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 neuroocclar 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

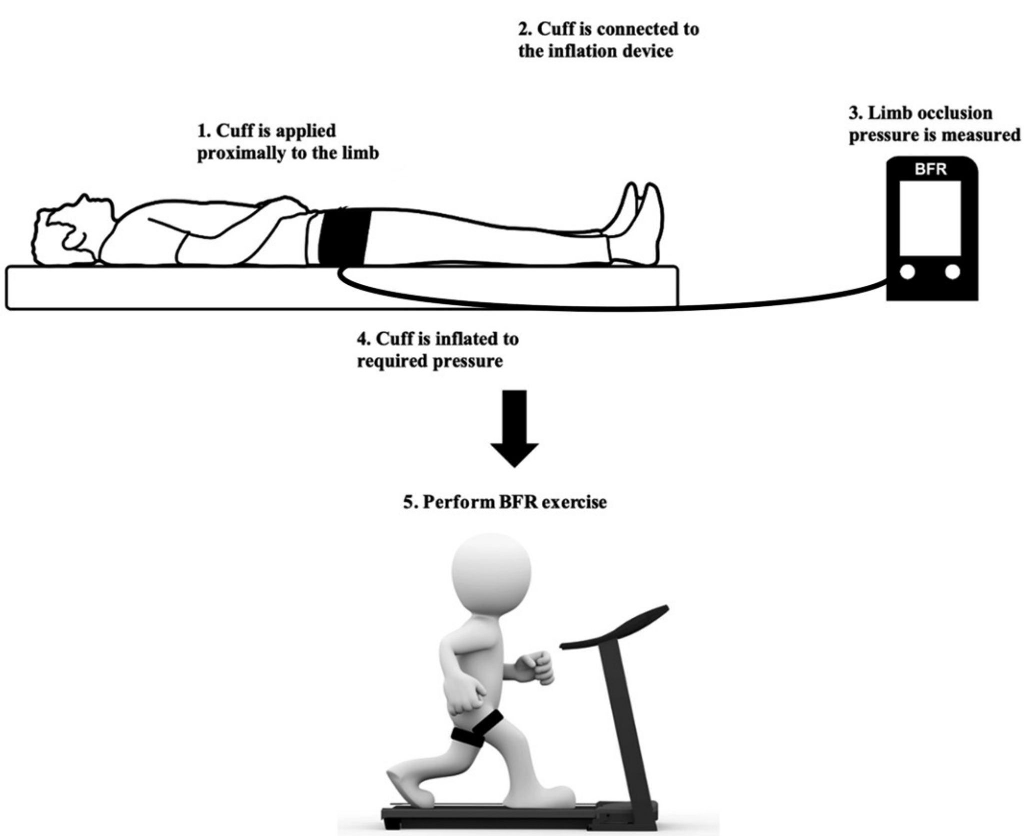

Fig. 1. Application of blood flow restriction exercise.

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 $\cdot$ L^{-1}), alongside a greater reduction in HCO_3^- (~24 to 20 mmol $\cdot$ 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 $\cdot$ 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 $\cdot$ 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]

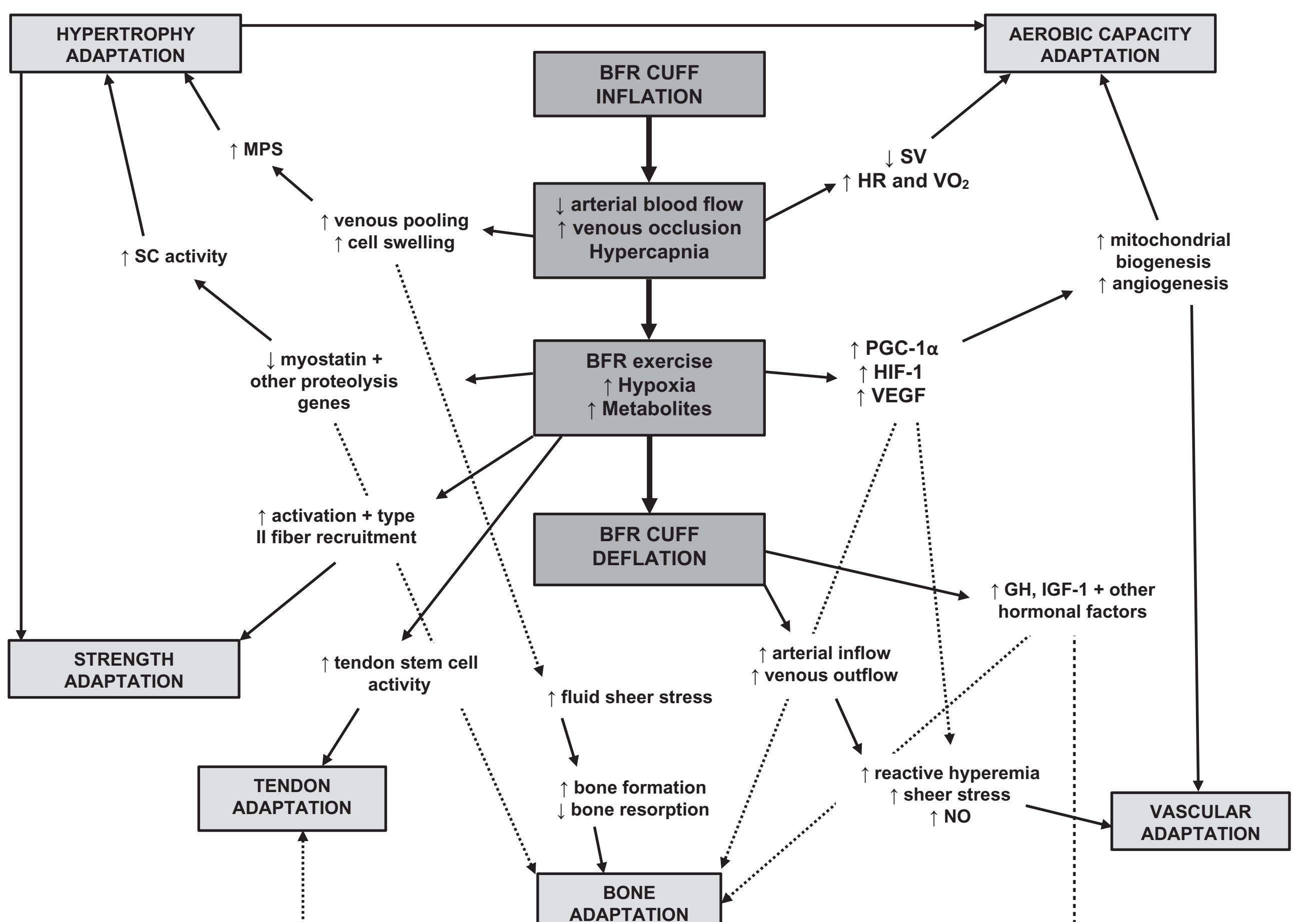

Fig. 2. The physiological effects of BFR exercise and possible mechanisms of adaptation.

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).

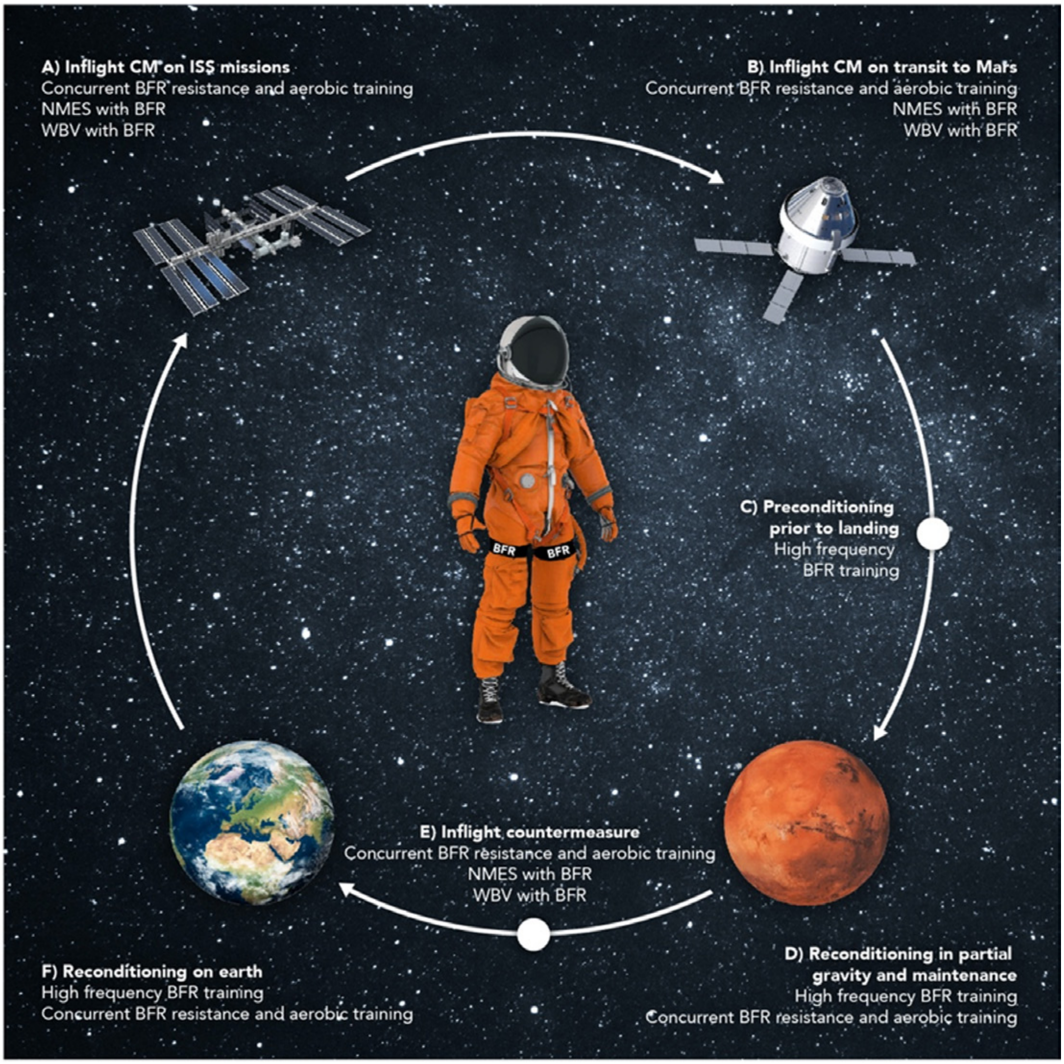

Fig. 3. The potential applications of blood flow restriction during spaceflight. CM, countermeasure; ISS, International Space Station; BFR, blood flow restriction; NMES, neuromuscular electrical stimulation; WBV, whole body vibration.

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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*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.

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