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Review

# Potential Role of Blood Flow Restricted Exercise for Older Adults

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**Abstract**

Sarcopenia is the age-related loss of muscle mass and strength which is associated with the loss of physical performance, lower quality of life, and other negative health outcomes. Resistance training (RT) is a recognized method to increase muscle strength and mass, however some older adults may be limited in their ability to perform RT with traditionally recommended higher-loads. Occluding blood flow to a limb, commonly referred to as muscle blood flow restriction (MBFR), has been investigated as an adjunct to RT to elicit muscle strength and hypertrophy adaptations while utilizing lower-loads of resistance as compared to traditional training recommendations. This technique could be of particular interest for older adults who may be limited in their ability to otherwise complete RT due to health reasons or may be debilitated due to a lack of muscle mass and strength. The aim of this narrative review is to discuss the current literature investigating the use of MBFR with and without a combination of exercise, in older adults and its effects on skeletal muscle strength, hypertrophy, and physical function.

**Keywords**
Muscle blood-flow restriction; hypertrophy; muscle strength; sarcopenia; older adults

## 1. Introduction

Aging is associated with the progressive loss of muscle mass and strength which is referred to as sarcopenia [1]. The decreased muscle mass, and strength result in loss of physical performance along with a lower quality of life and higher associated health care costs [2]. Sarcopenia is associated with negative health outcomes such as heart failure [3], respiratory disease [4], reduced functional capacity in daily activities [5], and an increased risk of falls and fractures [6]. Recently, under restrictions related to the COVID-19 pandemic, it has been suggested that confinement in the older populations has increased sarcopenia and frailty [7, 8] which could inhibit the older population's ability to prevent infection and lead to a poor prognosis if infected [9-12]. The underlying cause of sarcopenia is multifaceted and includes: lack of proper nutrition, physical inactivity, sedentary behavior, various types of diseases and/or iatrogenic effects of various drug treatments (e.g., long-term prednisone use which has a catabolic effect on skeletal muscle) [13]. Although the number of trials investigating various modes of exercise in individuals with sarcopenia is limited, and they utilize inconsistent exercise treatments, evidence supports the ability of exercise, especially resistance-exercise, to improve muscle mass and strength as well as balance [14].

Muscle blood flow restriction (MBFR) during exercise has been a concept around for a couple decades [15, 16] and involves the application of an inflatable cuff to the proximal aspect of an exercising limb to inhibit the arterial inflow and venous outflow of blood [17]. The partial occlusion of blood flow results in hypoxia of the exercising skeletal muscle [18, 19] as well as blood pooling [17]. Mechanistically, it has not been fully explained how MBFR induces beneficial effects compared to load-matched exercise without MBFR; however, several mechanisms of action have been proposed. MBFR results in an ischemic environment until the pressure is released and blood flow reperfusion and hyperemia occur resulting in increased nutrient delivery to the muscle post-exercise [20]. However, reactive hyperemia and nutrient delivery are not the primary stimuli for mammalian target of rapamycin complex 1 (mTORC1) and muscle protein synthesis which are upregulated post-MBFR exercise in older and younger adults [20-22]. Even though hyperemia and nutrient delivery are not the primary stimuli, mTORC1 stimulation and muscle protein synthesis still occur with MBFR [21, 22]. Metabolic stress is known to contribute to skeletal muscle adaptations associated with traditional resistance training [23], MBFR with low-load resistance training results in lactate accumulation in older and younger adults [24, 25] which may stimulate muscle hypertrophy. In cell cultures, C2C12 muscle cells incubated with lactate display increased follistatin and myogenin expression, and decreased myostatin expression [26] which all contribute to a positive environment for muscle hypertrophy. Muscle hypoxia induced during MBFR has also been postulated to contribute to muscle adaptations. Following aerobic exercise with MBFR hypoxia-inducible factor-1α (HIF1α) is upregulated [27]. However, it appears that hypoxia-inducible factors HIF1α and HIF2α do not contribute to normal muscle development [28]. More recently, the secretion of myokines in response to resistance training with and without MBFR has been investigated [29]. One study compared high-load resistance training, low-load resistance training and low-load resistance training with MBFR and found no difference in systemic decorin, interlukin-6 (IL-6), or IL-15 concentrations between conditions [29]; however, further studies are needed to fully understand the role, if any, myokines play mechanistically with MBFR training [30]. Many mechanisms have been postulated for the beneficial skeletal muscle adaptations in response to MBFR, but the role and level of contribution of each has not been fully elucidated.

The utilization of MBFR can result in increased skeletal muscle hypertrophy and strength for younger and older adults when combined with low-load resistance training (for systematic reviews and meta-analysis see [31-36]). The combination of resistance training with MBFR enhances skeletal muscle adaptations, however a lower load is required than those utilized with traditional resistance training programs. Therefore, MBFR training could be beneficial for individuals who could be unable or unwilling to complete traditional heavy-load training such as older adults and in the rehabilitative setting. Further, muscle has been deemed an endocrine organ which could be important in maintaining physiological homeostasis and communicating with other tissues [37]. As older adults are at increased risk of muscle mass loss, maintaining or improving muscle mass is vital for overall health. Resistance training with MBFR has been deemed an effective alternative to high-intensity resistance training exercise. Thus, the purpose of this narrative review is to evaluate and compare the current literature investigating the use of MBFR technology in the aging population and its influence on muscle strength, hypertrophy, and physical performance.

## 2. Discussion

### *2.1 Muscle Strength, Hypertrophy, and Functional Capacity Adaptations with Resistance Training and MBFR*

A study by Thiebaud et al. [38] investigated resistance training in non-active post-menopausal older women (age = 61 ± 5 yrs) who completed either elastic band resistance training (RT; n = 8; 3 sets of 10 repetitions (reps) at 7 to 9 on the OMNI Resistance for Active Muscle scale (~70-90% of their one repetition maximum (1-RM)) or low-load RT with MBFR (n = 6; 1 set of 30 reps followed by 2 sets of 15 reps completed at ~10-30% 1-RM) which progressed from 80 to 120 mmHg of pressure over 8 weeks. Although not explicitly stated, participants were medically cleared to participate in the study by a physician suggesting they were generally healthy. The exercises performed included seated chest press, seated row and seated shoulder press for the upper body, and knee extension, knee flexion, hip flexion, and hip extension for the lower body. They found that muscle thickness (measured with ultrasound) increased in the pectoralis major and upper thigh adductors following training with no difference between the groups. The finding that there was no difference between groups in muscle thickness of the pectoralis major is interesting as the pectoralis muscle group is proximal to the application of occlusion, while it would be expected the MBFR would elicit effects distal to the point of application. Additionally, both groups improved muscle strength to a similar extent. This suggests that the low-load RT with MBFR stimulates similar hypertrophy and strength adaptations to elastic band training in older women.

The following year, Yasuda et al. [39] published a study which supports the benefit of MBFR combined with low-intensity RT. Healthy older adults were recruited to complete either MBFR RT (male, n = 3 and female, n = 6; age = 71 ± 7 yrs) or be a non-exercising control (male, n = 2 and female, n = 8; age = 68 ± 6 yrs). The MBFR RT group completed leg extension and leg press exercises, 2 days/wk for 12 wks (30, 20, 15 and 10 reps for a total of 4 sets) at a load of 20% 1-RM for leg extension and 30% for leg press with cuff pressures progressing from 120 mmHg to 270 mmHg over the training period (pressure increased 10-20 mmHg with each subsequent training session). The MBFR RT resulted in increased 1-RM strength for leg extension (26.1% increase) and leg press (33.4% increase) and increased cross sectional area (determined with magnetic resonance imaging (MRI)) of the quadriceps (8.0%), adductors (6.5%) and gluteus maximus (4.4%), but not the hamstring muscles. As only lower limb measurements were included in the aforementioned study, the same group followed it up looking at the effects of MBFR on the arms [40]. The authors compared two groups of healthy older adults who performed low-load arm biceps curls and triceps exercises (completing 4 sets, with one of 35 reps and the remaining with 15 reps 2 days/wk for 12 wks) with an elastic band, with one group equipped with MBFR on the proximal aspect of both arms (male, n = 2 and female, n = 7; age = 72 ± 6 yrs; pressures progressing from 120 mmHg to 270 mmHg) and the other without MBFR (male, n = 1 and female, n = 7; age = 68 ± 5 yrs). The group who completed the training with MBFR increased muscle cross-sectional area (measured with MRI) and isometric contraction of their elbow flexors and extensors, while the other group did not. Of interest, to compare the relative exercise load, the authors assessed surface electromyography (EMG) during an acute bout of both low-load RT with and without MBFR and identified a greater integrated EMG ratio of agonist muscles with MBFR suggesting a greater relative exercise load. A limitation of this study was the lack of comparison to a moderate- to high-intensity resistance training program. Yasuda et al. [41] subsequently observed changes in muscle cross-sectional area (determined by MRI) and maximal strength of thigh muscles in healthy older women. Participants were divided into one of three treatments arms: 1) low-intensity elastic band training with MBFR (n = 10; age = 70 ± 6 yrs; approximately 35%-45% 1-RM; 4 sets were completed consisting of 30, 15, 15, and 15 reps; MBFR pressure progressing from 120 mmHg to 200 mmHg by the last training session as tolerated), moderate-to high-intensity elastic band training without MBFR (n = 10; age = 72 ± 7; approximately 70%-90% of 1-RM; 3 sets totaling 37-38 reps resulting in half the volume of the MBFR group) or a control group which completed no training (n = 10; age = 68 ± 6 yrs). The intervention consisted of two RT sessions per week for 12-weeks. Both groups that completed training saw improvements in leg press 1-RM and anterior mid-thigh muscle thickness (measured by ultrasound). However, the group which completed low-intensity RT with MBFR experienced greater improvements in cross-sectional area (determined by MRI) of the quadriceps muscle (6.9% increase) and maximal voluntary knee extension isometric contraction (13.7% increase), while no changes were observed for the other two groups.

A study by Libardi et al. [42] supports the finding that low-load RT with MBFR can induce similar changes in muscle mass and strength to traditional training in healthy older adults (n = 25; age = 64.7 ± 4.1 yrs). However, a slight difference in this study is the training protocol included an endurance training component 2-days per week (30-40 min at 50%-80% $VO_{2peak}$ with neither group utilizing MBFR during this component) in addition to the RT 2-days per week (leg press; traditional training, 4 sets of 10 reps at 70%-80% 1-RM and low-load MBFR, 1 set of 30 reps followed by 3 sets of 15 reps at 20%-30% 1-RM; occlusion pressure of 50% of maximal tibial arterial pressure (mean = 67 ± 8.0 mmHg)) for 12-weeks. Results demonstrated that both traditional and low-load MBFR RT induce similar increases in quadriceps cross-sectional area (traditional = 7.3% and MBFR RT = 7.6%) and maximal leg press strength (traditional = 38.1% and MBFR RT = 35.4%).

A small study by Silva et al.[43] found that in older women (n = 15; age = 62.2 ± 4.53 yrs) with osteoporosis, both low-load RT (4 set of reps to fatigue (mean = 7.0 ± 3.38 reps to fatigue) at 30%

1-RM for unilateral leg extension) with MBFR (occlusion pressure set at 80% of complete tibial artery occlusion (mean 104.2 ± 7.88 mmHg) and more high-intensity RT (4 sets of reps to fatigue (mean = 8.0 ± 2.01 reps to fatigue) at 80% 1-RM for unilateral leg extension) completed 2-days per week for 12-weeks both increased maximal leg extension strength (high intensity RT = 34.5% and low-load MBFR RT = 10.59%). Statistically there was no difference between the RT groups, however the high intensity training resulted in an absolute strength change twice as large as low-load RT with MBFR (Δ in 1-RM Pre-RT to Post-RT, Traditional RT = 9.59 kg vs. low-load MBFR RT = 4.55 kg). These findings suggest that larger studies, with increased statistical power, could be of value to determine the differences in strength adaptations with the two RT methods and if significant differences are present.

There is some research indicating that MBFR RT may not induce strength adaptations to the same extent as traditional RT in older adults. Vechin et al. [44] recruited healthy older adults (male, n = 14 and female, n = 9; age = 64.04 ± 3.81 yrs) who completed RT at a load of 80% of their 1-RM (4 sets of 10 reps) or RT with MBFR (occlusion pressure at 50% maximum tibial arterial pressure) at a load of 30% 1-RM (1 set of 30 reps followed by 3 sets of 15 reps) twice per week for 12-weeks. Both RT groups improved quadriceps muscles cross-sectional area (determined with MRI; traditional RT = 7.9% and low-load MBFR = 6.6%), however the group which completed traditional RT increased their 1RM leg press (~54% increase) but the low-load MBFR group did not (~17% increase, p = 0.067). The authors conclude that RT with a low-load and MBFR is effective to induce hypertrophic adaptations, but does not increase strength to the same extent as traditional RT.

Similar results were found in a group of older males and females (male, n = 15 and female, n = 21; mean age = 75.6 yrs (range: 69-82 yrs)) who performed either traditional RT (3 sets of reps to failure at 70% 1-RM, with loads increased when participants could complete more than 15 reps for 2 sets) or low-load MBFR RT (3 sets of reps to failure at 30% 1-RM for leg extension and leg curl, 50% 1-RM for leg press (loads were increased when more than 30 reps could be completed for 2 sets) with an occlusion pressure at 1.5 times brachial systolic blood pressure (mean occlusion = 184 ± 25 mmHg)) for the knee extensors and flexors twice per week for 12-weeks [45]. Participants were at risk of mobility limitations but medically cleared following a cardiac stress test prior to participation. The authors reported that at 6-weeks both RT methods increased strength and quadriceps cross-sectional area (determined with MRI), however the traditional RT increased 1-RM strength to a greater extent as well as increase maximum isometric voluntary contraction and strength-to-weight ratio which were not improved in the MBFR condition. By 12-weeks the traditional RT and low-load MBFR RT both improved leg-extension and leg-press 1-RM as well as quadriceps cross-sectional area. However, the traditional RT group also improved leg-curl 1-RM, maximal isometric voluntary contraction, and strength-to-weight ratio, while their improvement in leg-extension strength was greater than that found with low-load MBFR RT. Unfortunately, the authors found that increased muscle mass and strength did not result in improved physical function measured with the Short Physical Performance Battery or 400 metre walk test. The same research group [46] conducted another study in older adults at risk of mobility limitations (traditional RT, n = 11 (5 male and 6 female) and age = 76.3 ± 8.7 yrs; low-load MBFR RT, n = 10 (4 male and 6 female) and age = 76.4 ± 6.6 yrs) utilizing the identical protocol as the previously discuss study [45]. It was found that the traditional training resulted in greater knee extension 10-RM strength compared to low-load MBFR RT, but no differences were found in isometric maximum voluntary contraction between groups. Both groups experienced similar increases in quadriceps cross-sectional area (determined with MRI) (traditional RT = 6.5 ± 3.1% increase vs. low-load MBFR RT = 7.8 ± 8.2% increase). The authors postulate that the differences observed in 10-RM strength following the training could be due to the greater load utilized in traditional training or the faster rate of load progression over the 12-week period, along with the specificity of the testing modality.

In contrast to the study by Cook et al. [45], Letieri et al. [47] observed that low-load RT with MBFR is beneficial. Women were randomized into either a control group (n = 12; age = 69.0 ± 6.39 yrs) or a low-load RT with MBFR group (n = 11; age = 69.4 ± 5.73 yrs). The health status of participants was not explicitly stated but all individuals were medically cleared by a physician prior to participation. The RT group trained 3 times per week for 16-weeks performing 4 sets of 30, 15, 15 and 15 reps at 20%-30% 1-RM at an occlusion pressure equal to 80% of that which results in complete tibial artery blood flow interruption. The RT with MBFR resulted in improved handgrip strength, chair stand, arm curl, 2.44 m timed up-and-go, 6-min walk, sit-and-reach and back scratch test results. These results suggest the low-load RT with MBFR is sufficient in improving physical function of older women, but does not indicate if these adaptations are less, similar, or better than those observed with traditional RT protocols.

A more recent study by Bigdeli et al. [48] found that functional training with or without MBFR improved knee extension and chest press strength, modified Romberg, timed up and go, and chair sit and reach tests to the same extent with no difference between groups. The authors randomized healthy older men (n = 30; age = 67.7 ± 5.8 yrs) to perform functional training (including 11 exercises in a circuit format which included lower, upper and core muscle groups each performed for 10 reps and progressing from 2 sets to 4 sets for the final two weeks of training), functional training with MBFR (progressing from estimated 50% arterial occlusion pressure to 70% arterial occlusion pressure for the last two weeks of training) 3 times per week for 6-weeks, or to a control group. The exercise intensities progressed in intensity every two weeks (ie. Week 1-2 25% 1-RM, week 3-4 30% 1-RM, and week 5-6 35% 1-RM). However, the training resulted in reductions in C-terminal Argin Fragment, with the MBFR group demonstrating greater reductions, while reductions in N-terminal propeptide type III collagen were found in the group that trained without MBFR and control but was maintained in the MBFR group. The authors suggest that these findings indicate improved muscle quality indices with MBFR functional training compared to functional training alone.

The lack of consistency in multiple factors (i.e., training protocol, muscles of interest) including occlusion pressure may contribute to some of the variability in findings. Letieri et al. [49] randomized healthy, older, recreationally active women (n = 56; age = 68.8 ± 5.09 yrs) to one of five groups: 1) low-load RT (4 sets of 30, 15, 15 and 15 reps at 20%-30% 1-RM) with high occlusion pressure MBFR (mean occlusion pressure = 185.75 ± 5.45 mmHg), 2) low-load RT with lower occlusion pressure MBFR (mean occlusion pressure = 105.45 ± 6.5 mmHg), 3) traditional higher-load RT (3-4 sets of 6-8 reps at 70%-80% 1-RM), 4) low-load RT without MBFR, and 5) control. The exercise groups training included squats, leg press, knee extension and leg curls completing 3 training sessions per week for 16-weeks. All RT groups apart from low-load RT without MBFR improved their strength (maximal isokinetic torque) over the training period. However, the authors note that higher MBFR occlusion pressures are more effective than lower pressures for inducing strength changes (right leg extension, high MBFR = 27.2% vs. low MBFR = 15.75%; right leg flexion, high MBFR = 36.7% vs. low MBFR = 22.79%). These results suggest the lack of consistency in occlusion pressures utilized during RT with MBFR may contribute to some of the variability in study findings.

Additionally, the type of RT protocols being compared could be of importance. Shimizu et al. [50] compared a low-load RT program (leg extension, leg press, rowing and chest press performed at 20% predicted 1-RM; 3 sets of 20 reps) with MBFR (occlusion pressure of 100% of femoral systolic or brachial blood pressures at rest for lower and upper body exercises respectively) to a low-load RT program without MBFR performed 3 times per week for 4-weeks by healthy older adults (n = 40; age = 71 ± 4 yrs). The individuals who underwent low-load RT with MBFR increased their estimated 1-RM leg extension and leg press with training, but no adaptations were observed in the control group. Supporting these findings, a study by Patterson and Ferguson [51] used a within-subject design, where ten medically stable older adults (age = 67 ± 3 yrs) performed low-load plantar-flexion RT at 25% 1-RM (3 sets to maximal exertion) with MBFR applied (occlusion pressure of 110 mmHg) to one leg but not the other 3-times per week for 4-weeks. Training for the non-MBFR leg was performed after the MBFR limb and still consisted of 3 sets but the number of reps performed was matched to the number completed by the leg with MBFR. Training with MBFR resulted in greater maximal strength (MBFR = 14% vs control = 4% 1-RM improvements respectively), maximal voluntary contraction (MBFR = 18% vs control = 4% improvements respectively) and isokinetic torque at 0.52 rad/s (MBFR = 20% vs control = 0% improvements respectively).

### *2.2 Muscle Strength, Hypertrophy, and Functional Capacity Adaptations with Walk Training and MBFR*

So far, the studies discussed have evaluated the use of MBFR technology during RT protocols. However, there is some research investigating the benefits of MBFR of the lower limbs during walk training [52-57]. An early study by Abe et al. [52] found that including MBFR with treadmill walking (50 m/min; occlusion pressure progressed from 160-230 mmHg by day 8) performed twice per day, 6-days per week for 3-weeks increased thigh muscle cross-sectional area by 4-7% and isometric strength by 8-10%, while no changes were observed in the control group. However, this study was conducted in healthy younger adults (MBFR, n = 9; age = 21.2 ± 2.7 yrs vs. Control, n = 9; age = 21.5 ± 2.9 yrs), so a follow-up study was conducted to investigate the effects of walking with MBFR in older adults [53]. The follow-up study by Abe et al [53] had healthy older adults (n = 19; age range = 60-78 yrs) perform 20-minutes of treadmill walking (67 m/min) on 5-days per week for 6-weeks. Participants performed the exercise either with MBFR (occlusion pressure started at 160 mmHg and progressed to 200 mmHg by the final week) or without. The study found that individuals randomized to complete the walking with MBFR increased thigh and lower leg cross-sectional area (5.8% and 5.1%, respectively), and total and thigh muscle mass (6.0% and 10.7%, respectively), however changes were not observed in the control group. Additionally, the control group did not improve any measures of strength, while the MBFR group improved maximal isometric knee extension (11.8%) maximal isokinetic knee extension (7.1%-12.2% improvement at various testing speeds) and knee flexion strength (13.4%-16.1%).

In a group of healthy older adults who performed walk training (20 minutes walking on a treadmill at an intensity of 45% heart rate reserve) 4 times per week for 10-weeks, the group with MBFR applied to the proximal aspect of their legs (n = 13; age = 66 ± 1 yrs; occlusion pressure progressed from 140 mmHg to start and increased 10 mmHg each week until 200 mmHg) experienced increased thigh cross-sectional area (3% increase; measured with MRI) and knee extension (8.7% increase) and flexion strength (15.0% increase; determined with maximum isokinetic strength of the knee extensors and flexors) compared to no changes in the group which walked without MBFR (n = 10; age = 68 ± 1 yrs) [54]. These results were corroborated in another study by Ozaki et al. [55] where healthy older adults completed the same walk training previously described (20 minutes at 45% of their heart rate reserve) with either MBFR (140 mmHg occlusion pressure increasing by 10 mmHg each week until 200 mmHg is reached; n = 10; age = 64 ± 1 yrs) or without MBFR (n = 8; age = 68 ± 1 yrs) 4 days per week for 10-weeks. Participants who had MBFR included as part of their training had increased thigh muscle cross-sectional area (3.1%; determined by MRI) and volume (3.7%), as well as increased maximal isometric knee extension (5.9%) and isokinetic knee flexion (22.3%) and extension (8.4%) strength, while the control group saw no changes. Additionally, the authors evaluated physical function and found that the MBFR group improved their Up and Go test (-10.7% change in time) while no change was observed in the control group, with neither group experiencing changes in their chair stand test.

Clarkson et al. [56] recruited sedentary, but otherwise healthy, older men and women (n = 19) who performed either low-intensity walking with MBFR (age = 69 ± 6 yrs; 10-min walking at 4 km/hr with MBFR at 60% of limb occlusion pressure) or walking without MBFR (age = 70 ± 7 yrs; 10-min walking at 4 km/hr) for 4 times per week for 6-weeks. The authors found that the MBFR condition reported a higher perceived exertion for the exercise, but experienced greater improvements in 30-sec sit-to-stand, 6-min walk test and timed up-and-go (2.5-4.5 fold greater improvement) compared to control.

Incorporating MBFR with walking programs may also benefit mobility in special populations of older adults beyond those which are overall "healthy". Lamberti et al. [57] investigated the use of MBFR in older adults (n = 24; age = 58 ± 5 yrs) with progressive multiple sclerosis. Participants were randomized to either the control group (which performed physiotherapist-assisted walking for 40 minutes) or MBFR with walking (occlusion pressure of 30% of systolic pressure) twice per week for 6-weeks. The MBFR walking consisted of participants completing three 1-minute walks (pace starting at 60 steps per minute) followed by 1-minute of rest. Following the last 1-minute walk a 3-minute rest was provided and the participants repeated this process for a total of 5 times (5-times, 1-minute of walking: 1-minute of rest). It was determined that the group randomized to MBFR reported lower perceived exertion and heart rate than the control group, and although both groups improved gait speed the MBFR group saw greater improvements (control = 5% increase vs. MBFR = 13% increase). The MBFR group also improved their 6-minute walking distance, 5 sit-to-stand time, Modified Fatigue Impact Scale scores (MFIS) and 36-item short form survey (SF-36), while the control group improved their 6-minute walking distance, MFIS and SF-36 with no difference between groups. These findings suggest that although the individuals performing the MBFR walking treatment completed a lower training load, they experienced similar improvements to the control exercise with greater benefits in gait speed.

One study has compared the effects of MBFR with walking to MBFR with low-intensity RT and traditional high-intensity RT in older women (age = 61.4 ± 4.6 yrs; with osteoporosis) [58]. Twenty females were randomized to complete either a control condition (no exercise), walking with MBFR (15 minutes at 65% of maximal heart rate on a treadmill), low-intensity RT with MBFR (4 sets of unilateral knee extension to failure at 30% of 1-RM), or high-intensity RT (4 sets of unilateral knee extension to failure at 80% of 1-RM). Training sessions were performed twice per week for 12 weeks and occlusion pressure was set at 80% of pressure required to obstruct auscultatory pulse of the posterior tibial artery. All groups except for the control group improved their maximal strength as determined by their knee extension 1-RM from the start to end of the training protocol (walking and MBFR = 21.6% increase, low-intensity RT and MBFR = 24.2% increase, and high-intensity RT = 62% increase) with no statistical differences between training groups. These results suggest that walking with MBFR results in comparable increases in leg extension strength as low-intensity RT with MBFR and high-intensity RT.

Overall, the inclusion of MBFR during walking exercise appears to benefit skeletal muscle adaptations compared to walking under normal (non-occluded) conditions for older adults. When MBFR is included with RT, adaptations are variable. However, including MBFR with low-load RT appears to induce similar hypertrophic effects but lower strength gains compared to traditional high-load RT for older adults. The use of various cuff pressures and sizes to induce occlusion, exercise volume and frequency, and biological sex are all potential moderators which should be investigated in future studies to determine their influence on outcome measures for muscle mass, strength and physical function.

### *2.3 Blood Flow Restriction at Rest and with Passive Movement*

There has also been interest in the potential use of MBFR technology in settings where RT or aerobic exercise is not actively incorporated, however the studies specific to older adults are limited. In a study by Gorgey et al. [59] the effects of MBFR when included with neuromuscular electrical stimulation (NMES) in a group of men (n = 9) with incomplete tetraplegia following spinal cord injury was completed. Participants completed training for the wrist extensor muscles with NMES two times per week for 6-weeks, with the right arm having MBFR (occlusion pressure 30% of systolic blood pressure at rest) as well. Following training the cross-sectional area (determined with ultrasound) of the extensor carpi radialis longus muscle was greater in the arm which received MBFR (15% increase from pre-training and 17% greater than control arm). However, this study may have included some younger adults as the mean age was not indicated but the age range of eligibility was 18-65 yrs. Barbalho et al. [60] utilized a within subject design and randomly assigned one lower limb to receive MBFR during passive mobilization and the other limb passive mobilization alone in a group of intensive care unit patients who were in a coma (n = 20; age = 66 ± 4.3 yrs). The limb which received MBFR was occluded at a pressure of 80% of the patient's systolic pressure at the anterior tibial artery. The passive mobilization protocol consisted of 3 sets of 15 repetitions of knee flexion and extension movements. The intervention was performed until there was an interruption in sedation and the patient had independent control of their limbs (mean intervention length of 11 ± 2.2 days). Although, muscle atrophy occurred in both limbs the limb which received MBFR during passive mobilization had a lesser decrease in thigh circumference (control = 7.4% vs. MBFR = 5.2%) and muscle thickness (control = 25.4% vs. MBFR = 18.8%; determined with ultrasound).

Further research into the use of MBFR technology in times of immobilization or other passive or electrically stimulated movements in older adults. In younger populations there is some evidence to suggest that MBFR could be potentially useful to counteract strength loss and atrophy during immobilization (for a systematic review see [61]), however the evidence is still limited in younger adults.

### *2.4 Safety Considerations*

Although MBFR is generally deemed safe when carefully implemented [62], we must acknowledge the possible risks associated with its use. Implementation of MBFR results in several physiological responses which could result in unsafe outcomes for some individuals, and thus, may be contraindicated in certain cases. It has been suggested that the implementation of MBFR combined with exercise may result in the overactivation of the sympathetic nervous system due to increased muscle reflex and central command activity [63]. Although MBFR is often utilized with relatively lower-load exercise, it is suggested due to the impedance of vascular perfusion participants experience a similar mechanoreflex and metaboreflex induced activation of the sympathetic nervous system observed with high-load exercise [63]. Additionally, MBFR used following orthopaedic surgery may be of higher risk due to the patients increased risk of venous thromboembolism [64]. It has been proposed that the likelihood of MBFR directly causing a venous thromboembolism event is low, however, it is possible that MBFR may result in mobilization of a pre-existing venous thromboembolism and patients should be carefully screened for contraindications for the use of MBFR following orthopaedic surgery [64]. Ensuring appropriate pre-screening, methodology and application of MBFR is of utmost importance whether used with RT, aerobic training or in a passive manner (for a review see [17]). Some laboratories have successfully implemented MBFR interventions for individuals with Parkinson disease [65], chronic kidney disease [66, 67] and multiple sclerosis [57, 68], as well as following spinal cord injury [59], with results appearing to suggest the technique is tolerated and possibly beneficial, however evidence is still lacking for other diseased states. Although limited evidence exists for the use of MBFR in clinical populations, a risk stratification model has been proposed to identify risk factors prior to participating in exercise programs utilizing MBFR [69].

### *2.5 Limitations to the Existing Research*

The existing literature examining the use of MBFR is highly variable in methodologies for both occlusion parameters (cuff width, pressure and devices) as well as training programs; however, guidelines have been generated to address some of these considerations [17]. As described within this manuscript, the literature has used both absolute [38-41] and relative methods [42-44] for prescribing the pressure utilized during MBFR. It is suggested that higher cuff pressures induce greater discomfort [70, 71] and therefore pressures relative to arterial occlusion pressure should be used, with evidence supporting pressures in the range of 40-80% [17]. The width of the cuff utilized for the occlusion is also an important factor which influences the pressure required to reach a desired arterial occlusion pressure [72]. Evidence suggests that a given pressure applied to two different sized cuffs elicit different MBFR [73]. Various cuff materials are also utilized in the literature (pressure cuffs, elastic wraps, KAATSU bands, or/and pressure belts); however, we are unaware of any studies directly comparing the effectiveness of different cuff materials in older adults.

Given the limited research in older adults, the heterogeneity of exercise modalities and protocols makes interpretation difficult. Studies have utilized RT modalities from elastic bands to more traditional resistance equipment as well as protocols training a single exercise (i.e., leg extension), only upper or lower body, or a full body protocol (upper and lower body). These variations make the comparison of results between studies difficult. Another limitation of many studies is that they do not include a low-load RT group without MBFR to compare adaptations specific to the RT load. A current area which has not been well investigated in MBFR research, in young or older participants, is the potential sex differences in response [74]. There is some evidence suggesting sex differences exist for some physiological responses to MBFR but further investigation is needed [75].

### *2.6 Practical Considerations*

As MBFR with exercise seems to effectively enhance skeletal muscle hypertrophy, strength, and functional ability, its practical use should be considered in the older adult population. As emphasized in the Safety section above, screening older adult clients for a variety of disease states and reviewing their medical history is essential to avoid placing the client at undue risk because of underlying conditions/diseases that may be present. A recent published review manuscript suggests that those clients with impaired blood coagulability, those with established cardiovascular disease, and those with compromised antithrombotic mechanisms in the endothelium should avoid the use of MBFR [69]. Other healthy older adults could proceed with undertaking MBFR combined with exercise if they are supervised by a qualified exercise professional. If older adults are averse to completing high load resistance exercise, low-load resistance exercise with MBFR may be an option for them to see similar gains in muscle hypertrophy and some improvements in muscle strength. The pressure exerted by the cuffs used to induce blood flow restriction have previously been recommended to be between 40-80% of arterial occlusion pressure in healthy adults [17]. This is likely to be similar in older adults although more research on this topic is required [76]. A typically used resistance-exercise protocol using MBFR is to prescribe 1 set by 30 repetitions and then 3 further sets with 15 repetitions with 30-60 seconds of rest between sets and blood flow restriction on the entire duration of the 4 sets [17]. The pressure would then be released to the blood flow restricted limb to allow reperfusion of the affected limbs. The frequency of use is recommended to be between 2-3 times per week with 20-40% of 1-repetition maximum load being used [17]. Overall, the practical aspects of using MBFR with exercise have been covered very well by previous reviews on the topic and the interested reader is referred to them [17, 76].

## 3. Conclusions

The current literature investigating the use of MBFR in older adults to induce muscle hypertrophy, strength and improve physical functioning is limited. Current evidence supports the potential for MBFR when combined with low-load RT to induce skeletal muscle hypertrophy to a similar extent as traditional higher-load RT but may not result in strength adaptations to the same extent. Even though the increases in strength may not be as great as compared to traditional high-load RT, these adaptations are still of importance for older adults who may experience sarcopenia. Additionally, although the literature is even more limited than that investigating RT with MBFR, incorporating MBFR with walking appears to result in beneficial adaptations in muscle strength and hypertrophy of lower limbs, and may result in improved physical functioning for older adults. The use of MBFR during times of immobilization or during passive mobilization requires more investigation, but initial studies show promise for decreasing muscle mass loss caused by disuse. Prior to initiating MBFR interventions for older adults, appropriate pre-screening and monitoring during exercise should be ensured to minimize any risk of the occurrence of an adverse event. Due to the effects sarcopenia directly has on skeletal muscle and its associated health outcomes, additional studies investigating the use of MBFR technology with RT, walking, or immobilization would be advantageous and progress the evidence that it is a tool for treatment.

## Author Contributions

All authors contributed to conceptualization and writing of the original manuscript and have reviewed and agreed to the published version of the manuscript.

## Competing Interests

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