DR NICOLA LAMBERTI (Orcid ID : 0000-0001-5763-3069)

DR HIROFUMI TANAKA (Orcid ID : 0000-0002-1780-7471)

Article type : Original Article

Title: Effectiveness of blood flow-restricted slow walking on mobility in severe multiple sclerosis: a pilot randomized trial

Running head: blood flow restricted walking in MS

Authors

Lamberti Nicola[a], Straudi Sofia[b], Donadi Maria[b], Tanaka Hirofumi[c], Basaglia Nino[b], Manfredini Fabio[a,b].

Authors' affiliations

[a] Department of Biomedical and Surgical Specialties Sciences, Section of Sport Sciences. University of Ferrara, Ferrara, Italy. Via Luigi Borsari 46; 44121 Ferrara, Italy. nicola.lamberti@unife.it; fabio.manfredini@unife.it

[b] Neuroscience and Rehabilitation Department, Ferrara University Hospital, Ferrara, Italy. Via Aldo Moro 8; 44124 Ferrara, Italy. sofia.straudi@gmail.com; marydnd96@gmail.com; nino.basaglia@unife.it

[c] Cardiovascular Aging Research Laboratory, Department of Kinesiology and Health Education, The University of Texas at Austin, Austin, TX, USA. htanaka@austin.utexas.edu

Corresponding author

Dr. Nicola Lamberti, PhD

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/SMS.13764

Department of Biomedical and Surgical Specialties Sciences, Section of Sport Sciences, University of Ferrara. Via Luigi Borsari 46, 44121, Ferrara, Italy

e-mail: nicola.lamberti@unife.it

Phone: 0039 0532236187

Acknowledgements

We thank Dr. Andrea Baroni, Silvia Borsato, Tatiana Nesterova and Gian Maria Biral for their contribution to the supervision and rehabilitation of the patients.

Conflict of interest

The authors declare that they have no competing interests.

Abstract

Objective: We tested the safety, feasibility and effectiveness of blood flow restriction-empowered low-intensity interval walking exercise (BFR-W) compared with conventional intensive overground walking (CON-W) at improving gait speed and functional capacity in patients with multiple sclerosis (MS) and severe gait disabilities.

Methods: 24 patients (58±5 years; 7 males) with progressive MS (Expanded Disability Status Scale 5.5–6.5) were randomized to receive 12 rehabilitation sessions over 6 weeks. The BFR-W group (n=12) performed interval walking (speed paced by a metronome that increased weekly) with BFR bands at the thighs. The CON-W group (n=12) received physiotherapist-assisted overground walking therapy. The primary outcome was gait speed, measured by the timed 25-foot walk test. Secondary outcomes included walking endurance, balance, strength, fatigue and quality of life. The measurements were collected at baseline, at the end of training and a 6-week follow-up.

Results: The two groups did not present any baseline difference. BFR-W group safely walked without limitations due to sleeve compression, with lower increase of perceived exertion (RPE) ($p<0.001$) and heart rate ($p=0.031$) compared with the CON-W. Gait speed improved significantly in both groups (BFR-W +13%; CON-W +5%) with greater increases in the BFR-W group at end of the training ($p=0.001$) and at the follow-up ($p=0.041$). Most of the secondary outcomes significantly improved in the two groups, without between-group differences.

Conclusions: Slow interval walking with moderate BFR to the lower limbs was superior to overground walking in improving gait speed in patients with MS with a lower training load and a more durable clinical benefit.
Registration number: Clinicaltrials.gov NCT03544177

Keywords: exercise therapy; mobility; rehabilitation; exercise testing

Introduction

Multiple sclerosis (MS) is a progressive or relapsing neurological disease affecting the central nervous system. Muscle fatigue, weakness, spasticity, and impaired balance severely limit the physical activity and mobility in patients with MS[1]. These conditions lead to impaired coordination of posture and gait, a higher risk of falling, decreased quality of life, depression and a sedentary lifestyle[1-4]. Moreover, these patients have an increased risk of developing cardiovascular diseases, obesity, osteoporosis, and diabetes. Accordingly, mobility represents a primary focus of rehabilitation and clinical care for individuals with MS[5].

Favorable effects on mobility, although mild at best and person-specific in nature, have been reported after low to moderate endurance training[2-3,6], physical therapy[2], aerobic overground or treadmill walking performed with body weight support[2-3,7] or robot assistance[8-9]. Additionally, resistance training is well tolerated and has been shown to be beneficial on muscle size and function[3,10]. Considering the substantial muscle weakness and the association between muscle strength and gait parameters observed in patients with MS[11], combined endurance and resistance training may reduce patients' gait disabilities. However, special measures should be considered[12] for increased exercise load and time since patients with MS are susceptible to exercise-induced fatigue, heat intolerance, and falling. In recent years, some authors have reported that increases in muscle size and strength similar to traditional high-intensity resistance exercise training are possible, regardless of the individual's age[13,14], with a low exercise training intensity when blood flow restriction (BFR) is applied to the exercising limbs by, for example, an inflated external blood pressure cuff. This training has been applied to favorably managing skeletal muscle atrophy[15,16] as well as in healthy subjects[17,18], in elderly[19] and in chronic diseases affecting mobility and inducing deconditioning[20,21]. However, to the best of our knowledge, no studies investigating the effects of BFR training on gait speed in patients with MS have been conducted, despite its potential benefits.

We hypothesized that in MS patients, BFR training associated with low-intensity intermittent structured overground walking may favorably improve walking speed. Purposely, we empowered a training program, previously developed and successfully tested among patients on dialysis, those with peripheral artery disease or stroke survivors. This program, shown to be associated with mild pain and fatigue, showed significant improvements in gait speed, endurance, balance and strength[22-27] and a lower rate of hospitalizations[28,29].

This pilot randomized controlled trial aims to test the effectiveness of BFR-empowered slow interval walking exercise compared with conventional overground walking training at improving gait speed and functional capacity in patients with MS and severe gait disabilities.

Methods

Study design

This pilot randomized controlled, parallel-group clinical trial was conducted at the Rehabilitation Clinic in the Operative Unit of Physical and Rehabilitation Medicine at Ferrara University Hospital in Ferrara, Italy. The study was approved by the Local Ethics Committee (149/17), and all participants provided written informed consent. The trial (Clinicaltrials.gov NCT03544177) is reported following Consolidated Standards of Reporting Trials guidelines.

Eligibility criteria

The inclusion criteria were as follows: men and women aged between 18 and 70 years; primary or secondary progressive MS and severe gait impairments defined by an expanded disability status scale (EDSS) score ranging from 5.5 to 6.5; no MS worsening in the three months prior to enrollment. The exclusion criteria were as follows: an inability to perform the timed 25-foot walk test; medical conditions interfering with the safe completion of the program; impaired cognitive function, as defined by a Mini-Mental Status Examination score of <24/30; muscle spasticity, as defined by a

Modified Ashworth Scale score of >3 or contractures that may severely limit range of motion or function; and changes in pharmacological therapy during the study.

Randomization and blinding

After the baseline data were collected, the participants were randomly assigned to receive experimental training or conventional intensive overground walking with a randomization scheme (1:1 ratio) set up in permuted blocks of 4 to ensure a similar number of participants and sex distribution between groups. A computer-generated allocation sequence managed by an external administrator was employed. The outcome assessor was blinded to the patient allocation results.

Exercise Interventions

The participants in both groups received twelve one-hour training sessions over a 6-week period, resulting in a 2 sessions/week pattern. Physiotherapists and exercise physiologists specifically trained by members of the research team carried out the exercise interventions.

For both groups, every training session began and ended with a 10-minute warm-up and cool-down period and core stretching exercises. Active and passive stretching exercises for calves, ischiocrural muscles, femoral quadriceps to increase flexibility were performed, along with frontal and lateral physiotherapist-assisted abdominal exercises to improve core stability.

Participants who were randomly assigned to the BFR walking (BFR-W) group, before each training session underwent the arm systolic blood pressure measurement in a seated position with a standard sphygmomanometer and stethoscope, to determine the theoretical degree of compression corresponding to the limb occlusion pressure. Then blood flow was restricted using 6-cm BFR bands (The Occlusion Cuff LTD, Somerset, UK) worn around the most proximal regions of both legs. With the patient standing, the cuffs were inflated to the 30% of the systolic blood pressure (e.g. cuff inflation = systolic pressure * 0.30). The appropriate degree of compression exerted by the BFR bands was verified by the sphygmomanometer connected to the cuffs. After BFR bands positioning and using their habitual device/orthosis, patients performed a session including 5 bouts of walking at a slow prescribed speed (starting from 60 steps/minute) that was maintained by a metronome. Each bout was based on a minute of walk followed by one minute of rest (seated on a chair) to be repeated three times. Once completed each bout, a fixed resting period of 3 minutes was provided before starting a new bout. The pressure was released at the end of every six-minute period, and it was maintained at 0 mmHg for the total duration of the three-minute resting time. Otherwise during the 1-minute resting pauses within every walking bout, the BFR pressure was checked, and adjusted to the proper value, if needed. During the training session, the heat rate was continuously measured by a pulse oximeter at the finger and the rate of perceived exertion RPE score was requested at the end of each minute of work. At the end of each session, the total distance walked was recorded and the average RPE calculated.

The progression of the training load, implemented weekly only if the previous level was well tolerated by the patients, was obtained by increasing the walking speed of additional 3 steps/minute; the degree of BFR remained constant throughout the training sessions.

Patients in the conventional intensive overground walking (CON-W) group performed assisted overground walking for a total of 40 minutes. The patients continuously walked with their habitual walking device on an indoor 60-meter corridor until an effort corresponding to a value of 8 out of 10 for the Borg's rating of perceived exertion was reached; then, they were allowed to rest in a sitting position. After a suitable rest period, when patients felt ready to start again, the training was resumed. At the end of each session, the total meters walked as well as the effective walking time was recorded. The design/representation of a training session is reported in figure 1.

In case of necessity to interrupt a session of the experimental treatment due to pain or discomfort in the region around and below the compression site, the operator noted this fact as an adverse event.

Outcome measures

The outcome measures were evaluated at three time points: at baseline (prior to the first exercise session, T0), at the end of the treatment (after the completion of 12 exercise sessions, T1) and at the follow-up (6 weeks after the end of the training program). The primary outcome measure was gait speed, which was assessed by the timed 25-foot walk (T25FW) test. The test was performed two consecutive times, with the patients equipped with their habitual orthoses and walking devices. The gait speed was obtained by averaging the speeds from the two trials[30,31].

The secondary outcome measures included: the 6-minute walking test, performed on a 22m walkway with the patient aiming at covering the most distance as possible without encouragement, with the possibility to slow down and rest if necessary[9,25,32]. Balance was also assessed through the 14-item Berg Balance scale[33,34] and lower limbs strength by the 5-time Sit-to-Stand test[35]. Finally, impact of

MS on fatigue and quality of life was evaluated through, the fatigue severity scale[36], the modified fatigue impact scale (MFIS)[37], the 36-item short-form health survey (SF-36)[38] and the MS impact scale-29[39].

Statistical analyses

To the best of our knowledge, this is the first trial using BFR training to improve gait speed in MS patients; therefore, a sample size calculation could not be performed. We performed a post hoc power calculation, which is reported in the results section.

Statistical analysis was conducted using the intention-to-treat analysis. Missing values, despite being negligible, were treated using the multiple imputation procedure. The data distributions were assessed with the Shapiro-Wilk test. The comparisons of the baseline characteristics were performed by independent samples t-tests, Mann-Whitney tests or chi-squared tests, as appropriate.

A two-way repeated measure analysis of variance (factors: treatment, time) was run to compare differences in all outcomes. The statistical significance of outcome measures in score change between the groups was assessed using t-tests or Wilcoxon signed-rank test according to data distribution. To evaluate the clinical effect size (ES), Cohen's d was calculated for the primary and main secondary outcomes. A p-value of 0.05 was considered significant. Statistical analyses were performed with MedCalc Statistical Software version 19.2 (MedCalc Software bvba, Ostend, Belgium).

Results

The flow diagram showing the participant inclusion process is reported in Figure 2. Fifty-four patients were screened for eligibility. A total of 24 patients met the inclusion criteria and were randomly assigned to one of the two groups. One patient in each group did not start the rehabilitation program due to intercurrent disease or sudden family-related issues. At baseline, the two groups did not differ in terms of anthropometrics, disease duration, disease severity or any of the outcome measures (Table 1).

Training responses

All 11 patients in both groups completed the scheduled intervention by attending all 12 scheduled sessions. No adverse effects were reported. None of the 132 sessions of BFR-W was interrupted for muscle pain or discomfort in the region around and below the compression site.

During training, the BFR-W group, compared to the CON-W group, showed a significantly shorter distance walked (435 ± 115 vs 855 ± 478 m; p=0.010) and a significantly shorter effective walking time (15 ± 0 vs 30 ± 7 minutes; p<0.001). In addition, the BFR-W group registered a smaller increase in heart rate (3 ± 2 vs 7 ± 5 bpm; p=0.027) and a lower RPE (2 ± 2 vs 4 ± 1; p=0.004) than the CON-W group (Figure 3).

Primary outcome: gait speed

A significant time-treatment interaction was observed for primary outcome (p=0.003). At the end of the treatment, the gait speed improved significantly for both groups (BFR-W +13% vs CON-W +5%), with a significant between-group difference in favor of the experimental group (p=0.001). A moderate ES was observed for BFR-W group (Cohen's d = 0.41) but not for CON-W (d = 0.10).

Four patients in the BFR-W group and none in the CON-W group achieved a minimally clinical important difference with a variation greater than 20% of the baseline speed.

At the follow-up, the BFR-W group, but not the CON-W group had maintained gait speed values that were significantly higher than those at baseline (+13% vs +1%, respectively) with a significant between-group difference (p=0.041) (Figure 4).

Secondary outcomes

The two-way analysis of variance did not detect any significant between-group for the secondary outcomes.

In the BFR-W group, the 6-minute walking distance (both at T1; d = 0.47 and at follow-up), 5 sit-to-stand time (d = 0.37), the scores for several domains in the MFIS (d = 0.52) and SF-36 questionnaires improved significantly (Table 2).

The CON-W group also showed a significantly improved 6-minute walking distance (at T1 d = 0.37 and at follow-up) and significantly improved scores for domains in the MFIS (d = 0.69) and SF-36 at the end of treatment compared with the baseline. No significant improvements were observed in lower limb strength or balance.

Power calculation

In the absence of a previously published study, a post hoc power calculation was performed. For the primary outcome, a combined power of 92.5% was obtained, considering the mean deviation from baseline at the end of treatment for the two groups.

Discussion

The present study conducted in a population of severe MS patients demonstrated that supervised slow intermittent walking with moderate BFR applied to the lower limb muscles was safe, feasible, and more effective at improving gait speed compared with the conventional intensive overground walking. This novel training modality was also effective in reducing fatigue and enhancing quality of life, balance and mobility, even though the differences between this modality and conventional overground walking were not significant. Finally, this training modality showed long-lasting effects on selected outcomes.

To the best of our knowledge, this is the first time that walking exercise with BFR was tested with the aim of obtaining benefits in the gait speed of patients with MS and severe gait disabilities. There are two determinant factors of the experimental treatment to be considered: the walking program, progressively increasing from slow speed with rest periods, and the concomitant application of BFR to the lower limbs to boost specific adaptations.

The walking program was developed for frail subjects and patients with low mobility so that they could exercise with low levels of fatigue, muscle pain and cardiovascular load[22-27]. Compared to the conventional intensive overground walking, which requires walking at habitual speed as long as possible with sessions limited only by the individual perception of fatigue, the present program is based on walking at a slow speed interrupted by the rest periods, regardless of the desire to continue often reported by the patient in absence of fatigue. Indeed, interval walking seems particularly suitable for people with MS. In a randomized crossover trial subjects with MS walked farther and with less fatigue when walking intermittently (three 2-minute walking bouts) rather than continuously (6 uninterrupted minutes)[40]. However, in addition to interval training, we also prescribed a controlled speed below the spontaneous walking speed. The aim was to isolate work units at constant metabolic cost for the muscles of the lower limbs, avoiding an increasing degree of deoxygenation with progressive accumulation of muscle lactate, as supported in previous studies[41].

In the present study, this approach contributed to make the experimental procedure feasible and sustainable due not only to the absence of adverse effects of training, but also to the shorter time and distance walked. Moreover, the feasibility was ensured by a lower perceived exertion and cardiovascular load compared with the traditional walking treatment, even in the presence of BFR, the second pivotal element of the experimental treatment. These results are relevant considering the previous concerns of BFR exercise regarding heightened sympathetic nervous system activity and blood pressure responses[42], particularly for subjects with compromised cardiac functions[43,44]. Purposely, also considering the frailty and the autonomic dysfunction of the population under study[45], BFR was administered through an occlusion pressure around 30% of the systolic blood pressure, which is significantly lower than the values reported for BFR training in older adults, ranging from 50% of limb occlusion pressure to 200 mmHg[18]. The mild degree of occlusion pressure reduced the venous blood flow[46] with only a low-moderate degree of deoxygenation of the regions below the sleeve[47]. This partial flow restriction ensured the sustainability of the treatment in terms of local pain, perceived effort and cardiovascular load, in combination with walking.

If aerobic BFR training in older adults[19] or in patients with chronic diseases[20,21] has shown to improve objective measures of physical function, in our study even a low degree of occlusion pressure was associated to significant improvements in MS subjects. The changes in gait speed were significantly higher than those observed in the conventional intensive overground walking group and the magnitude of improvement was even greater than that reported in our previous studies in similar MS patients who underwent traditional overground walking or robot-assisted gait training[8,9]. In addition, in the present trial significant improvements in walking endurance, strength of the lower limbs, fatigue and quality of life were also observed at discharge. In patients with MS, these changes were also observed following conventional physiotherapy or robot-assisted gait training, confirming the positive response to rehabilitation in MS patients with severe walking impairment[9]. Notably, unlike the previously published trials[8,9], most of these beneficial effects on the primary and secondary outcomes were also retained at the follow-up in this trial.

The study, aiming at testing a new effective training method, does not allow to distinguish between the effects of the slow interval walking from those of the BFR. We hypothesize that the aerobic stimulus induced by the interval walking program[22,25,26] was enhanced by muscular adaptations favored by a mild blood flow restriction. Even though the mechanisms underlying the muscle adaptive changes with BFR have not been clarified, previous studies conducted in different populations have reported variable adaptive in aerobic determinants. This adaptations included the upregulation of factors modulating vasculogenesis and angiogenesis[48-49], the reduction in proteolysis and the induction of anabolic processes and muscle mass regulation[50-51], as well the proliferation of myogenic stem cells in human skeletal muscle[48,51].

The reduced venous return during BFR exercise with accumulation of metabolic end products, possibly determined in the present study, has been also considered as a potential mechanism for the muscle growth, with possible activation of mTORC signaling and activation of motor unit recruitment[52]. A higher motor unit activity and the potential recruitment of both slow and fast muscle fibers have been implicated in training with BFR[53,54], however this effect in MS patients was observed following training alone, with change of muscle fiber type I and II fibers proportion according to exercise intensity, after 12 weeks of training[55].

Considering that in people with MS various mechanisms of both muscular and neural origin affecting muscular functions, including the loss of muscle mass, reduced muscle fiber size, the transformation from type I to type II fibers and lower motor unit discharge rates[12], slow interval walking assisted by BFR might have yielded rapid and persistent adaptations with improved mobility. In addition, its versatility in terms of cuff width (5-13 cm), occlusion pressure, training load (intensity, number of sets and duration of a training unit) and type of exercise allows customizing training for given patients.

The study has several limitations. The study is a preliminary study with a small sample size, even though the observed differences between groups show that this sample size is sufficient to statistically observe the effects. We studied non-equivalent exercise groups, but we focused on the comparison of the experimental method with an effective walking therapy in this population[9]. The effects of the stimulus of BFR alone are not highlighted, but the results of the study might now justify a three-arm trial based on slow interval walking to discriminate the adaptive effects related to BFR. The evaluation of muscle strength was based on a functional test, and no information was obtained on muscle size or function in response to exercise training.

In conclusion, this randomized pilot study showed that a novel exercise training intervention based on low-intensity interval walking with moderate BFR to the working muscles was superior to high-intensity overground walking at improving gait speed in patients with progressive MS and severe gait disability. The study also showed a more persistent effect of the experimental treatment. Considering the necessity to develop exercise programs aimed at improving patients' ability to walk[12], the walking program with BFR seems promising, also for its potential progressive transfer to community-based centers and home-based training. A larger trial is needed to confirm the applicability of the training model in clinical practice in patients with MS and restricted mobility, and a study on the related plastic adaptations is needed to determine the effects and appropriate duration of treatment.

Perspectives

Low-intensity interval walking empowered by blood-flow restriction was feasible and safe in people with multiple sclerosis at a severe gait disability. This novelty open a third-way of approaching gait training in this population, in addition to the conventional intensive overground training and RAGT[9]. The low-intensity exercise both in terms of BFR degree of compression and walking bouts, highlights two advantages: at first the possibility for the patients to exercise at home or in a community-based centers; secondly the low training load does not add excessive fatigue to a population that experience fatigue in activities of daily living[1,6].

Finally, this global low-intensity approach should be tested in other fragile populations, to identify the minimum dose of exercise to achieve significant clinical benefits.

Funding

The study was partially supported by "Fondo per l'incentivazione alla ricerca (FIR), 2019" from the University of Ferrara in Italy.

Ethics

The study was approved by CE-AV Ethics Committee with number 149/17. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Data availability

Research data are available at http://dx.doi.org/10.17632/tjbbg9g9n3.1

References

1. Einarsson U, Gottberg K, Fredrikson S, von Koch L, Holmqvist LW. Activities of daily living and social activities in people with multiple sclerosis in Stockholm County. Clin Rehabil. 2006;20(6):543-51.
2. Benedetti MG, Gasparroni V, Stecchi S, Zilioli R, Straudi S, Piperno R. Treadmill exercise in early multiple sclerosis: a case series study. Eur J Phys Rehabil Med. 2009;45(1):53–9.
3. Dalgas U, Stenager E, Ingemann-Hansen T. Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training. Mult Scler 2008,14:35–53
4. Mayo NE, Bayley M, Duquette P, Lapierre Y, Anderson R, Bartlett S. The role of exercise in modifying outcomes for people with multiple sclerosis: a randomized trial. BMC Neurol 2013;13:69.
5. Motl RW, Balto JM, Ensari I, Hubbard EA. Self-efficacy and Walking Performance in Persons with Multiple Sclerosis. J Neurol Phys Ther. 2017;41(2):114-8.
6. Rietberg MB, Brooks D, Uitdehaag BM, Kwakkel G. Exercise therapy for multiple sclerosis. Cochrane Database Syst Rev. 2005;(1):CD003980
7. Pilutti LA, Lelli DA, Paulseth JE, et al. Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: a pilot study. Arch Phys Med Rehabil. 2011;92(1):31–6
8. Straudi S, Fanciullacci C, Martinuzzi C, et al. The effects of robot-assisted gait training in progressive multiple sclerosis: a randomized controlled trial. Mult Scler. 2016;22(3):373–84.
9. Straudi S, Manfredini F, Lamberti N, Martinuzzi C, Maietti E, Basaglia N. Robot-assisted gait training is not superior to intensive overground walking in multiple sclerosis with severe disability (the RAGTIME study): A randomized controlled trial. Mult Scler. 2020 May;26(6):716-724. doi: 10.1177/1352458519833901.
10. Dalgas U, Stenager E, Jakobsen J, Petersen T, Overgaard K, Ingemann-Hansen T. Muscle fiber size increases following resistance training in multiple sclerosis. Mult Scler. 2010;16(11):1367-76
11. Mevellec E, Lamotte D, Cantalloube S, Amarenco G, Thoumie P. Relationship between gait speed and strength parameters in multiple sclerosis. Ann Readapt Med Phys. 2003;46(2):85-90

12. Devasahayam AJ, Downer MB, Ploughman M. The Effects of Aerobic Exercise on the Recovery of Walking Ability and Neuroplasticity in People with Multiple Sclerosis: A Systematic Review of Animal and Clinical Studies. Mult Scler Int. 2017;2017:4815958. doi: 10.1155/2017/4815958.
13. Straudi S, Benedetti MG, Venturini E, Manca M, Foti C, Basaglia N. Does robot assisted gait training ameliorate gait abnormalities in multiple sclerosis? A pilot randomized-control trial. NeuroRehabilitation. 2013;33(4):555–63.
14. Walker DK, Dickinson JM, Timmerman KL, et al. Exercise, amino acids, and aging in the control of human muscle protein synthesis. Med Sci Sports Exerc. 2011;43(12):2249-58
15. Laurentino GC, Ugrinowitsch C, Roschel H, et al. Strength training with blood flow restriction diminishes myostatin gene expression. Med Sci Sports Exerc. 2012;44(3):406-12.
16. Martín-Hernández J, Marín PJ, Menéndez H, Ferrero C, Loenneke JP, Herrero AJ. Muscular adaptations after two different volumes of blood flow-restricted training. Scand J Med Sci Sports. 2013;23(2):e114-20.
17. Grønfeldt BM, Lindberg Nielsen J, Mieritz RM, Lund H, Aagaard P. Effect of blood-flow restricted vs heavy-load strength training on muscle strength: Systematic review and meta-analysis. Scand J Med Sci Sports. 2020 May;30(5):837-848. doi: 10.1111/sms.13632.
18. Clarkson MJ, May AK, Warmington SA. Chronic Blood Flow Restriction Exercise Improves Objective Physical Function: A Systematic Review. Front Physiol. 2019;10:1058. doi: 10.3389/fphys.2019.01058.
19. Clarkson MJ, Conway L, Warmington SA. Blood flow restriction walking and physical function in older adults: A randomized control trial. J Sci Med Sport. 2017 Dec;20(12):1041-1046. doi: 10.1016/j.jsams.2017.04.012.
20. Mattar MA, Gualano B, Perandini LA, et al. Safety and possible effects of low-intensity resistance training associated with partial blood flow restriction in polymyositis and dermatomyositis. Arthritis Res Ther. 2014;16(5):473
21. Cardoso RK, Araujo AM, Del Vechio FB, et al. Intradialytic exercise with blood flow restriction is more effective than conventional exercise in improving walking endurance in hemodialysis patients: a randomized controlled trial. Clin Rehabil. 2020;34(1):91-98. doi: 10.1177/0269215519880235.

22. Malagoni AM, Vagnoni E, Felisatti M, et al. Evaluation of patient compliance, quality of life impact and cost-effectiveness of a "test in-train out" exercise-based rehabilitation program for patients with intermittent claudication. Circ J. 2011;75(9):2128-34.
23. Manfredini F, Malagoni AM, Mascoli F, et al. Training rather than walking: the test in -train out program for home-based rehabilitation in peripheral arteriopathy. Circ J. 2008;72(6):946-52.
24. Malagoni AM, Catizone L, Mandini S, et al. Acute and long-term effects of an exercise program for dialysis patients prescribed in hospital and performed at home. J Nephrol. 2008;21(6):871-8.
25. Manfredini F, Mallamaci F, D'Arrigo G, et al. Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial. J Am Soc Nephrol. 2017;28(4):1259-1268.
26. Lamberti N, Straudi S, Malagoni AM, et al. Effects of low-intensity endurance and resistance training on mobility in chronic stroke survivors: a pilot randomized controlled study. Eur J Phys Rehabil Med. 2017;53(2):228-239.
27. Malagoni AM, Cavazza S, Ferraresi G, et al. Effects of a "test in-train out" walking program versus supervised standard rehabilitation in chronic stroke patients: a feasibility and pilot randomized study. Eur J Phys Rehabil Med. 2016 Jun;52(3):279-87.
28. Manfredini F, Lamberti N, Guerzoni F, et al. Rehabilitative Exercise Reduced the Impact of Peripheral Artery Disease on Vascular Outcomes in Elderly Patients with Claudication: A Three-Year Single Center Retrospective Study. J Clin Med. 2019;8(2). pii: E210. doi: 10.3390/jcm8020210.
29. Lamberti N, López-Soto PJ, Guerzoni F, et al. Changes in exercise capacity and risk of all-cause mortality in patients with peripheral artery disease: a 10-year retrospective cohort study. Intern Emerg Med. 2020 Mar;15(2):289-298. doi: 10.1007/s11739-019-02176-3.
30. Phan-Ba R, Pace A, Calay P, et al. Comparison of the timed 25-foot and the 100-meter walk as performance measures in multiple sclerosis. Neurorehabil Neural Repair. 2011;25(7):672-679. doi:10.1177/1545968310397204

31. Cutter GR, Baier ML, Rudick RA, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain. 1999;122(Pt 5):871-882. doi:10.1093/brain/122.5.871

32. Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. Mult Scler. 2008;14(3):383-390. doi:10.1177/1352458507082607
33. Berg K, Wood-Dauphinee S, Williams JI, Gayton D. Measuring balance in the elderly: Preliminary development of an instrument. Physiother Can. 1989;41:304–11.
34. Cattaneo D, Regola A, Meotti M. Validity of six balance disorders scales in persons with multiple sclerosis. Disabil Rehabil. 2006;28(12):789–95. doi: 10.1080/09638280500404289.
35. Fry DK, Pfalzer LA. Reliability of Four Functional Tests and Rating of Perceived Exertion in Persons with Multiple Sclerosis. Physiother Can. 2006;58(3),212–220. doi: 10.3138/ptc.58.3.212
36. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The Fatigue Severity Scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46(10):1121–3.
37. Rietberg MB, Van Wegen EE, Kwakkel G. Measuring fatigue in patients with multiple sclerosis: reproducibility, responsiveness and concurrent validity of three Dutch self-report questionnaires. Disabil Rehabil. 2010;32(22):1870-1876. doi:10.3109/09638281003734458
38. Isaksson AK, Ahlström G, Gunnarsson LG. Quality of life and impairment in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry. 2005;76(1):64–9.

39. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain. 2001;124(Pt 5):962–73
40. Karpatkin H, Cohen ET, Rzetelny A, et al. Effects of Intermittent Versus Continuous Walking on Distance Walked and Fatigue in Persons With Multiple Sclerosis: A Randomized Crossover Trial. J Neurol Phys Ther. 2015;39(3):172-178. doi:10.1097/NPT.0000000000000091
41. Manfredini F, Lamberti N, Malagoni AM, et al. The role of deconditioning in the end-stage renal disease myopathy: physical exercise improves altered resting muscle oxygen consumption. Am J Nephrol. 2015;41(4-5):329-36. doi: 10.1159/000431339.
42. Sugawara J, Tomoto T, Tanaka H. Impact of leg blood flow restriction during walking on central arterial hemodynamics. Am J Physiol Regul Integr Comp Physiol. 2015;309:R732-9.
43. Slysz J, Stultz J, Burr JF. The efficacy of blood flow restricted exercise: A systematic review & metaanalysis. J Sci Med Sport. 2016;19(8):669-75

44. Miyachi M, Kawano H, Sugawara J, et al. Unfavorable effects of resistance training on central arterial compliance: a randomized intervention study. Circulation. 2004;110:2858–63
45. Racosta JM, Sposato LA, Morrow SA, Cipriano L, Kimpinski K, Kremenchutzky M. Cardiovascular autonomic dysfunction in multiple sclerosis: a meta-analysis [published correction appears in Mult Scler Relat Disord. 2015 Jul;4(4):385. Kimpiski, Kurt [Corrected to Kimpinski, Kurt]]. Mult Scler Relat Disord. 2015;4(2):104-111. doi:10.1016/j.msard.2015.02.002
46. Raju S, Walker W, May C. Measurement of ambulatory venous pressure and column interruption duration in normal volunteers. J Vasc Surg Venous Lymphat Disord. 2020;8(1):127-136. doi: 10.1016/j.jvsv.2019.06.012
47. Manfredini F, Lamberti N, Rossi T, Mascoli F, Basaglia N, Zamboni P. A Toe Flexion NIRS assisted Test for Rapid Assessment of Foot Perfusion in Peripheral Arterial Disease: Feasibility, Validity, and Diagnostic Accuracy. Eur J Vasc Endovasc Surg. 2017;54(2):187-194. doi:10.1016/j.ejvs.2017.04.013
48. Conceição MS, Chacon-Mikahil MP, Telles GD, et al. Attenuated PGC-1α Isoforms following Endurance Exercise with Blood Flow Restriction. Med Sci Sports Exerc. 2016 Sep;48(9):1699-707.
49. 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;40:691–8
50. Wernbom M, Aagaard P. Muscle fibre activation and fatigue with low-load blood flow restricted resistance exercise-An integrative physiology review. Acta Physiol (Oxf). 2020;228(1):e13302. doi: 10.1111/apha.13302.
51. Hortobagyi T, Dempsey L, Fraser D, et al. Changes in muscle strength, muscle fibre size and myofibrillar gene expression after immobilization and retraining in humans. J Physiol 2000;524:293–304.
52. Walker DK, Dickinson JM, Timmerman KL, et al. Exercise, amino acids, and aging in the control of human muscle protein synthesis. Med Sci Sports Exerc. 2011;43(12):2249-2258. doi:10.1249/MSS.0b013e318223b037

53. Bjørnsen T, Wernbom M, Kirketeig A, et al. Type 1 Muscle Fiber Hypertrophy after Blood Flow-restricted Training in Powerlifters. Med Sci Sports Exerc. 2019;51(2):288-298.
54. Krustrup P, Söderlund K, Relu MU, Ferguson RA, Bangsbo J. Heterogeneous recruitment of quadriceps muscle portions and fibre types during moderate intensity knee-extensor exercise: effect of thigh occlusion. Scand J Med Sci Sports. 2009;19(4):576-584. doi:10.1111/j.1600-0838.2008.00801.x
55. Wens I, Dalgas U, Vandenabeele F, et al. High Intensity Exercise in Multiple Sclerosis: Effects on Muscle Contractile Characteristics and Exercise Capacity, a Randomised Controlled Trial. PLoS One. 2015;10(9):e0133697. Published 2015 Sep 29. doi:10.1371/journal.pone.0133697

Table 1. Characteristics of study participants at baseline.

	BFR-W (n = 11)	CON-W (n = 11)	p
Age, years	54 ± 11	56 ± 10	0.54
Male sex, n (%)	4 (36)	3 (27)	0.65
MS duration, years	14 ± 9	13 ± 10	0.46
EDSS	6.1 ± 0.2	6.0 ± 0.3	0.26
Primary progressive, n (%)	6 (55)	5 (45)	0.68
Secondary progressive, n (%)	5 (45)	6 (55)	0.68
Body mass index, kgm^{-2}	23.5 ± 3.0	23.5 ± 4.0	0.96
Medications for spasticity, n (%)	3 (27)	4 (36)	0.65
Primary outcome			
T25FW speed, ms^{-1}	0.78 ± 0.36	0.76 ± 0.37	0.93
Secondary outcomes			
6-minute walking distance, m	215 ± 94	183 ± 99	0.44
Berg balance scale	48 ± 8	44 ± 9	0.42
5-time sit to stand test, s	24.0 ± 21.0	27.4 ± 36.2	0.81
Fatigue severity scale	5.3 ± 0.7	5.2 ± 0.7	0.54
MSIS-29 motor component	62 ± 16	61 ± 16	0.92
MSIS-29 psychological component	24 ± 7	21 ± 7	0.27
MFIS total score	42 ± 15	33 ± 13	0.17
MFIS physical component	22 ± 4	19 ± 5	0.20
MFIS cognitive component	15 ± 12	11 ± 8	0.28
MFIS psychosocial component	4 ± 2	3 ± 2	0.14
SF-36 questionnaire domains			
Physical functioning	43 ± 17	36 ± 23	0.46

Bodily pain	60 ± 29	62 ± 34	0.91
General health	37 ± 16	40 ± 11	0.62
Physical role	57 ± 23	56 ± 35	0.98
Emotional role	70 ± 38	73 ± 31	0.80
Social activities	54 ± 19	49 ± 19	0.58
Vitality	53 ± 14	46 ± 12	0.22
Mental health	64 ± 22	66 ± 18	0.79

Abbreviations: EDSS, Expanded Disability Status Scale; T25FW, Timed 25-Foot Walk; MSIS, Multiple Sclerosis Impact Scale; MFIS, Modified Fatigue Impact Scale

Table 2. Outcome measures at the three time-points for both groups.

	BFR-W group (n=11)					CON-W group (n=11)					Between groups comparison	
	Pre	*Post*	*Follow-up*	*ΔPre-Post*	*ΔPre-Follow-up*	*Pre*	*Post*	*Follow-up*	*ΔPre-Post*	*ΔPre-Follow-up*	*p ΔPre-Post*	*p ΔPre-Follow-up*
T25FW speed, m/s	0.78 (0.54-1.03)	0.90* (0.64-1.16)	0.87* (0.62-1.12)	0.11 (0.05-0.18)	0.09 (0.03-0.13)	0.76 (0.51-0.99)	0.79* (0.54-1.03)	0.76 (0.49-1.02)	0.04 (0.01-0.06)	0.01 (-0.05-0.1)	0.001	0.041
6MWD, m	215 (153-278)	264* (188-340)	266* (186-345)	49 (20-78)	50 (22-78)	183 (120-245)	218* (152-285)	223* (155-291)	36 (15-56)	40 (12-69)	0.44	0.50
BBS	48 (43-54)	50 (45-54)	48 (42-54)	2 (-1-4)	0 (-4-4)	44 (39-50)	46 (39-54)	45 (37-53)	2 (-2-6)	1 (-5-7)	0.18	0.30
5STS time, s	24 (8-40)	18* (7-28)	20* (5-35)	-6 (-15-2)	-4 (-8-0)	27 (1-53)	23 (3-44)	24 (2-46)	-4 (-11-4)	-3 (-8-2)	0.23	0.20
FSS	5.3 (4.9-5.8)	5.1 (4.4-5.9)	5.0 (4.4-5.6)	-0.2 (-0.9-0.5)	-0.4 (-0.9-0.1)	5.2 (4.7-5.6)	4.8 (4.2-5.3)	5.0 (4.6-5.5)	-0.4 (-1.0-0.2)	-0.1 (-0.9-0.7)	0.45	0.50
MSIS-29 motor	62 (51-72)	58 (48-68)	57 (46-67)	-4 (-10-3)	-5 (-15-5)	61 (51-71)	51* (42-61)	53 (42-65)	-10 (-15--5)	-8 (-17-2)	0.07	0.52
MSIS-29 psychological	24 (19-29)	21* (16-26)	22* (16-27)	-3 (-5--1)	-3 (-5-0)	21 (17-25)	18 (14-22)	19 (14-23)	-3 (-7-1)	-2 (-7-2)	0.59	0.91
MFIS total	42 (32-52)	33* (20-46)	33* (21-45)	-9 (-17--1)	-9 (-17--2)	33 (25-41)	24* (14-33)	28 (17-38)	-9 (-20-1)	-5 (-16-5)	0.72	0.55
MFIS physical	22 (19-24)	17* (12-21)	18 (14-22)	-5 (-10-0)	-4 (-8-0)	19 (16-22)	15* (10-20)	19 (15-23)	-4 (-10-1)	0 (-4-4)	0.65	0.26
MFIS cognitive	15 (8-23)	12* (4-20)	11* (4-19)	-3 (-7-0)	-4 (-9-0)	11 (5-16)	7 (3-11)	7 (1-12)	-4 (-8-1)	-4 (-9-1)	0.94	0.97
MFIS psychosocial	4 (3-6)	4 (3-5)	4 (2-5)	0 (-2-2)	0 (-2-2)	3 (2-4)	3 (1-4)	3 (1-4)	0 (-2-2)	0 (-2-2)	0.77	0.52

SF-36 domains												
Physical functioning	43 (31-54)	48* (36-60)	45 (32-59)	5 (0-11)	3 (-8-13)	36 (21-51)	46* (29-64)	43* (27-59)	10 (1-20)	7 (1-14)	0.26	0.28
Bodily pain	60 (41-79)	66 (45-87)	64 (41-87)	6 (-12-24)	4 (-13-20)	62 (41-84)	75* (59-92)	75 (59-93)	13 (1-25)	13 (-4-31)	0.18	0.25
General health	37 (26-47)	43* (29-58)	36 (26-46)	6 (-2-15)	-1 (-9-7)	40 (33-47)	44 (33-54)	40 (30-50)	4 (-4-11)	0 (-7-7)	0.58	0.77
Physical role	57 (41-72)	86* (66-107)	70 (49-91)	30 (0-60)	14 (-20-48)	56 (34-78)	84* (62-106)	77 (53-101)	28 (-2-58)	21 (-16-59)	0.91	0.66
Emotional role	70 (44-95)	76 (53-98)	82 (59-105)	6 (-22-34)	12 (-17-42)	73 (53-92)	91 (81-101)	88 (73-103)	18 (-12-48)	15 (-20-50)	0.60	0.66
Social activities	54 (41-66)	64 (51-76)	64 (48-80)	10 (-8-29)	10 (-5-25)	49 (37-61)	62* (49-74)	60* (45-76)	13 (2-23)	11 (-2-25)	0.48	1.00
Vitality	53 (44-62)	54 (44-65)	52 (43-60)	1 (-9-10)	-1 (-9-6)	46 (38-54)	50 (39-60)	49 (37-61)	4 (-4-11)	3 (-8-15)	0.50	0.33
Mental health	64 (49-79)	63 (51-75)	67 (55-80)	-1 (-16-14)	3 (-7-13)	66 (54-77)	75 (63-87)	71 (55-85)	9 (-5-24)	5 (-12-21)	0.29	0.94

Abbreviations: T25FW, timed 25-foot walk test; 6MWD, 6-minute walking distance; BBS, Berg Balance Scale; 5STS, 5-time Sit-To-Stand; FSS, Fatigue Severity Scale; MSIS, multiple sclerosis impact scale; MFIS, modified fatigue impact scale; SF-36, 36-item short-form health questionnaire.

Legend:*: within-group p value < 0.05 determined by paired samples t-test or Wilcoxon test, as appropriate. Values are reported as mean (95% confidence interval).

Figure legends

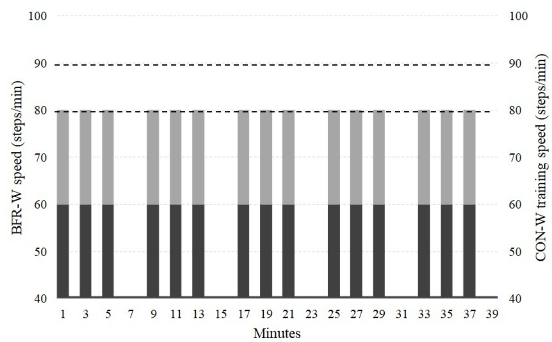
Figure 1. Graphic representation of the training program proposed to both groups.

Legend: Dark grey column: BFR-W group at first training session; Light grey column: speed of BFR-W group at the last training session; Dashed black lines: range of walking speed of CON-W group

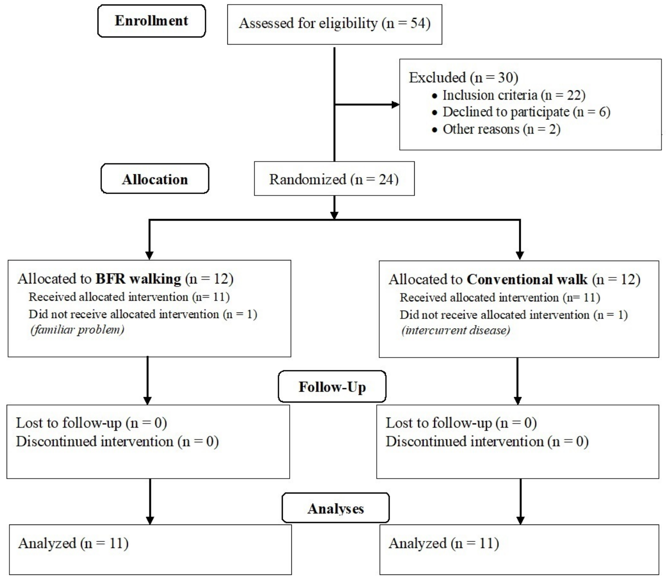
Figure 2. Study flow diagram

Figure 3. Exercise training load features in the low intensity walking with BFR group (BFR-W) and the conventional intensive overground walking group (CON-W). Legend: p-value obtained from independent samples t-test or Mann-Whitney u-test, as appropriate.

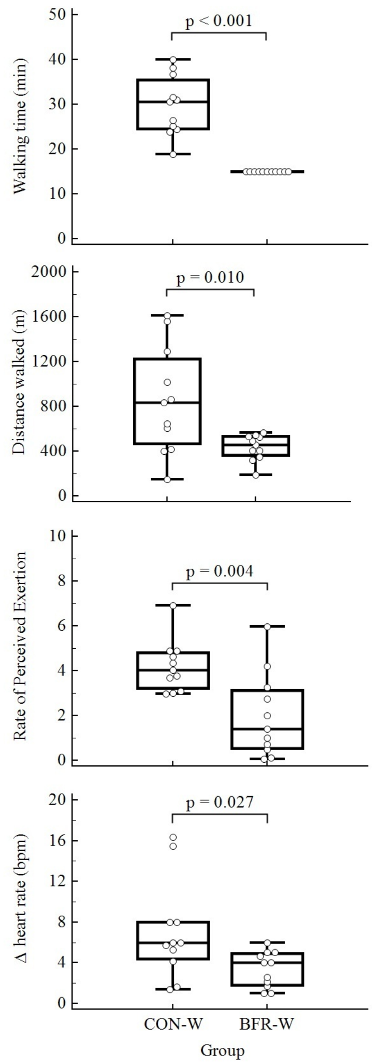
Figure 4. Changes in gait speed at the end of the exercise program (a) and at end of the follow up period (b) in the low intensity walking with BFR group (BFR-W) and the conventional intensive overground walking group (CON-W). Legend: p-value obtained from independent samples t-test or Mann-Whitney u-test, as appropriate.



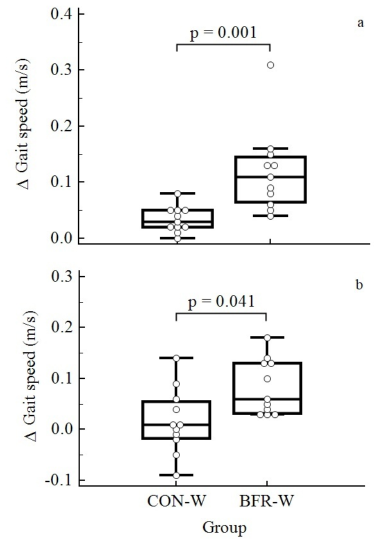
sms_13764_f1.jpg



sms_13764_f2.jpg



sms_13764_f3.jpg



sms_13764_f4.jpg