

Research Article

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The effects of blood flow restriction exercise on vascular function in the elderly: A systematic review

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Background: Blood flow restriction (BFR) exercise has been used to induce skeletal muscle and aerobic adaptations that are similar to those induced by high intensity training, but with less time and lower intensities. The lower time demand and exercise intensity appear advantageous, especially for older people but there may be risks associated with a potential impairment of vascular function after BFR trainings. Therefore, the purpose of this systematic review was to evaluate the effects of aerobic and resistance exercise with BFR on vascular function in the elderly.

Methods: PubMed, Embase, Scopus, Lilacs, Web of science, Pedro, Google Scholar and the Cochrane library were searched for articles published until January 2019. This review included randomized and non-randomized controlled trials of BFR exercise for ≥ 4 weeks in older humans.

Results: In the first step, 133 articles were identified, of which 22 articles met the inclusion criteria. Sixteen studies were excluded because of the short training period (< 4 weeks) or the average age of participants (< 60 years). Six articles were included in this review (n = 146 individuals, mean age = 69 years old, 71,46% women and 28,54% men). BFR combined with aerobic exercise (n = 2) enhanced arterial and venous compliance in healthy elders and resistance exercises (n = 4) demonstrated no significant effects on vascular function in healthy elders compared to exercise without BFR.

Conclusion: These results suggest that the addition of BFR to exercise does even improve vascular function in healthy elderly people. This is a first indication that superimposing BFR is safe also in sedentary elders. However, future research, especially in sedentary elders, is necessary to assess the safety of this method.

Introduction

Blood flow restriction (BFR) exercise is a well-established method to induce muscle hypertrophy in different age groups [1,2], athletes [3], healthy elderly [4-6] and patients with chronic diseases [7-12]. One of the main advantages cited is that this method elicits similar physiological adaptations to that seen in response to high intensity aerobic [8-10] or resistance training [15,16], but in less time (4-6 week) and with lower exercise intensities (20% to 50% of one maximum repetition) [17]. This demand for fewer exercise sessions and lower exercise intensities may be particularly advantageous for frail people, such as inactive elders [18], and persons with injuries or in post-surgery [19].

There is, however, some evidence that BFR may have a negative effects on hemodynamic system, as higher blood systolic and diastolic responses has been observed in elders and patients with hypertension [20]. Part of this may be attributable to accumulation of metabolites (lactate, protons, K⁺) by BFR and consequently, metaboreflex stimulation, that results in increased sympathetic activity and, elevated blood pressure and heart rate [20]. An impaired vascular function after BFR may be particularly of concern in elderly with comorbidities, and while there may thus be muscular benefits of BFR in this population, they may not outweigh the risks associated with a reduced vascular function. Therefore, here we review the literature on the effects of BFR combined with aerobic and resistance exercises on the vascular function in the elderly.

Methods**Search strategy**

The information in this review was obtained through a search of The National Library of Medicine (PubMed), Embase, Scopus, Lilacs, Web of science, Pedro, Google Scholar and the Cochrane library, considering the period until January 2019. The chart (PRISMA (Supplementary chart)) describes the selection process of the studies reviewed (Figure 1). A comprehensive search in databases and in additional sources such as theses revealed a total of 133 articles. Out of those, 111 publications were excluded based on the title and abstract information. The remaining 22 articles were selected for full-text reading; of these, 6 fulfilled the eligibility criteria, including methodological quality of the studies and the age of the participants. Subsequently, a systematic assessment of changes induced by BFR exercises in the vascular system of older individuals was performed. All selected articles were assessed independently by two reviewers

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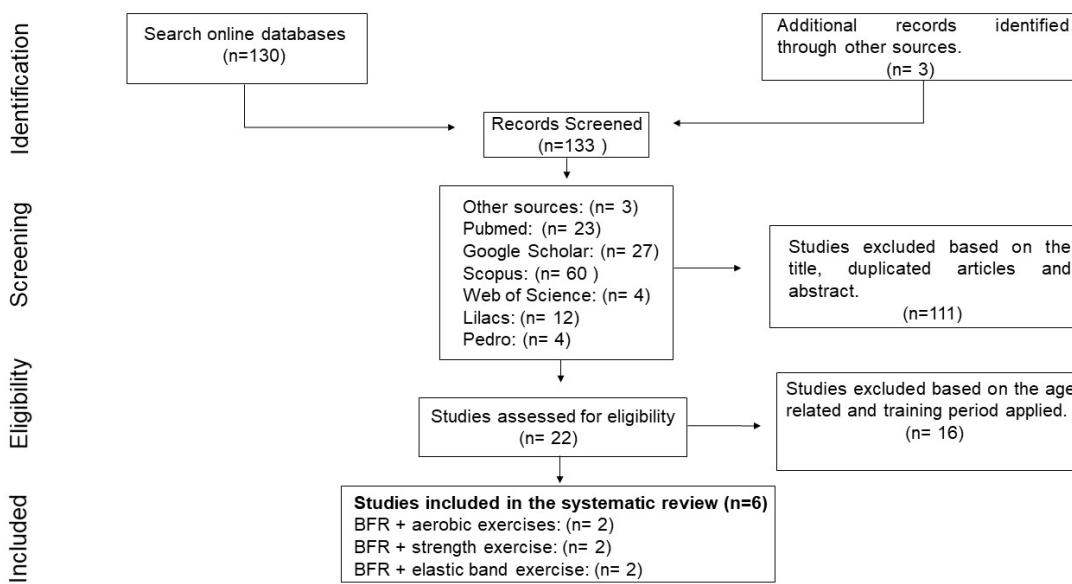


Figure 1: The flow diagram indicates the study selection

and disagreements were solved through discussion with the help of a third reviewer (3). In addition, both titles and abstracts were read in order to perform the screening. Then the studies which included relevant information were retrieved and read in full. The references section of the articles was examined to identify any potentially pertinent studies that had not been previously selected during the online search.

Definition of terms

The major English keywords and terms used to search were: ('kaatsu' or 'blood flow restriction training' or 'blood flow restriction exercise' or 'vascular occlusion training') AND ('vascular function' or 'endothelial function') AND ('arterial compliance or arterial stiffness') AND ('aging' or 'elderly' or 'ageing').

Inclusion and exclusion criteria

The inclusion criteria in this systematic review were organized according to the principle of PICOS (P: participants; I: intervention; C: comparison; O: outcomes; S: study designs). The details of inclusion criteria are explained as follows: P: humans with mean aged > 60 years; (2) I: the experimental group performed aerobic or resistance exercises with BFR and a specific description of exercise protocol was reported; (3) C: aerobic and resistance exercises (strength and elastic bands exercises); (4) O: the outcomes were vascular responses of training during ≥ 4 weeks; (5) S: randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs); and full-text articles with English language only. Therefore, conference abstracts, letters to the editor, theses, unpublished data, case report, and review articles were excluded.

Outcome measures

The outcome measures were focused on endothelial function, arterial stiffness, venous and arterial compliance. Some methods were used to evaluate the effects of BFR training on vascular function in the selected studies: cardio ankle vascular index (CAVI), ankle brachial index (ABI), flow mediated dilatation (FMD), von Willebrand factor (vWF) and reactive hyperemia index (RHI) (Table 1).

Quality assessment

According to the quality assessment of all eligible articles was evaluated using a modified version of Downs and Black checklist for assessing RCTs and NRCTs [21]. The 27 questions in checklist are related to reporting, external validity, internal validity and statistical power. In addition, the highest score for the checklist was 17. Hence, the studies were classified as excellent (26-28), good (20-25), fair (15-19), and poor (≤ 14).

Results

The summary of the results is presented in Table 2. There were 146 participants in the 6 selected studies, with an average age of 69 years. BFR was associated with aerobic exercise in two studies and resistance exercises in four (2 elastic bands and 2 strength exercises). The period of training ranged from four to twelve weeks.

Methodological quality assessment

The quality assessment of the studies is reported in Table 3. The main findings were that the external validity of studies included were poor and three studies were NRCTs. Furthermore, the studies were classified as poor and fair methodological quality.

Aerobic exercise combined with blood flow restriction

The studies that combined walking exercise with BFR showed positive effects on venous and arterial compliance in the elderly people with low level of physical activity [14,22].

Lida et al. [23] studied the effect of slow walking with BFR (20 minutes treadmill walking - 67 m min^{-1}) on venous compliance, measured by venous occlusion plethysmography, in untrained 59 to 78-year-old women (n = 9) versus a non-exercising control group (n = 7). They demonstrated a significant increase in leg venous compliance and maximal venous outflow in the intervention group only.

Ozaki et al. [22] examined the effects of walk training (20 min treadmill walking – exercise intensity: 45% of heart rate reserve with (n = 13) or without (n = 10) BFR on carotid artery compliance and muscle size in elderly. They found that carotid compliance improved in both

Table 1. The overview of outcome measures in the studies included in this systematic review

Study	Outcome	Mean (95% CI or SD)	
	BFR-R group	Pre-exercise	Post-exercise
Shimizu, et al. [27]	Reactive hyperemia index	1.8 ± 0.2	2.1 ± 0.3**
	Von Willebrand factor	175.7 ± 20.3	156.3 ± 38.1*
	Non BFR group		
	Reactive hyperemia index	NR	NR
	Von Willebrand factor	NR	NR
Yasuda, et al. [26]	BFR group		
	CAVI (m/s)	9.1(1.4)	9.0(1.5)
	ABI (unit)	1.13(0.07)	1.15(0.06)
	FMD (%)	2.8(2.0)	4.4(2.5)*
	Control group		
	CAVI (m/s)	8.7(0.8)	8.5(1.1)
	ABI (unit)	1.13(0.10)	1.13(0.09)
	FMD (%)	4.4(1.8)	3.9(2.5)
Yasuda, et al. [47]	BFR-Tr group		
	CAVI (m/s)	8.14(0.9)	8.5(0.8)
	ABI (unit)	1.14(0.06)	1.15(0.04)
	MH-Tr		
	CAVI (m/s)	8.4(0.9)	8.5(0.8)
	ABI (unit)	1.11(0.05)	1.11(0.08)
	Control group		
	CAVI (m/s)	8.3(0.8)	8.4(0.7)
	ABI (unit)	1.11(0.06)	1.12(0.05)
Yasuda, et al. [26]	BFR group		
	CAVI (m/s)	8.9(1.2)	9.2(1.1)
	ABI (unit)	1.17(0.07)	1.14(0.09)
	FMD (%)	3.6(2.1)	4.3(3.1)
	Control group		
	CAVI (m/s)	8.5(0.7)	8.2(0.8)
	ABI (unit)	1.10(0.10)	1.10(0.09)
	FMD (%)	4.3(1.6)	3.5(2.0)
Lida et al. [48]	BFR walking group		
	Venous compliance ($\text{ml } 100\text{ml}^{-1} \text{ mmHg}^{-1}$)	0.0518 ± 0.0084	0.0518 ± 0.0084*
	Control group		
	Venous compliance ($\text{ml } 100\text{ml}^{-1} \text{ mmHg}^{-1}$)	0.0686 ± 0.0160	0.0637 ± 0.0067
Ozaki et al. [49]	BFR walking group		
	Arterial compliance	0.984 (0.012)	0.118 (0.016)*
	Control group		
	Arterial compliance	0.079 (0.009)	0.114 (0.010)*

BFR: Blood Flow Restriction; BFR-R: Blood Flow Restriction Training; Non BFR- Low Intensity Resistance Training, BFR-Tr: Low Intensity Elastic Band BFR Training; MH-Tr: Middle to High Intensity Elastic Band Resistance Training; CAVI: Cardio Ankle Vascular Index; ABI: Ankle Brachial Index; FMD: Flow Mediated Dilatation, NR: Not Reported

*Significant difference from pre-exercise

**Significant difference from Non-BFR group

groups (BFR group = 50% and control group = 59%), but only walking combined with BFR improved MRI-measured thigh muscle cross-area (3%) and strength (15%).

Resistance exercises combined with blood flow restriction

Yasuda et al. [24-26] demonstrated in three studies that elastic band and strength exercises combined with BFR increased muscle cross-sectional area and muscle strength, without negative effects on hemodynamic parameters (heart rate and blood pressure), coagulation factors, or alterations in arterial stiffness and endothelial function in older people assessed by ABI, CAVI and FMD, respectively.

Shimizu et al. [27] reported that four weeks of BFR combined with resistance exercises enhanced vascular endothelial function and peripheral blood circulation above that induced by resistance exercise training without BFR in healthy elderly people. This study evaluated endothelial function by reactive hyperemia index (RHI), endothelial cell

damage by von Willebrand factor (vWF), and peripheral circulation by transcutaneous oxygen pressure in the foot (Foot-tc-PO2). The authors showed that there was an increase in RHI and decrease in vWF after 4-weeks of BRF resistance training. In addition, the BFR demonstrated a significant indicating enhanced peripheral circulation compared with the group without BFR.

These studies thus suggest that BFR combined with resistance exercise does not impair vascular function and may in fact even improve vascular function beyond that induced by resistance exercise alone, and thus be safely applied in older healthy people.

Discussion

The data of BFR exercise in the older population so far suggests that BFR superimposed on both aerobic and resistance exercise not only enhances muscle hypertrophy, but also has no significant negative effect, or even improves vascular function. This is a potentially

Table 2. The effects of blood flow restriction exercise on vascular function in the elderly

Author (year)	Subjects	Trial design	Age (yrs)	Type of Exercise	Exercise intensity	Occlusion time (min)	Exercise prescription (reps, sets, time and rest periods)	Period of Training	Cuff width (cm)	Applied Cuff pressure (mmHg)	Inflator Devices	Main results
Shimizu, et al. [27]	33 men 7 women	R	71	KE, LP, R, BP	20% 1RM	15	3 sets of 20 reps for each exercise with 30s between sets/ 60s between exercises.	3 days a week 4 weeks	7(UB) 10(LB)	NR	Tourniquet 9000	VEGF (+)
Yasuda, et al. [26]	5 men 14 women	R	61-84	KE, LP	20% - 30% 1RM	11	1 set of 30 reps + 1 set of 20 reps + 1 set of 15 reps + 1 set of 10 reps with rest periods around 30s between sets and 90s between exercises.	2 days a week 12 weeks	5	120-270	KAATSU Master	FMD (~), CAVI (~), ABI (~)
Yasuda, et al. [47]	30 women	R	61-86	KE, S	EB: black and gold	10 - 11.	1 set of 30 reps + 3 sets of 15 reps with rest periods of 30s between sets and 90s between exercises.	2 days a week 12 weeks	5	160-200	KAATSU Master	FMD (~), CAVI (~), ABI (~)
Yasuda, et al. [25]	3 men 14 women	NR	61-85	BF, TP	EB: Yellow	9.5	1 set of 30 reps + 1 set of 20 + 1 set of 15, 10 reps with rest periods of 30s between sets and 90s between exercises.	2 days a week 12 weeks	3	180-270	KAATSU Master	FMD (~), CAVI (~), ABI (~)
Lida et al. [48]	16 women	NR	59-78	Walking	67 m/min	23	20 minutes	5 days a week 6 weeks	NR	180-200	KAATSU Master	DBP (+), LVC (+)
Ozaki et al. [49]	3 men 10 women	NR	57-76	Walking	45% HRR	20	20 minutes	4 days a week 10 weeks	5	140-200	KAATSU Master	AC (+)

Abbreviations: **R:** Randomized; **NR:** Not Randomized; **SBP:** Systolic Blood Pressure; **DBP:** Diastolic Blood Pressure; **HRR:** Heart Rate Reserve; **BW:** Body Weight; **S:** Squat; **BF:** Biceps Flexion; **TP:** Triceps Press; **BP:** Bench Press; **R:** Rowing; **KE:** Knee Extension; **KF:** Knee Flexion; **LP:** Leg Press; **EB:** Elastic Bands; **VF:** Vascular Function; **CAVI:** Cardio Ankle Vascular Index; **PWV:** Pulse Wave Velocity; **ABI:** Ankle-Brachial Blood Pressure Index; **AC:** Arterial Compliance; **RM:** Repetition Maximum; **FMD:** Flow Mediate Dilatation; **SV:** Stroke Volume; **VEGF:** Vascular Endothelial Growth Factor; **UB:** Upper Body; **LB:** Lower Body; **LVC:** Limb Venous Compliance; +: Positive Effect, -: Negative Effect, ~: No Effect; **NR:** Not Reported

Table 3. Quality assessment

Study	Communication	External Validity	Internal Validity (bias)	Internal Validity confounding (selection bias)	Power	Total score	Rating
Shimizu, et al. [27]	7	1	4	4	1	17	Fair
Yasuda, et al. [26]	7	1	4	3	1	16	Fair
Yasuda, et al. [47]	7	1	5	3	1	17	Fair
Yasuda, et al. [25]	7	1	4	4	1	17	Fair
Lida et al. [48]	5	1	3	3	1	13	Poor
Ozaki et al. [49]	7	1	3	1	1	13	Poor

significant observation as in particular older frail people may benefit from an increased skeletal muscle mass, but often find high intensity resistance exercises may too demanding and with BFR it is possible that the intensity and frequency of exercise can be reduced while eliciting the same benefits [28].

Ageing is associated with loss of skeletal muscle mass and decrements in cardiovascular function that may hamper rehabilitation in the older person.

Although training with BFR appears to be as an interesting option, it is important to keep in mind that ageing is accompanied by vascular modifications, such as endothelial dysfunction, increased arterial stiffness, diminished responsiveness of local vascular control mechanisms and reduction in cardiac pump effectiveness [29]. This is an important consideration as one study in older people and hypertensive individuals reported BFR-induced deterioration of hemodynamic function [20].

Dysfunction of the vascular endothelium might be caused by oxidative stress, reduction of nitric oxide synthesis and consequently attenuated arteriolar dilation [30].

For this review, we found only six studies that evaluated the impact of BFR superimposed on exercise on vascular function in healthy and sedentary elders. None of these studies reported any undesirable side effects on vascular function, irrespective of the training type combined BRF.

It is important to highlight that most of the studies were conducted with the KAATSU master device (5 studies) and only one with an adapted BFR technique (Tourniquet 9000). Importantly, there are no studies with other adapted blood flow restriction methods associated with training that evaluated their safety in relation to the vascular function in the elderly.

The studies with aerobic exercise enhanced limb venous and carotid arterial compliance in sedentary elders [14,22]. However, in Ozaki's study, the increase in carotid arterial compliance was similar in the walking with and without BFR groups (without - pre: 0.079 mm²/mmHg, post: 0.114 mm²/mmHg P < 0.01 and with BFR pre: 0.084 mm²/mmHg, post: 0.118 mm²/mmHg - P < 0.01) (29). These results suggest that walking exercise was, by itself, responsible for these responses and

the KAATSU training did not have any additional effect. Even so, BFR did not attenuate the benefits of walking.

It has been reported that older people who regularly perform aerobic exercise, such as master athletes have better vascular endothelial function and better compliance large elastic artery [30,31]. On the other hand, high intensity resistance exercises can increase arterial stiffness and should be avoided in older people [32].

The studies of BFR with elastic bands did not show any significant modification of the vascular function in either the upper or lower body. Similarly, low intensity strength exercises with BFR induced no changes in arterial stiffness [26], but rather enhancements in the endothelial function and peripheral circulation were found [27]. These positive results could be related to the training frequency. While in the Yasuda et al. study [25] the frequency of training was twice a week, Shimizu et al. [27] did the exercise three times a week. It is known that training variables such as occlusion pressure, cuff size, exercise session time, training volume, rest time and training intensity influence hemodynamic responses, and also have an effect on vascular function [3,17,33-35]. However, this bias is minimized as in both studies training with BFR was compared to an identical training without BFR and hence any differences can be ascribed to BFR.

It is generally thought that, the additional benefits of BFR superimposed on exercise are attributable to the hypoxic stress, that would cause an augmented secretion of factors such as lactate (Lac), norepinephrine (NE), vascular endothelial growth factor (VEGF) and growth hormone (GH) [16,36]. Indeed, it has been demonstrated that BRF stimulates VEGF release from both vascular endothelium and skeletal muscle cells [37]. VEGF bound to its receptors on the endothelial cell membrane in turn increases eNOS expression, increasing local NO production [38] and thereby stimulates vasodilation and endothelial cell proliferation. Thus, increased VEGF in response to the reduction of muscle blood flow during an exercise session may well induce proliferation and migration of endothelial cells and accelerate angiogenesis in the skeletal muscles [39,40] (Figure 2).

In parallel, it has been demonstrated that the serum concentration of GH after a single bout of low intensity resistance training increases more after resistance exercise with BFR compared to that induced by resistance exercise without BRF [22]. Growth hormone has, like VEGF, been shown to upregulate eNOS expression in endothelial cells and thereby improve vascular endothelial function [41,42], and may also play a role in the development of muscle hypertrophy [27,39].

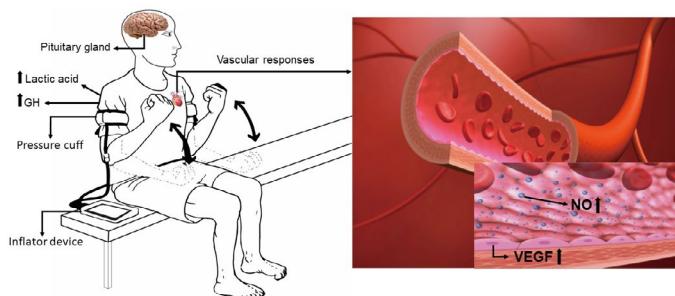


Figure 2. Illustration demonstrating the influence of BFR method in vascular responses and the physiological effects

Legends: GH – Growth hormone, NO - Nitric Oxide, VEGF – Vascular endothelial growth factors.

Part of this positive response may not only be due to hypoxia, but also to a lesser endothelial cell damage as reflected by increased RHI and reduction of Von Willebrand factor (vWF) [43]. VWF is an important glycoprotein, which has function in homeostasis and thrombus formation [43]. During ageing, the levels of vWF increase significantly, and is associated with an increased risks of coronary heart disease and thrombotic disorders [45,46]. Therefore, the BFR induced reduction vWF, may improve the coagulation system, circulation and thereby the risk of cardiovascular complications.

Limitations

Although the studies published so far favor the use of BFR with aerobic and resistance training, they are few and many from the same research group. In addition, the types of exercise and methods of analysis of vascular function were heterogeneous hindering detailed statistical analysis. Hence, the methodological quality of studies was considered poor and fair, especially external validity that contains questions regarding the study population. For the wide use of this technique and its expansion for the elderly population with comorbidities, future research is necessary, mainly in relation to the safety of the method and to further evaluate whether indeed the superimposing BFR enhances the gains of conventional aerobic or resistance exercise.

Conclusion and future directions

The studies with BFR combined with aerobic and resistance exercises in healthy elderly people showed positive or neutral results with respect to vascular function. However, the number of studies focused on both methods in elders are still limited and more studies to evaluate the safety of these types of training should be conducted, especially in sedentary and frail elderly people. Nevertheless, the first indications are that training and therapy with BRF may be applied safely and with enhanced benefits of muscle hypertrophy and vascular function in rehabilitation of the older person.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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