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Effects of Blood Flow Restriction Exercise on Hemodynamic and Cardiovascular Response in Hypertensive Subjects: a Systematic Review

Efeito do Exercício Físico com Restrição do Fluxo Sanguíneo Sobre as Respostas Hemodinâmicas e Cardiovasculares em Indivíduos Hipertensos: uma Revisão Sistemática

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Abstract

Blood flow restriction (BFR) exercise is an effective approach for increasing muscle mass and muscle strength. However, it remains unclear if the magnitude of those positive adaptations will lead to similar responses for hemodynamic variables in hypertensive subjects. The present systematic review aimed to assess the effects of exercise with and without BFR on acute and chronic hemodynamic and cardiovascular responses in hypertensive subjects. Studies published between 2000 and 2019 were included. Randomized controlled trials (RCTs) and non-randomized trials (NRCTs) which evaluated hemodynamic and cardiovascular response in hypertensive subjects practicing exercise with BFR or those comparing hemodynamic and cardiovascular response during exercise with and without BFR were also eligible. A literature research of English and non-English-language articles for review was conducted across PubMed and Science Direct databases, including reference lists of relevant papers. Level of evidence was determined according to the criteria described by Oxford Center for Evidence-Based Medicine. In addition, risk of bias was assessed using the modified version of Downs and Black checklist. Four studies were included involving 60 participants; from those, three were NRCTs and one was a RCT. Three studies included in this review evaluated the effect of resistance training with and without BFR and only one the effect of aerobic exercise. The score on Downs and Black checklist was 11. The main findings were that the included patients' characteristics were not clearly reported, and all the revised studies contained significant methodological limitations. Thus, all studies were classified as being of poor methodological quality. In addition, the evidence level provided in all the revised studies was level IIb only (i.e. poor-quality studies). Considering the limited available evidence, no definitive recommendation about BFR exercise in hypertensive subjects can be addressed due to the weak methodological design of the studies.

Keywords: Resistance Training. Hypertension. Vascular Occlusion. Blood Flow Restriction.

Resumo

O exercício físico com restrição do fluxo sanguíneo (RFS) é uma abordagem eficaz para o aumento da massa muscular e força muscular. No entanto, ainda não está claro se a magnitude dessas adaptações positivas levará a respostas semelhantes para as variáveis hemodinâmicas e cardiovasculares em indivíduos hipertensos. A presente revisão sistemática objetivou avaliar os efeitos do exercício físico com e sem RFS sobre respostas hemodinâmicas e cardiovasculares agudas e crônicas em hipertensos. Estudos publicados entre 2000 e 2019 foram incluídos. Ensaios clínicos randomizados e não-randomizados em que avaliaram a resposta hemodinâmica e cardiovascular em hipertensos que praticavam exercício físico com RFS ou aqueles que compararam a resposta hemodinâmica e cardiovascular durante o exercício com e sem RFS também foram elegíveis. Uma pesquisa bibliográfica de artigos em inglês e não inglês para a presente revisão foi realizada nas bases de dados PubMed e Science Direct, incluindo listas de referência de artigos relevantes. O nível de evidência foi determinado de acordo com os critérios descritos pelo Oxford Center for Evidence-Based Medicine. Além disso, a qualidade dos artigos foi avaliada usando a versão modificada da lista de verificação de Downs e Black. Foram incluídos quatro estudos envolvendo 60 participantes nesta revisão. Destes, três eram ensaios clínicos não randomizados e somente um era ensaio clínico randomizado. Três estudos incluídos nesta revisão avaliaram o efeito do treinamento resistido com e sem RFS e apenas um avaliou o efeito do exercício aeróbico. A pontuação na lista de verificação de Downs e Black foi 11. Os principais achados foram que as características dos pacientes incluídos não foram claramente relatadas e todos os estudos revisados continham limitações metodológicas significativas. Assim, todos os estudos foram classificados como de baixa qualidade metodológica. Além disso, o nível de evidência fornecido em todos os estudos revisados era apenas de nível IIb (ou seja, estudos de baixa qualidade). Considerando as poucas evidências disponíveis, nenhuma recomendação definitiva sobre o exercício físico com RFS em indivíduos hipertensos pode ser abordada devido ao fraco desenho metodológico dos estudos.

Palavras-chave: *Treinamento Resistido. Hipertensão. Oclusão Vascular. Restrição do Fluxo Sanguíneo.*

1 Introduction

The use of blood flow restriction exercise (BFR) or any type of planned, structured and repetitive movement paired with reduction of blood flow by a specially-designed belt or cuffs has been shown to positively influence bone metabolism, attenuates muscle strength loss after knee arthroscopy, induce hypoalgesia in subjects suffering from anterior knee pain and treat tendon ruptures during rehabilitation process[1-6]. Furthermore, studies have shown that it can increase the functional capacity and strength using water-based exercise and when used with low load resistance training (i.e. ≤30% of one repetition maximum [1RM]) induces similar gains in muscle strength and hypertrophy as promoted by high-load resistance training (e.g., ≥65% of 1RM)[1-6].

The use of low-load resistance training (RT) with BFR is also useful in enhancing functional capacity and to relief pain in elderly subjects with knee osteoarthritis without increasing knee pain discomfort[7-8]. It is also known to prevent muscle atrophy in post-surgery patients that underwent anterior cruciate ligament reconstruction[9]. Moreover, low-load RT with BFR is tolerable in subjects suffering from musculoskeletal weakness, as it promotes lower joint forces and stress, acting as a surrogate for high-load RT in a broad range of clinical populations[10].

Although positive effects on muscle strength and hypertrophy were reported[11-13], attention must be drawn to the adverse effects of BFR training on hemodynamic and cardiovascular response in subjects with established cardiovascular disease, such as hypertensive individuals[14].

Recent studies with young normotensive subjects concluded that low load RT with BFR promoted hypotensive responses similar to traditional high-load RT[13,15,16]. Moreover, recent data demonstrated that when low-load RT is performed with BFR, endothelial function and peripheral blood circulation were improved[17]. However, studies included young healthy subjects[13-17] and the hemodynamic and cardiovascular response to low-load RT with BFR might be different in hypertensive subjects.

Concerning neuro-humoral response promoted by BFR exercise, higher plasma noradrenaline levels, vasopressin, renin activity, sympathetic nervous activity, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and increments on arterial resistance were observed in non-hypertensive during BFR exercise with low load when compared with traditional exercises without BFR[14,17-21]. In addition, a preview research[22] reported an increase in mean blood pressure (MBP) and DBP after four weeks of low-load RT with BFR in healthy men, reinforcing the health hazard perspective in that repetitive exposure to ischemic exercise stimulus might elicit increases in diastolic blood pressure due to chronic and constant exposure to higher neuro-humoral response induced by BFR exercise. Although no previous study had addressed the effect of aerobic exercise combined with BFR in hypertensive subjects, a greater cardiac work and decrements in endothelial function in non-hypertensive-subjects were promoted even at low intensity walking with BFR, suggesting that ischemia-reperfusion might affect the vascular endothelial function[23].

Regarding the importance of systematic reviews, all relevant research must be considered in decisions about the treatment used in clinical practice and the evidence available[46]. Treatment decisions must be informed by synthesis of all relevant evidence synthesized rigorously in systematic reviews, including previous research, with similar topic[47]. However, a previous concise study cannot be expected to cover all the relevant research about BFR exercise in hypertensive subjects[46,47]. Furthermore, systematic review must be used to explain the differences in ways that may help insure safety and correct use of BFR exercise in hypertensive subjects according to the quality of the studies used.

Domingos and Polito[47] in a recent systematic review and meta-analysis evaluated blood pressure response between RT with and without BFR in hypertensive and normotensive subjects, but their study did not report the effect of aerobic exercise on hemodynamic and cardiovascular response. Curiously, they used the tool for the assessment of study quality and reporting in Exercise (TESTEX) scale that assess the quality of randomized controlled trials (RCTs)[48], but the studies included with hypertensive subjects were non-randomized trials (NRCTs). In this context, using a better scale as Black and Down checklist that to evaluate controlled and non-controlled randomized studies such as the list of Black and |down verification compared to TESTEX[28] is necessary. In addition, aerobic exercise in combination with BFR might result in the same hemodynamic and cardiovascular differences observed with RT, which makes it potentially useful to compare in hypertensive subjects suffering from musculoskeletal weakness that use water-based exercise or any type of aerobic activity with BFR to increase functional capacity and strength.

Considering that, hypertensive subjects present an increase in pressor exercise reflex, and an excessive restriction promoted by BFR during exercise could lead to overactivation of muscle reflexes with consequent development of sympathetic hyperreactivity and increased risk for cardiovascular-related events[14]. Several intrinsic and extrinsic factors must be considered before using BFR exercise in subjects with coronary artery disease, unstable hypertension, peripheral vascular disease, vascular endothelial dysfunction, and varicose veins[24].

Another concern is that shear stress (i.e. the blood frictional force on the arterial wall), an important variable to induce endothelial adaptation during exercise may be blunted in the cuffed limb exposed to a lower shear stress during BFR exercise[49]. Previous research demonstrated that BFR exercise negatively influenced acute and chronic measures of flow mediate dilation (FMD, an important index of nitric oxide mediated endothelial function), which might be detrimental to endothelial function[49-51].

In addition, the disturbed blood flow induced by the cuff elicits an injurious stimulus to the endothelium and the decrease in FMD might be related to a proinflammatory and proapoptotic effect of disturbed blood flow, such as retrograde shear stress[38]. Considering that older subjects already exhibit age-related increases in arterial stiffness, hyperactive sympathetic system, increased vascular tone, and depressed sensitivity to nitric oxide (NO) that contribute to attenuated FMD[52]. The use of BFR exercise in hypertensive subjects must be critically investigated.

For this purpose, the aim of the present study was to perform a systematic review of BFR exercise effects on acute and chronic hemodynamic and cardiovascular response in hypertensive subjects and to provide recommendations regarding safety and effective implementation of BFR exercise.

2 Material and Methods

2.1 Search strategy

A systematic review was conducted, and the recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) were considered[25]. The search strategies were reported to ensure the integrity of the results, and to allow the updating using the same methods to bring emerging evidence into the review with enough detail as previous studies[26,27]. The Boolean and/or proximity operators were used, and the search strategy was correctly adapted for each database used (Table 1). Studies were identified by searching the following electronic databases: PubMED/MEDLINE (via National Library of Medicine) (2000 to 2019), and Science Direct (Elsevier) (2000 to 2019). The last search was conducted in June 2019.

Table 1 - Search strategies

Database	Search strategy	Hits	N (%) of Trials Finally Selected
PubMED/MEDLINE – via National Library of Medicine	“Kaatsu training” AND “Resistance training” AND “Hypertension”	3	4
	“Vascular occlusion” AND “Resistance training” AND “Blood pressure”	14	
	“Vascular occlusion” AND “Strength training” AND “Blood pressure”	6	
	“Blood flow restriction” AND “Exercise” AND “Hypertension”	8	
Articles that fulfil the inclusion criteria	(Araújo et al., 2014); (Pinto et al., 2016); (Pinto et al., 2018); (Barili et al., 2018)		
		Total: 31	
Science Direct (Elsevier)	“Kaatsu training” OR “Vascular occlusion” AND “Hypertension”	29	0
	“Blood flow restriction” OR “Vascular occlusion” AND “Exercise” AND “Hypertension”	35	
		Total: 64	

“”= quotation marks is used to specify terms, which must appear next to each other.
Source: Research data.

Once the abstracts were reviewed, the complete papers versions that met the criteria were obtained. Furthermore, the papers reference lists that fulfilled the inclusion criteria were analysed for the identification of additional studies that had not been identified during online research. The studies exclusion with irrelevant content and duplicates was carried out in three steps. The title, abstract and full-text articles were read.

The title, abstract, and full-text articles were read by two reviewers (DCN and BP). The reviewers assessed the eligibility of each study based on inclusion/exclusion criteria, and in case of disagreements, a third review (JP) evaluated the article, considering the recommendation of Systematic Review registration in the International Prospective Register of Systematic Reviews (PROSPERO). Unfortunately, on-going data extraction are not accepted anymore in 2019 in PROSPERO platform.[

2.2 Definition of Terms

The following terms registered in the database from Medical Subject Headings (MeSH), and free terms were also used: ‘resistance training’, ‘strength training’, ‘exercise’, ‘vascular occlusion’, ‘Kaatsu training’, ‘blood flow restriction’ associated with ‘hypertension’ and ‘blood pressure’.

2.3 Inclusion and Exclusion Criteria

The inclusion criteria in this systematic review were constructed according to the principle of PICOS (P: Participants; I: Intervention; C: Comparison; O: Outcomes; S: Study design). The details of inclusion criteria are explained as follows: (1) P: subjects with hypertension; (2) I: the experimental group received BFR exercise (i.e. that is, the use of any type of planned, structured, and repetitive movement associated with blood flow reduction by a specially-designed belt or cuffs); (3) C; conventional exercise training without BFR, or no-intervention control; (4) O; the primary outcomes were hemodynamic and cardiovascular response during pauses between sets and during different exercise sessions; (5) S: randomized controlled trials (RCTs) and non-controlled trials (NRCTs). Only full-text articles citations with no restriction to language were included.

The exclusion criteria were as follows: (1) meeting or conference abstracts, unpublished data, case reports, case series, letter do the editor, thesis, or review articles; (2) the full text of the article was unavailable, despite the effort to contact the original authors.

2.4 Outcome Measures

The outcome measures assessed for the acute and chronic effects (during pauses between sets and during different exercise sessions) of exercise were: systolic blood pressure (SBP), diastolic blood pressure (DPB), mean blood pressure (MBP), heart rate (HR), and systemic vascular resistance (SVR). These mediators were chosen after an initial analysis and review of the literature. They were identified as the main outcomes in studies published with normotensive subjects during BFR exercise[17-21].

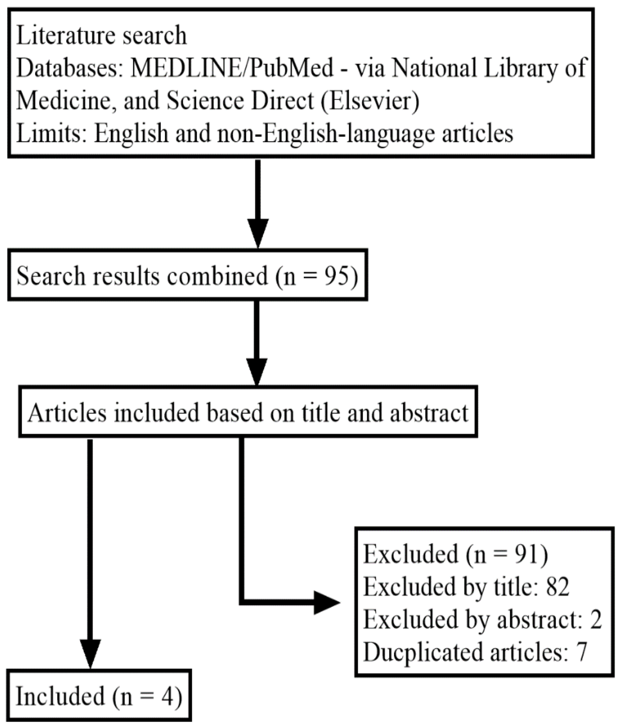
2.5 Quality and levels of evidence assessment

The quality of all eligible articles was evaluated using a modified version of Downs and Black checklist for assessing RCTs and NRCTs (comprising 27 questions)[28]. Items 1-10 refer to reporting, 11-13 refer to external validity, 14-26 refer to internal validity, and 27 relates to statistical power. In the current investigation, the item 27 was modified based on whether the study presented a power calculation or not. Thus, the maximum score for item 27 was 1 (a power analysis was conducted) and 0 (a power analysis was not conducted). The highest score for the checklist was 28 (instead of 32). Studies were classified as being excellent (26-28), good (20-25), fair (15-19), and poor (≤ 14)[29]. Disagreements between authors were discussed and subsequently solved. The level of evidence of each article was determined according to the criteria described by the Oxford Center for Evidence-Based Medicine[30] that ranges between level 1a to 5.

3 Results and Discussion

Results of study selection and research strategy used are shown in Figure 1 and Table 1, respectively. Among the 95 papers fully assessed in this systematic review, four studies were included[31-34]. The search of PubMED and Science Direct provided 95 citations. After adjusting for duplicates, 88 remained. Of these, 82 were discarded after reviewing the title and two after reviewing the abstract. Four studies met the inclusion criteria and were included in the systematic review. Furthermore, three studies consisted of NRCTs[13,32,33] and only one was a RCT[34]. All studies verified the effects of acute BFR exercise on haemodynamic and cardiovascular response in hypertensive subjects.

Figure 1 – Flow diagram of study selection



Source: Authors.

3.1 Methodological Quality Assessment

The studies quality assessment is summarized in Table 2. The main findings were that the included patients' characteristics were not clearly reported. All the revised studies contained significant methodological limitations, and were classified as poor methodological quality, failed to report the blinding procedures, and/or failed to report if there was compliance with the intervention. Furthermore, intervention group sizes were too small, and not representative of populations. The lack of power was a significant issue for most studies, albeit only one addressed this deficiency[34]. The most common issue was the failure to report possible adverse events that may be a consequence of the BFR exercise. Furthermore, all studies were classified as being of low methodological quality. The level of evidence provided in all the revised studies was level IIb only (i.e. poor quality studies).

Table 2 - Quality Assessment

Barili et al., 2018	Pinto et al., 2018	Pinto et al., 2016	Araújo et al., 2014	Items	
1	1	1	1	1	Reporting[a]
1	1	1	1	2	
1	1	1	1	3	
1	1	1	1	4	
1	1	1	1	5	
1	1	1	1	6	
0	1	1	1	7	
1	0	0	0	8	
0	0	0	0	9	
0	0	0	0	10	External Validity[b]
0*	0*	0*	0*	11	
0*	0*	0*	0*	12	
1	1	1	1	13	
0	0	0	0	14	Internal Validity (bias)[c]
0	0	0	0	15	
0	0	0	0	16	
1	1	1	1	17	
1	1	1	1	18	
0*	0*	0*	0*	19	
1	1	1	1	20	
0*	0*	0*	0*	21	Internal Validity – confounding (selection bias)[d]
0*	0*	0*	0*	22	
1	0	0	0	23	
0	0	0	0	24	
0	0	0	0	25	
0*	0*	0*	0*	26	
1	0	0	0	27	Power
13-Poor	11-Poor	11-Poor	11-Poor		Total score

1 = yes and 0 = no for questions 1, 2, 3, 4, 6, 7, 8, 9, and 10.
For question 5 - 2 = yes, 1 = partially, and 0 = no.
For other questions 1 = yes, 0 = no, and 0* = unable to determine.
[a] Reporting category includes items such as, study aims, reported outcomes, patient characteristics, confounders, adverse events, and loss to follow-up.
[b] External validity includes questions regarding the study population.

[c] Internal validity: bias includes items such as blinding, follow-up, and compliance.
[d] Internal validity: confounding includes items such as study selection, randomization, and study power.
Source: Research data.

3.2 Characteristics of the Studies and Summary of Outcome Measures

A total of 60 participants were included in the four studies. Two studies reported trainability[32,33], and all the studies were conducted with middle-aged, and elderly hypertensive women[31,34]. Considering that before BFR exercise prescription, intrinsic and extrinsic factors should be considered[24], and only one study reported time of hypertensive diagnosis, associated comorbidities, and drug therapy of the participants[34].

Furthermore, three studies used RT with BFR[31,33] and only one study used aerobic exercise with BFR[34]. Moreover, occlusion pressure was based on 80% of vascular occlusion[31,32], occlusion pressure was not reported in one study[33], and another study used 130% of SBP[34].

Another important information was that cuff width was the same (18 cm) in three studies[31-33], and only one study used a cuff width of 9 cm[34]. A summary of characteristics of selected studies and outcomes are presented in Table 3 and Table 4, respectively.

The low-load RT with BFR included protocols that ranged between 20 and 30% of 1RM, and traditional RT ranged between 65 and 80% of 1RM. Furthermore, only exercises for lower limbs were used[31,33].

Table 3 - Exercise intervention characteristics of the studies included in the systematic review

Study	Participants (n)	Study groups	Training status	Time of hypertensive diagnosis (years)	Sex (M:F)	Age [mean (SD)]	Types of Training	Training Scheme	Exercise	OP	Cuff width and length
Araújo et al., 2014	14	EG (14)	NR	NR	EG (0:14)	45.71	TRT (80% of 1RM) BFR training (30% of 1RM)	TRT: 3 sets/ 15 rep/1 minute RI BFR training: 3 sets/15 reps/ 45 seconds of RI – maximum repetitions performed BFR during whole training	Bilateral knee extension	80% arterial occlusion	18 cm and 80 cm
Pinto et al., 2016	12	EG (12)	Sedentary	NR	EG (0:12)	57.0 (7.0)	TRT (65% of 1RM) BFR training (20% of 1RM)	TRT: 3 sets/ 8 reps/1 minute RI BFR training: 3 sets/15 reps/30 seconds of RI –BFR during whole training	Bilateral leg press	NR	18 cm and 70 cm
Pinto et al., 2018	18	EG (18)	Sedentary	NR	EG (0:18)	67.0 (1.7)	TRT (65% of 1RM) BFR training (20% of 1RM)	TRT: 3 sets/ 10 reps/1 minute RI BFR training: 3 sets/10 rep/1 minute of RI – BFR during whole training	Bilateral knee extension	80% arterial occlusion	18 cm and 90 cm
Barili et al., 2018	16	EG (16)	NR	15 (8.8)	EG (0:16)	67 (3.7)	HIAE (50% of VO_2max) LIAE (30% of VO_2max) LILIAE + BFR (30% of VO_2max)	Aerobic Exercise	Treadmill	130% of SBP	9.5 cm and 92 cm

EG = experimental group, NR = not reported, reps = repetitions, RI = rest interval, RM = repetition maximum, TRT = traditional resistance training, BFR = blood flow restriction, HIAE = high intensity aerobic exercise, LIAE or LILIAE = low intensity aerobic exercise; OP = occlusion pressure.
Source: Research data.

Table 4 - Summary of outcome measures in the studies included in the systematic review.

Outcome	**Mean (95% CI or SD)]**					
	Pre-exercise	**1st set**	**2nd set**	**3rd set**	**Post-exercise**	**15/30/45/60 min**
BFR training[A]	**Araújo et al.,[31]**					
Heart rate	NR	107.2 (7.7)	115.0 (6.8)	108.7 (7.3)		NR
SBP	NR	167.4 (8.0	183.0 (10.0)†	173.7 (9.0)†		NR*
DBP	NR	96.0 (5.0)	107.0 (4.0)†	88.0 (9.0)		NR
Traditional RT[A]						
Heart rate	NR	93.5 (7.7)	100.5 (6.84)	108.7 (7.3)		NR
SBP	NR	141.0 (6.0)	147.0 (10.0)	146.0 (10.0)		NR
DBP	NR	87.0 (4.0)	86.0 (5.0)	87.0 (5.0)		NR
BFR training[A]	**Pinto et al.,[33]**					
Heart rate	76.0 (10.4)	99.6 (13.7)	114.3 (26.2)†	120.3 (21.7)†	81.0 (10.4)	
SBP	146.2 (19.6)	187.4 (27.5)	225.0 (30.1)†	237.2 (33.2)†	154.9 (18.4)	
DBP	82.2 (12.5)	109.8 (13.7)	130.2 (16.4)†	139.4 (22.2)†	86.3 (10.7)	
SVR	26.2 (10.9)	29.4 (10.4)	33.6 (11.5)†	37.2 (13.1)†	26.6 (10.1)	
Traditional RT[A]						
Heart rate	75.3 (10.5)	105.3 (17.4)	105.2 (13.8)	108.0 (17.5)	77.6 (11.7)	
SBP	145.0 (23.8)	184.2 (27.0)	192.8 (25.1)	195.7 (25.5)	147.0 (23.1)	
DBP	80.9 (16.1)	107.6 (20.1)	111.5 (17.7)	110.1 (18.2)	82.2 (16.6)	
SVR	25.0 (10.5)	24.2 (10.2)	26.1 (10.9)	24.6 (9.8)	25.2 (10.9)	
BFR training[B]						
Heart rate	76.0 (10.4)	79.0 (11.2)	87.1 (11.0)			
SBP	146.2 (19.6)	168.5 (25.1)	182.1 (25.7)			
DBP	82.2 (12.5)	89.7 (15.0)	94.6 (14.1)			
SVR	26.2 (10.9)	35.3 (16.1)	40.5 (17.9)			
Traditional RT[B]						
Heart rate	75.3 (10.5)	76.8 (10.5	74.0 (13.6)			
SBP	145.0 (23.8)	144.1 (19.0)	143.3 (22.9)			
DBP	80.9 (16.1)	74.4 (13.6)	73.9 (14.7)			
SVR	25.0 (10.5)	24.7 (9.5)	26.8 (9.2)			
BFR training[A]	**Pinto et al.,[32]**					
Heart rate	80.2 (3.0)	96.1 (2.6)	99.8 (3.2)	97.9 (2.9)	73.7 (2.0)	
SBP	132.7 (3.1)	179.8 (5.4)	210.7 (6.8)	212.2 (7.5)	129.8 (2.9)	
DBP	76.0 (2.3)	100.9 (3.2)	120.9 (4.5)	123.6 (5.5)	74.2 (2.5)	
SVR	24.8 (2.3)	29.0 (3.0)	36.6 (3.6)	41.3 (5.2)	35.2 (3.7)	
Traditional RT[A]						
Heart rate	75.3 (10.5)	100.9 (3.7)	102.9 (3.4)	107.8 (4.0)	74.7 (3.4)	
SBP	145.0 (23.8)	196.8 (7.1)	213.3 (8.2)	221.7 (8.2)	138.5 (5.9)	
DBP	80.9 (16.1)	100.8 (3.5)	119.5 (4.5)	122.6 (3.9)	71.1 (2.4)	
SVR	25.0 (10.5)	26.6 (2.0)	28.7 (2.6)	28.8 (2.7)	31.1 (3.5)	
BFR training[B]						
Heart rate		76.7 (2.3)	76.4 (2.6)			
SBP		140.4 (3.6)	155.3 (5.1)†			
DBP		78.2 (1.7)	86.8 (3.5)†			
SVR		34.7 (3.7)†	44.5 (4.8)†			
Traditional RT[B]						
Heart rate		78.7 (2.6)	74.7 (3.9)			
SBP		140.3 (6.0)	138.5 (5.9)			
DBP		72.4 (2.3)	71.1 (2.4)			
SVR		28.0 (2.9)	33.1 (3.5)			
HIAE (50% of	**Barili et al.,[34]**					
VO_2max)	**Pre-Exercise**	**After exercise**	**30 min recovery**			
HR	NR	NR	NR			
PAS	NR	NR	NR			
PAD	NR	NR	NR			
LIAE (30% of						
VO_2max)	NR	NR	NR			
HR	NR	NR	NR			
PAS	NR	NR	NR			
PAD						
LILIAE +						
BFR (30% of	NR	NR	NR			
VO_2max)	NR	NR	NR			
HR	NR	NR	NR			
PAS						
PAD						

BFR = blood flow restriction, RT = resistance training, HIAE = high intensity aerobic exercise, LIAE or LILIAE = low intensity aerobic exercise. SBP = systolic blood pressure, DBP = diastolic blood pressure, SVR = systemic vascular resistance, NR = not reported.

A = hemodynamic responses during different sessions.

B = Hemodynamic responses during pauses between sets.

† = Difference between groups at the same time-point.

* = Significant difference from pre-exercise.

Source: Research data.

3.3 Comparisons between BFR exercises and Traditional exercises on Hemodynamic and Cardiovascular Response in Hypertensive subjects

One study included in this systematic review demonstrated that low-load RT with BFR resulted in a higher SBP and DBP response when compared with traditional RT[31] (Table 4). Moreover, status of trainability was not reported and intensity (30% 1RM) was higher when compared with previous studies (20% 1RM)[32,33] (Table 4). The same study verified that both types of RT induced hypotension. Furthermore, a prior research[33] demonstrated that HR, SBP, DBP and SVR were higher in the second and third set for the low-load RT with BFR when compared with traditional RT during different sessions without differences during pauses between sets.

A preview study[32] demonstrated that HR, SBP, DBP, and SVR was similar between types of RT protocols during different sessions, but significantly higher during pauses in the first set for SVR, and significantly higher for SBP, DBP, and SVR in the second set during low-load RT with BFR when compared with traditional RT protocol. Finally, a recent study[34], using treadmill exercise reported no differences on hemodynamic and cardiovascular response between high intensity aerobic exercise, low intensity aerobic exercise and low intensity aerobic exercise with blood flow restriction protocols (Table 4).

3.4 Discussion

A systematic search of the literature revealed four unique publications regarding the effects of BFR exercise on hemodynamic and cardiovascular response in hypertensive subjects. Three of these aimed to determine the RT effects with and without BFR on the hemodynamic and cardiovascular response during and after exercise[31-33]; whereas a single study demonstrated, no differences between low intensity aerobic exercises without BFR compared with low intensity aerobic exercise with BFR, with conflicting results[34]. The primary findings of this present review demonstrate that acute hemodynamic responses between RT with BFR exercises and traditional exercises without BFR in hypertensive subjects are different. Low-load RT with BFR demonstrated higher hemodynamic and cardiovascular response when compared with traditional RT. Thus, a greater HR, SBP, DBP, and SVR during different exercise sessions and pauses were observed. In addition, adverse effects that might be a consequence of the interventions were reported in only one study[34].

One noteworthy finding is the side effects associated with BFR exercise that must be verified, such as cold feeling, bruising, fainting, numbness, subcutaneous haemorrhage, and venous thrombus already reported in previous studies[35-37].It is important to highlight that some essential variables, such as systemic arterial compliance, flow-mediated dilatation, markers such as CD31 expressed on endothelial micro-particles from apoptotic cells and inducible markers as CD62E that indicate endothelial activation induced by pro-inflammatory events were not measured[23,38]. Thus, further studies should elaborate appropriate study designs before placing unnecessary circulatory burden to hypertensive subjects during acute and chronic interventions.

In the first in-vivo experimental evidence in humans, acute effects of disturbed blood flow on the release of endothelial microparticles from the human vascular endothelium promoted by the use of forearm arm cuff occlusion in ten healthy young men were evaluated[38]. Two pneumatic cuffs were placed on the cuffed arm during a 20-minute intervention: A distal cuff inflated to 200 mmHg to produce a localized environment of disturbed blood flow, and a proximal cuff inflated to 40 mmHg to partially occlude venous flow from the arm. Results showed that endothelial microparticles increased substantially in the experimental arm, indicating endothelial activation and apoptosis. Moreover, a significant increase in retrograde shear stress was also noted. These data suggest that disturbed blood flow elicits an injurious stimulus to the endothelium and the decrease in FMD might be related to a proinflammatory and proapoptotic effect of disturbed blood flow, such as retrograde shear stress[38].

Another study[23] determined the acute effects of BFR combined with slow walking exercise on the cardiovascular function in healthy young people compared with a control session. Blood pressure (SBP, DBP, MBP, and total peripheral resistance) was significantly higher during BFR session when compared with the control session. In addition, systemic arterial compliance and flow mediated dilatation decreased significantly after acute leg BFR with slow walking. These results demonstrate the hypothesis that exercises with BFR should be cautiously prescribed in higher risk populations, such as hypertensive subjects, coronary artery disease, unstable hypertension, peripheral vascular disease, vascular endothelial dysfunction, and varicose veins[24]. However, a single study included in this systematic review, observed no differences between low intensity aerobic exercises without BFR compared with low intensity aerobic exercise with BFR in hypertensive subjects, with conflicting results[34]. In addition, a mercury column sphygmomanometer for blood pressure measurements at rest, immediately after exercise and after 30 min recovery were used[34.]. The possible reason for no differences between protocols was that studies with RT and BFR in hypertensive subjects, blood pressure was monitored continuously and non-invasively during exercise using a digital photoplethysmography device (FinometerTMPRO, Finapres Medical System, Amsterdam The Netherlands)[31-33]. The pneumatic regulation is adjusted simultaneously by a servo-controlled system that keeps the digital artery volume constant by varying the cuff pressure proportionally, thus providing continuous blood pressure readings[31-33].

Concerning clinical importance, a previous study demonstrated a more prominent increment in peripheral arterial stiffness in the limb exposed to low-load RT with BFR when compared with the contralateral limb that performed the same exercise without vascular occlusion in middle-aged subjects[39]. In addition, in another study after four weeks of training or frequent low-load RT with BFR, there was an elevation in pre-exercise diastolic arterial pressure[22].

It is possible that acute and chronic exposure to ischemic exercise stimuli, and higher neurohumoral response to BFR associated with increments in endothelial micro-particles (CD31 and CD62E), and overactivation of exercise pressor reflex might chronically affect blood pressure. However, this hypothesis must be confirmed in future trials.

Furthermore, cuff width can affect cardiovascular response[40]. Wide cuffs (13.5 cm) cause a greater hemodynamic and cardiovascular response when compared with narrow cuffs (5 cm) during low-load RT with BFR[40]. Considering that, three studies included in this systematic review used wide cuffs (18 cm)[31-33]. Thus, future studies should consider this difference and its effect on hemodynamic and cardiovascular response to low-load RT with BFR when compared with traditional RT.

Interestingly, during low-load RT, the sphygmomanometer was inflated during the whole exercise protocol for all the studies included in this systematic review and was deflated immediately after the end of the last set. One possible hypothesis might be the fact that the time under BFR *per se* could contributed to an increase in HR, SBP, DBP and SVR. This might be confirmed by the use of cyclical BFR model that attenuated sympathetic activity and hemodynamic response when compared with traditional BFR resistance exercise session and could potentially be adapted to clinical populations including hypertensive subjects[41].

More recently, some papers have questioned the safety of BFR exercise[35,42]. As an example, some populations are contraindicated to BFR due the risks and conditions that may promote the coagulation at sites of vascular damage and atherosclerosis (i.e. venous thromboembolism, peripheral vascular disease, blood clotting disorders, vascular endothelial dysfunction, and varicose veins). Thus, intrinsic factors must be considered before BFR[24] prescription. Given the nature of the BFR application, there might be a concern associated with blood flow obstruction, that may promote an overactivation of exercise pressor reflex[14,43,44]. However, the effects of BFR exercise on hemodynamic and cardiovascular responses in hypertensive subjects remain speculative.

Concerning the clinical significance that hemodynamic changes might place an unnecessary circulatory burden in hypertensive subjects[14], exercises with BFR should be prescribed carefully in patients by health professionals during rehabilitation and exercise training. The caution is relevant because hypertensive, peripheral artery disease and chronic heart failure subjects already present an overactivation of exercise pressor reflex[14,44,45].

It is worth noting that systematic reviews are better at assessing strength of evidence than single studies[43]. Although, OCEBM level of evidence was reported in this study, the level is not sufficient to provide with a recommendation. Thus, even if a treatment effect is supported by the best evidence (if any), one must consider: (1) If there is a good reason to believe that his or her patient is sufficiently similar to the subjects in the studies that he or she examined? (2) Does the treatment have a clinically relevant benefit that outweighs the harms? (3) Is there another better treatment?[43].

A previous systematic review[47], evaluated blood pressure response between RT with and without BFR in hypertensive and normotensive subjects, but their study did not report the effect of aerobic exercise on hemodynamic and cardiovascular response. Curiously, they used the tool for the assessment of study quality and reporting in Exercise (TESTEX) scale that assess the quality of randomized controlled trials (RCTs)[48], but the studies included with hypertensive subjects were non-randomized trials (NRCTs). In this context, a better scale as Black and Down checklist that assess NRCTs outperforms TESTEX[28]. Further, aerobic exercise in combination with BFR might result in the same hemodynamic and cardiovascular differences observed with RT. Finally, our conclusion differs from the previous study[47] and is based on the quality assessment and risk of bias.

To avoid untoward outcome and ensure that BFR can be properly used in hypertensive subjects[14], we are aware that very large randomized trials might often contribute the overwhelming weight of evidence on particular therapeutic questions[46] (i.e. do acute and chronic BFR exercise affect negatively hemodynamic and cardiovascular response in hypertensive subjects?), but there is no reason to ignore the evidence from smaller RCTs and non-RCTs judge likely to be biased or poor methodological quality trials.

4 Conclusion

Considering the limited available evidence, no definitive recommendations of BFR exercise in hypertensive subjects can be made due to the weak methodology of the revised studies.

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The first author wants to dedicate this paper to his family (Rita de Cassia and Nicolas Cunha).

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