini M, D'Arcangelo G, Tancredi V, et al. Effects of simulated microgravity on muscle stem cells activity. Cell Physiol Biochem. 2020; 54(4):736–747.
177. Thijssen DHJ, Vos JB, Verseyden C, Van Zonneveld AJ, Smits P, et al. Haematopoietic stem cells and endothelial progenitor cells in healthy men: effect of aging and training. Aging Cell. 2006; 5(6):495–503.
178. Thomas HJ, Scott BR, Peiffer JJ. Acute physiological responses to low-intensity blood flow restriction cycling. J Sci Med Sport. 2018; 21(9): 969–974.
179. Trappe S, Costill D, Gallagher P, Creer A, Peters JR, et al. Exercise in space: human skeletal muscle after 6 months aboard the International Space Station. J Appl Physiol. 2009; 106(4):1159–1168.
180. Tucker KL, Hannan MT, Kiel DP. The acid-base hypothesis: diet and bone in the Framingham Osteoporosis Study. Eur J Nutr. 2001; 40(5):231–237.
181. Tuday EC, Meck JV, Nyhan D, Shoukas AA, Berkowitz DE. Microgravity-induced changes in aortic stiffness and their role in orthostatic intolerance. J Appl Physiol. 2007; 102(3):853–858.
182. Wall BT, Dirks ML, Verdijk LB, Snijders T, Hansen D, et al. Neuromuscular electrical stimulation increases muscle protein synthesis in elderly type 2 diabetic men. Am J Physiol Endocrinol Metab. 2012; 303(5): E614–E623.
183. Wang P, Tian H, Zhang J, Qian J, Li L, et al. Spaceflight/microgravity inhibits the proliferation of hematopoietic stem cells by decreasing Kit-Ras/cAMP-CREB pathway networks as evidenced by RNA-Seq assays. FASEB J. 2019; 33(5):5903–5913.
184. Wenger HA, Bell GJ. The interactions of intensity, frequency and duration of exercise training in altering cardiorespiratory fitness. Sports Med. 1986; 3(5):346–356.
185. Wernbom M, Apro W, Paulsen G, Nilsen TS, Blomstrand E, Raastad T. Acute low-load resistance exercise with and without blood flow restriction increased protein signalling and number of satellite cells in human skeletal muscle. Eur J Appl Physiol. 2013; 113(12):2953–2965.
186. Wernbom M, Augustsson J, Raastad T. Ischemic strength training: a low-load alternative to heavy resistance exercise? Scand J Med Sci Sports. 2008; 18(4):401–416.
187. Willis SJ, Borrani F, Millet GP. High-intensity exercise with blood flow restriction or in hypoxia as valuable spaceflight countermeasures? Front Physiol. 2019; 10:1266.
188. Winnard A, Scott J, Waters N, Vance M, Caplan N. Effect of time on human muscle outcomes during simulated microgravity exposure without countermeasures—systematic review. Front Physiol. 2019; 10:1046.
189. Yasuda T, Abe T, Brechue WF, Iida H, Takano H, et al. Venous blood gas and metabolite response to low-intensity muscle contractions with external limb compression. Metabolism. 2010; 59(10):1510–1519.
190. Yasuda T, Fujita T, Miyagi Y, Kubota Y, Sato Y, et al. Electromyographic responses of arm and chest muscle during bench press exercise with and without KAATSU. Int J KAATSU Train Res. 2006; 2(1):15–18.
191. Yasuda T, Fujita S, Ogasawara R, Sato Y, Abe T. Effects of low-intensity bench press training with restricted arm muscle blood flow on chest muscle hypertrophy: a pilot study. Clin Physiol Funct Imaging. 2010; 30(5):338–343.
192. Yasuda T, Ogasawara R, Sakamaki M, Bemben MG, Abe T. Relationship between limb and trunk muscle hypertrophy following high-intensity resistance training and blood flow-restricted low-intensity resistance training. Clin Physiol Funct Imaging. 2011; 31(5):347–351.
193. Yin H, Price F, Rudnicki MA. Satellite cells and the muscle stem cell niche. Physiol Rev. 2013; 93(1):23–67.
194. Yong KW, Choi JR, Choi JY, Cowie AC. Recent advances in mechanically loaded human mesenchymal stem cells for bone tissue engineering. Int J Mol Sci. 2020; 21(16):5816.
195. Young LR, Oman CM, Watt DGD, Money KE, Lichtenberg BK. Spatial orientation in weightlessness and readaptation to Earth's gravity. Science. 1984; 225(4658):205–208.
196. Zhang J, Wang JHC. Human tendon stem cells better maintain their stemness in hypoxic culture conditions. PLoS One. 2013; 8(4):e61424.
197. Zhao J, Zhang P, Qin L, Pan XH. Hypoxia is essential for bone-tendon junction healing: The molecular biological evidence. Int Orthop. 2011; 35(6):925–928.
198. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol. 2005; 25(5):932–943.
199. Zwart SR, Davis-Street JE, Paddon-Jones D, Ferrando AA, Wolfe RR, Smith SM. Amino acid supplementation alters bone metabolism during simulated weightlessness. J Appl Physiol. 2005; 99(1):134–140.