EDITORIAL

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Exercise with blood flow restriction: an effective alternative for the non-pharmaceutical treatment for muscle wasting

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Abstract

Significant muscle wasting is generally experienced by ill and bed rest patients and older people. Muscle wasting leads to significant decrements in muscle strength, cardiorespiratory, and functional capacity, which increase mortality rates. As a consequence, different interventions have been tested to minimize muscle wasting. In this regard, blood flow restriction (BFR) has been used as a novel therapeutic approach to mitigate the burden associated with muscle waste conditions. Evidence has shown that BFR *per se* can counteract muscle wasting during immobilization or bed rest. Moreover, BFR has also been applied while performing low intensity resistance and endurance exercises and produced increases in muscle strength and mass. Endurance training with BFR has also been proved to increase cardiorespiratory fitness. Thus, frail patients can benefit from exercising with BFR due to the lower cardiovascular and join stress compared with traditional high intensity exercises. Therefore, low intensity resistance and endurance training combined with BFR may be considered as a novel and attractive intervention to counteract muscle wasting and to decrease the burden associated with this condition.

Keywords Blood flow restriction; Muscle wasting; Physical frail patients; Low intensity exercise

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Rationale to the application of partial blood flow restriction as a treatment against muscle wasting

Skeletal muscle wasting, or myopenia,[1] occurs in specific conditions such as muscle fibre denervation, reduced mechanical loading (i.e. unloading),[2] and prolonged fasting. In general, muscle wasting is triggered by limiting diseases (e.g. renal failure),[3,4] syndromes (e.g. cancer cachexia),[5–10] or ageing (e.g. sarcopenia).[11,12] Significant muscle wasting is associated with decrements in muscle strength,[2] cardiorespiratory capacity ($<$30 mL·min^{-1}·kg^{-1}),[13] functional capacity,[2] and quality of life, greatly increasing mortality rates.[14,15] Additionally, muscle wasting can occur rapidly and irreversibly in some conditions. For instance, gastric cancer patients exhibit muscle wasting of ~10% within 7 days after surgery,[16] similar to the values observed after 5 days of bed rest in elderly.[17] Thus, strategies able to reduce muscle wasting and/or increase muscle mass are needed.

Different interventions (e.g. nutritional, pharmacologic, and physical exercise training) have been tested to minimize muscle wasting. Thus far, moderate to high intensity resistance training (RT) [i.e. ~70–85% of one repetition maximum (1-RM)] has been shown to effectively counteract muscle wasting increasing muscle strength and cross sectional area (i.e. muscle hypertrophy) in many patients.[18–20] However, moderate to high intensity RT may not be suitable for physically frail patients due to the significant cardiorespiratory stress[21–23] or after joint surgery due to the high mechanical load.[24] In this regard, alternative therapeutic approaches that may induce lower cardiovascular stress and joint load, while counteracting muscle wasting, in physically frail patients should be considered.

Blood flow restriction (BFR) has been tested as a new therapeutic approach to counteract muscle wasting. It uses a pneumatic pressure cuff wrapped around the proximal region of the target limb, which is maintained inflated throughout the session to reduce the blood flow to the limb. Evidence has demonstrated that 14 days of BFR are more effective than isometric exercise to prevent muscle waste and weakness induced by immobilization and unloading.[25] Moreover, BFR has been applied during exercise training to further minimize muscle wasting.

Two of the most common training methods are the low intensity RT and endurance training (ET) associated with BFR.[26–28] Several randomized controlled trials and meta-analyses have shown that RT with BFR (RT-BFR) produces similar muscle hypertrophy response to high intensity RT, in different populations.[26,28–34] The similar muscle hypertrophy response between low intensity RT-BFR and high intensity RT may be due to the fact that both training strategies activate similar physiological/molecular mechanisms. For instance, there is evidence that these training strategies produce similar changes in circulating anabolic hormones (e.g. growth hormone and testosterone),[35,36] activation of intracellular signalling pathways that control muscle protein synthesis (e.g. Akt–mTOR pathway),[37,38] satellite cell activity,[31,39] myocyte transcriptome,[40] and motor unit recruitment pattern.[41] Besides the similarities in the activation of physiological/molecular mechanisms, in a recent meta-analysis, our group showed that both high intensity RT and RT-BFR increase muscle strength, but to a lesser extent in the former (~7%),[42] regardless of the population (i.e. young and older individuals). Similarly, we showed that 24 training sessions of low intensity (20% of 1-RM) RT-BFR increased muscle strength (~17%) and hypertrophy (~7%) to a similar extent to high intensity (80% of 1-RM) RT (54% and 8%, respectively)[40] in elderly. We also investigated the effects of low intensity RT-BFR in a patient diagnosed with inclusion body myositis (idiopathic inflammatory myopathy that leads to remarkable muscle atrophy), to whom high intensity RT failed to produce the aforementioned muscle adaptations.[43] After 12 weeks of low intensity RT-BFR, we found significant increases in muscle strength (19%) and hypertrophy (5%). Furthermore, the functional capacity, measured by the timed up-and-go test, improved from 16 to 10 s (i.e. 37% faster). This training-induced adaptations likely influenced the important increase (~600%) in the quality of life perception of the patient.[43] A recent study showed that a 74-year-old male diagnosed with inclusion body myositis also increased muscle strength by 68% and improved the maximal horizontal gait speed by 19%, after performing 12 weeks of very low intensity RT-BFR.[44] Although RT-BFR can counteract muscle wasting and improve functionality, it has small effects on cardiorespiratory capacity, which is critical for maintaining functionality.

Moderate to high intensity ET promotes significant increases in cardiorespiratory capacity, with no or small improvements in muscle strength and hypertrophy. However, when ET is performed with BFR (ET-BFR), there is a significant increase in aerobic power (i.e. maximum oxygen consumption $\dot{V}O_2max$), as well as increases in muscle strength and hypertrophy.[45–48] In young subjects (~23 years), Abe *et al.*[45] reported that 24 ET-BFR sessions (15 min cycling at 40% of $\dot{V}O_2max$) increased muscle strength by 7.7%, muscle hypertrophy by 5.1%, and $\dot{V}O_2max$ by 6.4%, suggesting BFR caused the metabolic disruption required to enhance exercise-induced adaptations. Additionally, we compared the effects of three training interventions—low intensity ET-BFR and high intensity RT and ET—on muscle strength and hypertrophy, and aerobic power ($\dot{V}O_2max$). Muscle hypertrophy response was similar between ET-BFR (10.7%) and high intensity RT (12.5%), while high intensity ET increase muscle hypertrophy only by 3.8%, adding support to the efficacy of ET-BFR to produce RT-likely muscle adaptions. The ET-BFR also increased muscle strength (9%) and $\dot{V}O_2max$ (11%), although to a lower magnitude compared with RT (35%) and ET (21%), respectively. These results suggest that ET-BFR is a potential alternative training protocol to improve muscle strength, mass, and cardiorespiratory capacity, particularly for older adults or clinical cohorts not able to exercise with high training loads. Regarding fragile older individuals, it has been shown that low intensity (67 $m \bullet min^{-1}$ for 20 min) treadmill walking with BFR, performed 5 days per week for 6 weeks, increased isometric (11%) and isokinetic (7%) knee extension torque, and isokinetic (16%) knee flexion torque.[49] Moreover, the low intensity ET-BFR hypertrophied thigh and shank muscles by 5.8% and 5.1%, respectively. In functional tests, elderly men and women improved their performance in the 30 s sit to stand test, 6-minute walk test, timed up-and-go test, and in a modified Queen's College step test, after 6 weeks of walking with BFR (10 min walking at 4 $km \cdot h^{-1}$).[50] Importantly, there are few studies comparing ET-BFR effects between men and women;[50–52] however, current evidence does not suggest any differences in training-induced adaptations between genders. Furthermore, no study has investigated the efficacy of ET-BFR in patients with muscle wasting conditions.

Despite the lack of studies investigating the effects of ET-BFR in muscle wasting conditions, it is reasonable to suggest that ET-BFR can counteract muscle wasting and declines in cardiorespiratory capacity in patients with non-refractory muscle wasting conditions. Accordingly, Clarkson *et al.*[53] reported that the effects of ET-BFR will be tested in end stage kidney disease patients, who experience significant muscle wasting. Authors hypothesized that the group performing ET-BFR will present higher gains in muscle strength and

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hypertrophy, and in functional capacity, compared with a group that will perform the same exercise protocol but with no BFR. In confirming this hypothesis, more studies will be required to establish safe and efficient ET-BRT training protocols to reduce muscle waste.

Is exercise with blood flow restriction safe?

The question of safety is always raised due to the partial BFR produced by the cuff pressure during a BFR exercise session. However, the BFR approach has been applied to >12 000 people in Japan across different physical conditions, such as cerebrovascular, orthopaedic, cardiac, respiratory, and neuromuscular diseases, as well as obesity, diabetes, and hypertension, with no significant side effects reported on rheological response. From 300 000 training sessions, only 0.055% of practitioners developed venous thrombus, 0.008% developed pulmonary embolism, and 0.008% of the cohort presented rhabdomyolysis.[54] Additionally, the same authors showed that markers of intravascular clot formation, D-dimer, and fibrin degradation product and markers of coagulation activity, prothrombin time, and thrombin time were not significantly increased after low intensity BFR exercise.[55] Moreover, Madarame *et al*.[56] demonstrated in 10 patients with ischaemic heart disease that four sets of low intensity RT-BFR did not increase fibrinogen/fibrin degradation products and the high-sensitive C-reactive protein, suggesting that RT-BFR does not affect haemostatic and inflammatory responses.

Regarding the haemodynamic response, we recently showed that the systolic blood pressure, diastolic blood pressure, and heart rate were lower after RT-BFR than after high and low intensity RT[27] in young men. However, young individuals have distinct haemodynamic responses to exercise compared with elderly. There is evidence that a RT-BFR exercise session induces higher systolic and diastolic blood pressure increments and slower parasympathetic recovery compared with high intensity RT in elderly.[57] Nonetheless, a recent meta-analysis[58] showed that blood pressure responses to RT-BFR are similar to those observed during high intensity RT, regardless of the ageing group. Taken together, there is evidence suggesting that changes in blood pressure during RT-BFR are similar to traditional high intensity RT in different populations.[27,58] Carotid compliance also does not seem to be affected by RT-BFR. Yasuda *et al*.[59] showed that 12 weeks of RT-BFR did not increase arterial stiffness or humeral coagulation factors in elderly. Similarly, Ozaki *et al*.[60] showed that low intensity RT-BFR did not affect carotid compliance, but 6 weeks of high intensity RT decreased the carotid arterial compliance in young participants, suggesting that RT but not RT-BFR can increase systolic blood pressure over time.[61] Despite these promising results, there is a necessity of long-term trials to address this issue.

Regarding ET-BFR and the cardiovascular risks, Ferreira *et al*.[62] showed lower heart rate variability and haemodynamic responses after a low intensity endurance exercise with BFR (40% of VO_2max) than after a high intensity endurance exercise without BFR (70% VO_2max), in elderly. Accordingly, Barili *et al*.[63] showed that the haemodynamic response of hypertensive older individuals, as assessed by heart rate and systolic and diastolic blood pressures, was similar between low intensity ET-BFR and moderate intensity ET, supporting the safety of the former.

Despite the alleged safety of BFR training in young and elderly individuals, long-term studies involving patients affected by diseases like cancer, heart failure, diabetes, and pulmonary diseases are needed to ensure that exercise with BFR is safe for each specific condition/disease. Furthermore, as muscle wasting may occur both in skeletal and cardiac muscles, additional studies are also required to determine whether BFR training guidelines may be applicable to individuals experiencing different degrees of muscle wasting or whether a more individualized training parameterization is required.

Training guidelines

The characteristics of the RT-BFR and ET-BFR seem to affect training-induced adaptations and, as a consequence, the ability to counteract muscle wasting. Usually, training intensity (i.e. percentage of the maximal load or capacity), occlusion pressure, cuff width, number of sets and repetitions per training session, and exercise duration are manipulated during BFR training protocols. BFR training is usually prescribed at low intensity, between 20% and 40% of the 1-RM load for RT-BFR and ~40% of VO_2max for ET-BFR. Regarding the occlusion pressure, we showed that high occlusion pressure (80% of the occlusion pressure) produces greater muscle hypertrophy than moderate occlusion pressure (40% of the occlusion pressure) when exercising at low intensities (20% of 1-RM). Conversely, occlusion pressure does not seem to play a role when exercise intensity at ~40% 1-RM.[30] There is a lack of studies investigating whether different occlusion pressures could interfere on muscle and cardiorespiratory adaptations when undergoing ET-BFR. Our study suggested that 80% of individual's arterial blood pressure is effective to increase muscle strength, hypertrophy, and VO_2max after a ET-BFR protocol.[48]

Although cuff width may change the relative pressure, our meta-analysis showed that using wide or narrow cuffs in a RT-BFR protocol produces similar muscle hypertrophy compared with high RT.[42]

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Regarding the number of sets and repetitions in a typical RT-BFR session, the standard protocol is performing four sets (1st set—30 repetitions, 2nd set—15 repetitions, 3rd set—15 repetitions, and 4th set—15 repetitions)[28,40] with 30–60 s of interval between sets. The cuff should be kept inflated throughout the training session. ET-BFR usually encompasses cycling per 15 to 30 min to increase VO_2max or walking (i.e. two to five sets of 2–3 min at 4–6 km•h^{-1}).[46,64,65]

Future directions

There is mounting evidence that performing resistance and ET with BFR can increase muscle hypertrophy to a similar extent than high intensity RT (usual exercise prescription). In some cases, physically frail patients are not able to perform high intensity RT, and thus, low intensity resistance or ET with partial BFR could be considered as an important strategy to counteract muscle wasting in ageing and disease conditions. However, long-term studies are needed to ensure the safety of BFR training in patients with chronic diseases diagnosed with muscle wasting (e.g. cancer patients).

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Conflict of interest

The authors declare no conflicts of interest.

References

1. Fearon K, Evans WJ, Anker SD. Myopenia—a new universal term for muscle wasting. *J Cachexia Sarcopenia Muscle* 2011;**2**:1–3.
2. Coker RH, Hays NP, Williams RH, Wolfe RR, Evans WJ. Bed rest promotes reductions in walking speed, functional parameters, and aerobic fitness in older, healthy adults. *J Gerontol A Biol Sci Med Sci* 2015;**70**:91–96.
3. Johansen KL, Shubert T, Doyle J, Soher B, Sakkas GK, Kent-Braun JA. Muscle atrophy in patients receiving hemodialysis: effects on muscle strength, muscle quality, and physical function. *Kidney Int* 2003;**63**:291–297.
4. Kim JK, Choi SR, Choi MJ, Kim SG, Lee YK, Noh JW, et al. Prevalence of and factors associated with sarcopenia in elderly patients with end-stage renal disease. *Clin Nutr* 2014;**33**:64–68.
5. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nature Rev Dis Primers* 2018;**4**:17105.
6. Blum D, Stene GB, Solheim TS, Fayers P, Hjermstad MJ, Baracos VE, et al. Validation of the consensus-definition for cancer cachexia and evaluation of a classification model—a study based on data from an international multicentre project (EPCRC-CSA). Annals of oncology: official journal of the European Society for. *Med Oncol* 2014;**25**:1635–1642.
7. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;**12**:489–495.
8. Kubo Y, Naito T, Mori K, Osawa G, Aruga E. Skeletal muscle loss and prognosis of breast cancer patients. *Supportive Care in Cancer.* 2017;**25**:2221–2227.
9. Farkas J, von Haehling S, Kalantar-Zadeh K, Morley JE, Anker SD, Lainscak M. Cachexia as a major public health problem: frequent, costly, and deadly. *J Cachexia Sarcopenia Muscle* 2013;**4**:173–178.
10. Daly LE, Ni Bhuachalla EB, Power DG, Cushen SJ, James K, Ryan AM. Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer. *J Cachexia Sarcopenia Muscle* 2018;**9**:315–325.
11. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc* 2011;**12**:249–256.
12. von Haehling S, Morley JE, Anker SD. From muscle wasting to sarcopenia and myopenia: update 2012. *J Cachexia Sarcopenia Muscle* 2012;**3**:213–217.
13. de Oliveira RJ, Bottaro M, Motta AM, Pitanga F, Guido M, Leite TK, et al. Association between sarcopenia-related phenotypes and aerobic capacity indexes of older women. *J Sports Sci Med* 2009;**8**:337–343.
14. Pourhassan M, Norman K, Muller MJ, Dziewas R, Wirth R. Impact of sarcopenia on one-year mortality among older hospitalized patients with impaired mobility. *J Frailty Aging* 2018;**7**:40–46.
15. Landi F, Cruz-Jentoft AJ, Liperoti R, Russo A, Giovannini S, Tosato M, et al. Sarcopenia and mortality risk in frail older persons aged 80 years and older: results from ilSIRENTE study. *Age Ageing* 2013;**42**:203–209.
16. Huang DD, Ji YB, Zhou DL, Li B, Wang SL, Chen XL, et al. Effect of surgery-induced acute muscle wasting on postoperative outcomes and quality of life. *J Surg Res* 2017;**218**:58–66.
17. Martone AM, Bianchi L, Abete P, Bellelli G, Bo M, Cherubini A, et al. The incidence of sarcopenia among hospitalized older patients: results from the Glisten study. *J Cachexia Sarcopenia Muscle* 2017;**8**:907–914.
18. Lonkvist CK, Vinther A, Zerahn B, Rosenbom E, Deshmukh AS, Hojman P, et al. Progressive resistance training in head and neck cancer patients undergoing concomitant chemoradiotherapy. *Laryngoscope Investig otolaryngol* 2017;**2**:295–306.
19. Almstedt HC, Grote S, Perez SE, Shoepe TC, Strand SL, Tarleton HP. Training-related improvements in musculoskeletal health and balance: a 13-week pilot study of female cancer survivors. *Eur J Cancer Care* 2017;**26**.
20. Rosa C, Nishimoto DY, Souza GDE, Ramirez AP, Carletti CO, Daibem CGL, et al. Effect of continuous progressive resistance training during hemodialysis on body composition, physical function and quality of life in end-stage renal disease patients: a randomized controlled trial. *Clin Rehabil* 2018;269215518760696.
21. MacDougall JD, Tuxen D, Sale DG, Moroz JR, Sutton JR. Arterial blood pressure response to heavy resistance exercise. *J Appl Physiol (1985)* 1985;**58**:785–790.
22. Queiroz AC, Kanegusuku H, Chehuen MR, Costa LA, Wallerstein LF, Dias da Silva VJ, et al. Cardiac work remains high after strength exercise in elderly. *Int J Sports Med* 2013;**34**:391–397.
23. Rojek M, Rajzer M, Wojciechowska W, Gasowski J, Pizon T, Czarnecka D. The relation between blood pressure components

and left atrial volume in the context of left ventricular mass index. *Medicine* 2017;**96**: e9459.

24. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. *Br J Sports Med* 2017;**51**:1003–1011.
25. Kubota A, Sakuraba K, Sawaki K, Sumide T, Tamura Y. Prevention of disuse muscular weakness by restriction of blood flow. *Med Sci Sports Exerc* 2008;**40**:529–534.
26. Laurentino GC, Ugrinowitsch C, Roschel H, Aoki MS, Soares AG, Neves M Jr, et al. Strength training with blood flow restriction diminishes myostatin gene expression. *Med Sci Sports Exerc* 2012;**44**:406–412.
27. Libardi CA, Catai AM, Miquelini M, Borghi-Silva A, Minatel V, Alvarez IF, et al. Hemodynamic responses to blood flow restriction and resistance exercise to muscular failure. *Int J Sports Med* 2017;**38**:134–140.
28. Libardi CA, Chacon-Mikahil MP, Cavaglieri CR, Tricoli V, Roschel H, Vechin FC, et al. Effect of concurrent training with blood flow restriction in the elderly. *Int J Sports Med* 2015;**36**:395–399.
29. Laurentino GC, Loenneke JP, Teixeira EL, Nakajima E, Iared W, Tricoli V. The effect of cuff width on muscle adaptations after blood flow restriction training. *Med Sci Sports Exerc* 2015.
30. Lixandrao ME, Ugrinowitsch C, Laurentino G, Libardi CA, Aihara AY, Cardoso FN, et al. Effects of exercise intensity and occlusion pressure after 12 weeks of resistance training with blood-flow restriction. *Eur J Appl Physiol* 2015;**115**:2471–2480.
31. Nielsen JL, Aagaard P, Bech RD, Nygaard T, Hvid LG, Wernbom M, et al. Proliferation of myogenic stem cells in human skeletal muscle in response to low-load resistance training with blood flow restriction. *J Physiol* 2012;**590**:4351–4361.
32. Karabulut M, Bemben DA, Sherk VD, Anderson MA, Abe T, Bemben MG. Effects of high-intensity resistance training and low-intensity resistance training with vascular restriction on bone markers in older men. *Eur J Appl Physiol* 2011;**111**:1659–1667.
33. Kim D, Loenneke JP, Ye X, Bemben DA, Beck TW, Larson RD, et al. Low-load resistance training with low relative pressure produces muscular changes similar to high-load resistance training. *Muscle Nerve* 2017;**56**:E126–E133.
34. Kubo K, Komuro T, Ishiguro N, Tsunoda N, Sato Y, Ishii N, et al. Effects of low-load resistance training with vascular occlusion on the mechanical properties of muscle and tendon. *J Appl Biomech* 2006;**22**:112–119.
35. Takarada Y, Nakamura Y, Aruga S, Onda T, Miyazaki S, Ishii N. Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J Appl Physiol* 2000;**88**:61–65.
36. Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. *Sports Med* 2005;**35**:339–361.
37. Fujita S, Abe T, Drummond MJ, Cadenas JG, Dreyer HC, Sato Y, et al. Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *J Appl Physiol* 2007;**103**:903–910.
38. Camera DM, Edge J, Short MJ, Hawley JA, Coffey VG. Early time course of Akt phosphorylation after endurance and resistance exercise. *Med Sci Sports Exerc* 2010;**42**:1843–1852.
39. Bellamy LM, Joanisse S, Grubb A, Mitchell CJ, McKay BR, Phillips SM, et al. The acute satellite cell response and skeletal muscle hypertrophy following resistance training. *PLoS One* 2014;**9**:e109739.
40. Vechin FC, Libardi CA, Conceicao MS, Damas FR, Lixandrao ME, Berton RP, et al. Comparisons between low-intensity resistance training with blood flow restriction and high-intensity resistance training on quadriceps muscle mass and strength in elderly. *J Strength Cond Res* 2015;**29**:1071–1076.
41. Takarada Y, Takazawa H, Sato Y, Takebayashi S, Tanaka Y, Ishii N. Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. *J Appl Physiol* 2000;**88**:2097–2106.
42. Lixandrao ME, Ugrinowitsch C, Berton R, Vechin FC, Conceicao MS, Damas F, et al. Magnitude of muscle strength and mass adaptations between high-load resistance training versus low-load resistance training associated with blood-flow restriction: a systematic review and meta-analysis. *Sports Med* 2017.
43. Gualano B, Neves M Jr, Lima FR, Pinto AL, Laurentino G, Borges C, et al. Resistance training with vascular occlusion in inclusion body myositis: a case study. *Med Sci Sports Exerc* 2010;**42**:250–254.
44. Jorgensen AN, Aagaard P, Nielsen JL, Frandsen U, Diederichsen LP. Effects of blood-flow-restricted resistance training on muscle function in a 74-year-old male with sporadic inclusion body myositis: a case report. *Clin Physiol Funct Imaging* 2016;**36**:504–509.
45. Abe T, Fujita S, Nakajima T, Sakamaki M, Ozaki H, Ogasawara R, et al. Effects of low-intensity cycle training with restricted leg blood flow on thigh muscle volume and VO_2max in young men. *J Sports Sci Med* 2010;**9**:452–458.
46. Abe T, Kearns CF, Sato Y. Muscle size and strength are increased following walk training with restricted venous blood flow from the leg muscle, Kaatsu-walk training. *J Appl Physiol (1985)* 2006;**100**:1460–1466.
47. Ozaki H, Sakamaki M, Yasuda T, Fujita S, Ogasawara R, Sugaya M, et al. Increases in thigh muscle volume and strength by walk training with leg blood flow reduction in older participants. *J Gerontol A Biol Sci Med Sci* 2011;**66**:257–263.
48. Conceição MS, Junior EMM, Telles GD, Libardi CA, Castro A, Andrade ALL, et al. Augmented anabolic responses following 8-weeks cycling with blood flow restriction. *Med Sci Sports Exerc* 2018;1.
49. Abe T, Sakamaki M, Fujita S, Ozaki H, Sugaya M, Sato Y, et al. Effects of low-intensity walk training with restricted leg blood flow on muscle strength and aerobic capacity in older adults. *J Geriatr Phys Ther* 2010;**33**:34–40.
50. 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;**20**:1041–1046.
51. Paton CD, Addis SM, Taylor LA. The effects of muscle blood flow restriction during running training on measures of aerobic capacity and run time to exhaustion. *Eur J Appl Physiol* 2017;**117**:2579–2585.
52. de Oliveira MF, Caputo F, Corvino RB, Denadai BS. Short-term low-intensity blood flow restricted interval training improves both aerobic fitness and muscle strength. *Scand J Med Sci Sports* 2016;**26**:1017–1025.
53. Clarkson MJ, Fraser SF, Bennett PN, McMahon LP, Brumby C, Warmington SA. Efficacy of blood flow restriction exercise during dialysis for end stage kidney disease patients: protocol of a randomised controlled trial. *BMC Nephrol* 2017;**18**:294.
54. Nakajima T, Kurano M, Iida H, Takano H, Oonuma H, Morita T, et al. Use and safety of KAATSU training: results of a national survey. *Int J KAATSU Training Res* 2006;**2**:5–13.
55. Nakajima T, Takano H, Kurano M, Iida H, Kubota N, Yasuda T, et al. Effects of KAATSU training on haemostasis in healthy subjects. *Int J KAATSU Train Res* 2007;**3**:11–20.
56. Madarame H, Kurano M, Fukumura K, Fukuda T, Nakajima T. Haemostatic and inflammatory responses to blood flow-restricted exercise in patients with ischaemic heart disease: a pilot study. *Clin Physiol Funct Imaging* 2013;**33**:11–17.
57. Sardeli AV, do Carmo Santos L, Ferreira MLV, Gaspari AF, Rodrigues B, Cavaglieri CR, et al. Cardiovascular responses to different resistance exercise protocols in elderly. *Int J Sports Med* 2017;**38**:928–936.
58. Domingos E, Polito MD. Blood pressure response between resistance exercise with and without blood flow restriction: a systematic review and meta-analysis. *Life Sci* 2018;**209**:122–131.
59. Yasuda T, Fukumura K, Fukuda T, Uchida Y, Iida H, Meguro M, et al. Muscle size and arterial stiffness after blood flow-restricted low-intensity resistance training in older adults. *Scand J Med Sci Sports* 2014;**24**:799–806.
60. Ozaki H, Yasuda T, Ogasawara R, Sakamaki-Sunaga M, Naito H, Abe T. Effects of high-intensity and blood flow-restricted low-intensity resistance training on carotid arterial compliance: role of blood pressure during training sessions. *Eur J Appl Physiol* 2013;**113**:167–174.
61. O'Rourke M. Arterial stiffness, systolic blood pressure, and logical treatment of arterial hypertension. *Hypertension* 1990;**15**:339–347.
62. Ferreira MLV, Sardeli AV, Souza GV, Bonganha V, Santos LDC, Castro A, et al. Cardiac autonomic and haemodynamic recovery after a single session of aerobic exercise with and without blood flow restriction in older adults. *J Sports Sci* 2017;**35**:2412–2420.
63. Barili A, Corralo VDS, Cardoso AM, Manica A, Bonadiman B, Bagatini MD,

et al. Acute responses of hemodynamic and oxidative stress parameters to aerobic exercise with blood flow restriction in hypertensive elderly women. *Mol Biol Rep* 2018;**45**:1099–1109.

64. Mendonca GV, Vaz JR, Pezarat-Correia P, Fernhall B. Effects of walking with blood flow restriction on excess post-exercise oxygen consumption. *Int J Sports Med* 2015.
65. Park S, Kim JK, Choi HM, Kim HG, Beekley MD, Nho H. Increase in maximal oxygen uptake following 2-week walk training with blood flow occlusion in athletes. *Eur J Appl Physiol* 2010;**109**:591–600.
66. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the journal of cachexia, sarcopenia and muscle: update 2017. *J Cachexia Sarcopenia Muscle* 2017;**8**:1081–1083.