DOI: 10.48305/jrrs.2026.46151.1137 Published by Vesnu Publications

Compare the Effect of Eight Weeks of Resistance Training with and without Blood Flow Restriction on Nitric Oxide and Endothelin-1 Levels in Inactive Men with Prehypertension: A Simple Randomized Clinical Trial

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Original Article

Abstract

Introduction: Prehypertension is associated with endothelial dysfunction and a disrupted balance of vascular mediators. Resistance training with blood flow restriction (BFR) has emerged as a novel strategy for improving vascular indices. The present study aimed to investigate the effects of 8 weeks of resistance training, with and without BFR, on nitric oxide (NO) and endothelin-1 (ET-1) levels in sedentary men with prehypertension.

Materials and Methods: A total of 36 sedentary young men with prehypertension were randomly assigned to one of three groups: a control group (CON), a resistance training with blood flow restriction group (RT+BFR), and a resistance training without blood flow restriction group (RT). The training intervention was conducted over eight weeks. Systolic and diastolic blood pressure, as well as NO and ET-1 plasma levels, were measured 48 hours prior to and 48 hours following the intervention. Data were analyzed using a paired-sample T-test and analysis of covariance (ANCOVA), with a Bonferroni post hoc correction applied at $P \leq 0.05$.

Results: Both resistance training modalities (with and without BFR) produced significant increases in NO levels compared to the control group ($P = 0.001$ and $P = 0.006$, respectively) and significant reductions in ET-1 concentrations ($P = 0.001$ and $P = 0.003$, respectively). Blood pressure also improved significantly in both experimental groups. However, no significant differences were observed between the two resistance training modalities with respect to NO ($P = 0.123$), ET-1 ($P = 0.571$), or blood pressure levels.

Conclusion: Low-intensity resistance training combined with BFR improves endothelial mediators and blood pressure to levels comparable to those achieved with traditional high-intensity resistance training. This approach may therefore serve as an effective, mechanically less demanding exercise alternative for enhancing vascular health in men with prehypertension.

Keywords: Prehypertension; Resistance training; Blood flow restriction; Nitric oxide; Endothelin-1

Citation: Yari A, Hosseinpour-Delavar S, Zabet A. **Compare the Effect of Eight Weeks of Resistance Training with and without Blood Flow Restriction on Nitric Oxide and Endothelin-1 Levels in Inactive Men with Prehypertension: A Simple Randomized Clinical Trial.** J Res Rehabil Sci 2025; 21.

Received date: 31.12.2024 Accept date: 04.02.2025 Published: 03.04.2025

Introduction

Prehypertension (PHTN), defined as systolic blood pressure ranging from 120 to 139 mmHg and diastolic blood pressure ranging from 80 to 89 mmHg, is a major public health concern that independently increases the risk of developing hypertension and cardiovascular disease (1). Although this condition is not classified as a distinct disease, individuals with

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prehypertension are not typically candidates for drug therapy; rather, lifestyle modification is a recommended strategy for preventing disease progression (2). Regular physical activity, particularly resistance training, has been identified as a major approach for the management and prevention of hypertension (3). Although traditional high-intensity resistance training may transiently induce oxidative stress and mechanical strain on the vascular wall, emerging evidence indicates that these effects are intensity- - and volume-dependent. That appropriately designed protocols can elicit favorable endothelial responses (4, 5). Consequently, the development of safe, low-risk training modalities for individuals with prehypertension is of considerable importance.

The selection of sedentary men with prehypertension, aged 30 to 45 years, as the target population for this study was predicated on the clinical significance of this demographic group. Men in the 30 -45-year age range undergo a critical transitional period characterized by the onset and consolidation of pathological vascular changes, including arterial stiffening and endothelial dysfunction (6, 7). Furthermore, a sedentary lifestyle and low aerobic capacity are among the most robust predictors of the transition from prehypertension to clinical hypertension in this population (8, 9). Exercise intervention at this stage, before irreversible structural damage to the vascular wall develops, has the potential to restore endothelial function and prevent cardiovascular disease in subsequent decades.

Resistance training combined with low-load BFR using pneumatic cuffs (20-30% of one-repetition maximum) has emerged as a novel approach in this context (10, 11). This modality, by inducing local hypoxia, stimulates hypoxia-inducible factor (HIF-1α) and upregulates vascular endothelial growth factor (VEGF) expression, which plays a key role in angiogenesis and vasculogenesis (12). Increased VEGF levels also enhance endothelial NO synthase (eNOS) activity, promoting NO synthesis and thereby improving endothelial function and facilitating vasodilation (13). Conversely, the hypoxic conditions induced by BFR may modulate ET-1 — the most potent vasoconstrictor — thereby contributing to the regulation of blood pressure (5, 14).

Numerous studies have previously evaluated the effects of BFR training across various populations. For instance, significant increases in muscle strength and mass have been reported in physically active young men (15, 16), improvements in metabolic indices in sedentary middle-aged men (17), enhanced athletic performance in male judokas (18), improved muscle strength and endurance in postmenopausal women (19), and hormonal alterations in young females (20). At the cellular level, Ferguson et al. (12) demonstrated that BFR training significantly upregulates the mRNA expression of VEGF, VEGFR2, HIF-1α, and eNOS. Larkin et al. (21) reported that BFR increases muscle hemoglobin (Hb) concentrations and potentiates VEGF and NOS expression. Similarly, Drummond et al. (22) and domestically, Basiri et al. (23) have reported comparable findings regarding enhanced angiogenesis indices.

Furthermore, Rahmani and Mehrani (24) investigated the effects of resistance exercise combined with a training mask and blood flow restriction on myocardial oxygen cost, blood pressure, and cardiac autonomic function in young male athletes. Their findings demonstrated that this training modality significantly improved myocardial oxygen cost variables and reduced both systolic and diastolic blood pressure following exercise. In a separate study, Farhani and Riahi (25) compared the effects of various resistance training protocols combined with blood flow restriction on cardiorespiratory preparedness and functional factors in military soldiers. Their results indicated that BFR training significantly enhanced cardiovascular endurance indices, increased muscle strength, and improved balance in this population. The purpose of citing this study in the present investigation is to substantiate the efficacy and versatility of the BFR method in improving cardiovascular and muscular indices concurrently, even across populations with varying readiness levels.

Despite the aforementioned evidence, data on the effects of BFR training on key direct mediators of blood pressure regulation — namely NO and ET-1 — in at-risk populations remain exceedingly limited. Karimi Ahmadabadi et al. (26) and Bazgir et al. (27) demonstrated that BFR significantly influences systolic and diastolic blood pressure. This effect may be attributable to the modulation of NO and ET-1 secretion. In an international study, Schamneh et al. (28) investigated cardiac autonomic responses to exercise combined with varying levels of BFR (cuff pressures corresponding to 40%, 60%, and 80% of arterial occlusion pressure) in men with prehypertension. Their findings indicated that although the application of high cuff pressures (e.g., 80%) may transiently elevate blood pressure and cardiovascular stress indices, these responses do not necessarily indicate non-adverse or unsafe hemodynamic consequences over the course of the entire protocol. The authors suggested that low-intensity exercise combined with BFR, provided

that cuff pressure is carefully and precisely regulated, may serve as a novel training modality capable of replacing traditional high-intensity resistance training. However, in the study by Schamneh (28), as well as in similar investigations such as that of Collier et al. (29), the impact of this modality on molecular variables, including NO and ET-1, was not directly assessed.

Therefore, despite the investigation of BFR across various populations (e.g., women, athletes, and young individuals), the existing research gap pertains to the absence of direct and simultaneous comparisons of traditional resistance training and BFR training on the levels of two key blood pressure regulation mediators — NO and ET-1 — specifically in sedentary men with prehypertension.

Thus, in light of the aforementioned evidence and the significance of prehypertension as a major cardiovascular risk factor, in the present study, attempts were made to compare the effects of 8 weeks of resistance training with and without blood flow restriction on NO, ET-1, and systolic and diastolic blood pressure in sedentary men with prehypertension. This investigation seeks to determine whether low-intensity BFR training could match traditional training in improving endothelial function and serve as a safe, effective alternative for this population.

Materials and Methods

The present study was a preliminary randomized clinical trial (pilot study) and was registered with a clinical trial registration code. A total of 36 sedentary young men from Ilam, Iran, with prehypertension (systolic blood pressure ranging from 120 to 139 mmHg, diastolic blood pressure ranging from 80 to 89 mmHg, or both) volunteered to participate.

The sample size was calculated using G*Power (3.1.9.7, freeware, University of Düsseldorf, Düsseldorf, Germany). Based on the sample size calculation formula implemented in this software, for the key variable of NO, with a significance level set at $\alpha = 0.05$, power set at 80% ($1-\beta = 0.80$), and a medium-to-large effect size ($d = 0.70$), the minimum required sample size was estimated at 64. This effect size estimate was based on prior evidence in the literature demonstrating increased NOS expression and vasodilatory capacity. Specifically, Collier et al. (29) indicated enhanced vasodilatory capacity following resistance training (even without BFR), which could be attributed to increased NO levels. Furthermore, although Drummond et al. (22) did not observe a significant difference in HIF-1α gene expression between the resistance training with blood flow restriction (REFR) group and the control group, the increases in HIF-1α levels reported in studies such as those of Ferguson (12) and Larkin (21) were nonetheless considered a potential pathway for NO production.

As for the ET-1 variable, given that this marker has not been directly addressed in the literature, evidence exists regarding transient increases in blood pressure and cardiovascular stress indices (as reported by Schamneh et al. (28)). Given the potential association between increased arterial stiffness and elevated ET-1 levels (based on the findings of Collier et al. (29)), a more conservative effect size was adopted (d ranging from 0.40 to 0.50). Applying the same parameters for type I error ($\alpha = 0.05$) and type II error ($1-\beta = 0.80$), the required sample size for the ET-1 variable was calculated to be approximately 128 participants.

Hence, taking into account both variables, a more comprehensive sample size of 128 participants was set as the target to ensure adequate statistical power to detect potential effects on both markers. However, due to implementation and practical limitations in accessing the target population within the study region (specifically, difficulties recruiting participants who fully met the inclusion criteria), the final sample size for this study was set at 36 participants. Consequently, the study was conducted as a preliminary (pilot) investigation.

Initially, a written informed consent form was provided to all participants. This form comprehensively and transparently outlined the research objectives, the precise details of the training protocol (particularly the blood flow restriction application procedure and blood sampling stages), potential risks and side effects, the benefits of participation, the guarantee of confidentiality regarding personal and medical information, and the right to withdraw freely from the study at any stage without any consequences. Following a full explanation of these points and a careful review of the forms, participants' signed written consent for voluntary participation was obtained. Subsequently, a demographic questionnaire was completed to collect and record participants' personal information and medical-exercise history. In addition, the Physical Activity Readiness Questionnaire (PAR-Q) was administered to assess daily physical activity levels and confirm participants' baseline health status prior to exercise. The PAR-Q was originally developed by Thomas C. Warburton et al. in Canada during the 1970s (29).

The PAR-Q is a simple, rapid screening tool that assesses individuals' readiness to engage in physical activity and helps prevent cardiac events and other health complications associated with exercise. In the initial stages, the reliability and validity of the PAR-Q

were examined and confirmed. For instance, Warburton et al. (30) reported a test-retest reliability coefficient of approximately 0.80 and acceptable construct validity when compared against standard medical criteria. In Iran, Persian versions of the PAR-Q have been normed and validated by various researchers. Among the credible investigations in this context, the study by Azghandi et al. (31) reported a reliability coefficient of 0.76 (Cronbach's α).

Furthermore, through content analysis, they established satisfactory face and content validity, indicating the instrument's cultural and environmental appropriateness for the Iranian population. In another study, Naderi et al. (32) examined test-retest reliability and convergent validity, reporting a reliability coefficient of 0.79 and acceptable construct validity. Based on the findings of these studies, the Persian version of the PAR-Q has been deemed appropriate and valid for use in research and exercise programs in Iran. The questionnaire assessment process involves collecting participants' responses to seven yes/no items. Individuals who respond negatively to all items are classified as ready for physical activity and may initiate exercise without restriction. In the case of any positive response, further medical consultation and specialized evaluation are required to mitigate potential risks associated with physical activity.

Subsequently, the 36 selected participants were randomly assigned [using Microsoft Excel] to one of three groups of 12 participants each: (1) a control group, (2) a resistance training with blood flow restriction group (RT+BFR), and (3) a resistance training without blood flow restriction group (RT). The control group performed their training at the same low intensity as the resistance training group, but without applying a tourniquet. Furthermore, to minimize bias, the present study was conducted as a single-blinded investigation; that is, the laboratory technician (responsible for blood sampling and variable assessment), the blood pressure evaluator, and the statistical analyst were completely blinded to group allocation.

The inclusion criteria for the study were as follows: age range of 30 to 45 years; diagnosis of prehypertension (systolic blood pressure between 120 and 139 mmHg and/or diastolic blood pressure between 80 and 89 mmHg, to ensure that the target population fell precisely within this clinical range); and sedentary lifestyle. In the present study, "sedentary" was defined as individuals who had not engaged in any regular and consistent training program during the 3 to 6 months prior to the start of the study, and who performed less than 30 minutes of moderate-intensity physical activity on at least 3 days per week.

The exclusion criteria (which resulted in the removal of volunteers from the study process) were as follows: use of any antihypertensive medication (due to alterations in physiological mechanisms, cardiovascular responses, and confounding of result interpretation); history of smoking or tobacco use (owing to the adverse effects of nicotine on vascular function and blood pressure); history of musculoskeletal pain or illness (e.g., chronic pain, active inflammation, muscle weakness, spasm, or movement restriction in the upper or lower extremities that would compromise the correct execution of resistance training); history of therapeutic or reconstructive surgery in the limbs (e.g., knee arthroplasty, ACL reconstruction, or shoulder surgery); and diagnosis of any systemic, metabolic, or chronic disease, including hepatic, renal (due to disruption of fluid and electrolyte balance), neurological, endocrine (e.g., type 1 or type 2 diabetes, or thyroid disorders), known cardiovascular, respiratory, as well as active or treated cancers.

Experimental Procedures

To control for potential confounding variables, all participants were instructed to refrain from any vigorous physical activity, alcohol consumption, caffeine intake, and dietary supplementation for 48 hours prior to pre- and post-test blood sampling. Furthermore, to ensure that nutritional status did not influence the results, a 24-hour dietary recall was recorded at the pre-test phase, and participants were asked to adhere to the same dietary pattern on the day preceding the post-test, as well as to maintain their habitual dietary intake without any changes throughout the 8-week intervention period.

In the initial phase, participants attended three familiarization sessions to become acquainted with the correct execution of resistance exercises, proper use of equipment, and appropriate breathing techniques (to avoid the Valsalva maneuver, which is dangerous in individuals with prehypertension). Subsequently, baseline assessments were performed, including measurements of height, weight, body mass index, systolic and diastolic blood pressure at resting conditions, and blood sampling. To determine training intensity, participants' one-repetition maximum (1RM) was predicted using an indirect test based on the Brzycki equation (33) (Equation 1).

Equation 1
$$1RM = \frac{\text{Weight lifted}}{1.0278 - (0.0278 \times \text{Reps-to-fatigue})}$$

The exercise intervention was conducted over 8 consecutive weeks, with 3 training sessions per week on non-consecutive days (even days), totaling 24 sessions. Prior to each session, participants performed a 10-minute warm-up consisting of calisthenics and

dynamic stretching, followed by a 5- - to 7-minute cool-down comprising static stretching. The training exercises included leg extensions, seated leg presses, prone leg curls, and calf raises.

Groups' protocols

Resistance Training Without Blood Flow Restriction (RT): For this group, training was performed at 75% of 1RM, consisting of 3 sets of 10 repetitions, with a 2-minute rest interval between sets and 5 minutes between exercises.

Resistance Training with Blood Flow Restriction (RT+BFR): For this group, training was performed at 30% of 1RM, 3 sessions per week, with 4 sets of 30-15-15-15 repetitions. The rest interval was set at 45 seconds between sets and 3 minutes between exercises.

To ensure complete transparency of the intervention protocol, detailed information on the training procedures (including exercises, sets, repetitions, intensity, rest intervals, and the method for applying progressive overload over the 8 weeks) is presented in Table 1.

During this period, the control group was also asked to perform their training at the same low intensity as the resistance training group, but without a tourniquet, at 30% of 1RM, with a 45-second rest interval between sets and 3 minutes between exercises. To enable precise comparison of the effects of the two training modalities, “training load volume” was matched across all three groups. Training volume was calculated as the product of the total number of repetitions multiplied by the percentage of training intensity, demonstrating equality in mechanical load across all three groups:

$$22.5 = 75\% \times (10 + 10 + 10) \text{ versus}$$
$$22.5 = 30\% \times (30 + 15 + 15 + 15)$$

In the BFR group, pneumatic compression cuffs (Ghamat Puyan Co., Iran) with a width of 5 cm were used. The cuffs were secured around the upper end of both thighs.

Research Standards

Although contemporary methodological guidelines for BFR training — such as the expert consensus statement by Patterson et al. and the methodological standards proposed by Rolnick et al. — recommend the use of a percentage of arterial occlusion pressure (AOP) determined via Doppler ultrasound (29, 34), the present study employed a cuff pressure based on blood pressure at rest due to clinical constraints in equipment availability for continuous AOP assessment for each individual. Based on relevant methodological literature that has confirmed the applicability of a percentage of systolic blood pressure (SBP) at rest as a safe and effective alternative method for determining cuff pressure in the absence of Doppler ultrasound (8, 35), the cuff pressure in the present study was set at 80% of each participant's SBP at rest. Cuff pressure was maintained during each exercise set and throughout the 30-second rest intervals between sets (to allow metabolite accumulation). However, it was immediately released upon completion of all sets for each exercise to avoid prolonged ischemia.

All training sessions were conducted under the direct supervision of a qualified strength-training coach and researcher to ensure proper exercise execution, precise cuff pressure adjustments, and proper breathing control. Participant attendance was recorded at each session (85% attendance was considered the minimum adherence threshold for continued inclusion in the study). Throughout the 8-week intervention, participants' vital signs were monitored, and no adverse side effects (e.g., severe dizziness, syncope, abnormal bruising, thrombosis, or debilitating muscle pain) were reported.

Laboratory Procedures

Blood sampling was performed on two occasions: prior to the commencement of the intervention and 48 hours following the final training session. To control for the effects of nutrition and circadian rhythm, all samples were collected between 8:00 and 10:00 a.m. following a 12-hour overnight fast, by a specialist laboratory technician.

Table 1. Details of the Resistance Training Protocol in the Study Groups

Training group	Exercises	Training intensity	Number of sets and repetitions	Rest between sets	Rest between exercises	Training progression (load update)
RT	Leg extension, seated leg press, prone leg curl, and calf raises.	%75 RM1	3 sets of 10 repetitions	2 min	5 min	The 1RM was reassessed at the end of weeks 2, 4, and 6 to update training loads and ensure that the relative intensity remained at 75% of the current 1RM.
RT+BFR	Leg extension, seated leg press, prone leg curl, and calf raises.	%30 RM1	4 sets (30-15-15-15 repetitions)	45 sec	3 min	The 1RM was reassessed at the end of weeks 2, 4, and 6 to update training loads and ensure that the relative intensity remained at 30% of the current 1RM.

From each participant, 11 mL of venous blood was drawn from the antecubital vein of the right arm while in a seated position after 5 minutes of rest. Blood samples were immediately collected into 11-mL tubes containing EDTA as an anticoagulant. After gentle, thorough mixing of the blood sample with the anticoagulant, the samples were centrifuged at 3500 rpm for 10 minutes at 4°C to separate the plasma. The obtained plasma was aliquoted into microtubes and stored at -80°C until biochemical analyses were performed.

All biochemical analyses were conducted at the Central Pathobiology Laboratory of Ilam, Iran. Plasma nitric oxide (NO) concentration was measured using a human ELISA kit (Eastbiopharm, USA), with a detection sensitivity of 0.1 mmol/L and intra-- and inter-assay % CVs of less than 8%. ET-1 concentration was measured using an ELISA kit (Glory Science Co., USA), with a detection sensitivity of 0.1 pg/mL and %CVs of less than 10%.

Statistical Analysis

The sample size was calculated prior to the commencement of the study using G*Power (3.1.9.7, freeware, University of Düsseldorf, Düsseldorf, Germany) For this purpose, the F-test (ANCOVA), a medium effect size (f = 0.25), a type I error rate of $\alpha = 0.05$, and statistical power of 80% ($1-\beta = 0.80$) were applied, indicating that a minimum of 15 participants per group was required to achieve adequate power.

Data were analyzed using IBM SPSS Statistics (version 24.0). The Shapiro-Wilk test was used to assess the normality of the data distribution. Paired t-tests were employed to examine intra-group changes, and ANCOVA was used for between-group comparisons (post-test), with pre-test values as covariates. To pinpoint significant differences, the Bonferroni post hoc test was applied. Effect sizes were reported using partial eta squared.

Furthermore, final data analyses were conducted using the intention-to-treat (ITT) approach. To address missing data resulting from potential participant attrition, the last observation carried forward (LOCF) method was employed to minimize bias. In all analyses, the significance level was set at $p < 0.05$.

Results

In the present study, data from all 36 participants assigned to the groups at the outset were included in the final analysis. As no participant attrition occurred during the intervention, there was no need to use missing-data replacement methods, and the ITT analysis was not performed. Table 2 presents the demographic characteristics of the participants (age, height, weight, and body mass index) for both the total sample and by group. The ANOVA results indicated that at the pre-test stage, there were no significant differences among the three groups on any demographic variable ($p > 0.05$), confirming group homogeneity.

The paired samples t-test and ANCOVA results are presented in Table 3.

Intra-group analysis (paired-samples t-tests) revealed that in both the RT+BFR and RT groups, systolic blood pressure (SBP), diastolic blood pressure (DBP), and plasma ET-1 levels significantly decreased. In contrast, plasma NO levels significantly increased from pre-test to post-test ($p < 0.05$). In contrast, no significant changes were observed in any variable in the control group.

Furthermore, between-group analysis (ANCOVA and post hoc tests) revealed that both intervention groups (the RT+BFR and RT groups) differed significantly from the control group across all variables, including reductions in SBP and DBP, increases in NO, and decreases in ET-1 ($p < 0.05$). However, direct comparison of the two training protocols indicated no significant differences between the RT+BFR and RT groups in the magnitude of changes in SBP, DBP, NO, or ET-1 ($p<0.05$).

Table 3 presents the intra-group and between-group changes in blood pressure and vascular indices. The results of paired-samples t-tests indicated that following the 8-week intervention, SBP significantly decreased in both the RT+BFR group ($P \leq 0.001$) and the RT group ($P = 0.002$). DBP also significantly decreased in both the RT+BFR group ($P \leq 0.001$) and the RT group ($P = 0.039$). Regarding biochemical indices, plasma NO levels significantly increased in both the RT+BFR group ($p \leq 0.001$) and the RT group ($p = 0.002$), while ET-1 levels significantly decreased in both the RT+BFR and RT groups ($P \leq 0.001$). In the control group, none of the intra-group changes were significant ($P< 0.05$).

Table 2. Participant Demographic Characteristics

Group characteristics	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m²)	Participant count
RT	39.25 ± 4.8	179.25 ± 4.57	77.3 ± 3.14	24.1 ± 1.69	12
RT+BFR	39.5 ± 5.26	176.91 ± 4.29	78.66 ± 2.43	25.17 ± 1.39	12
CON	38.5 ± 4.14	173.41 ± 5.72	78.87 ± 2.37	26.28 ± 1.59	12
p (intergroup comparison)	0.866	0.021	0.306	0.006	—
Total sample size	39.08 ± 4.64	176.52 ± 5.34	78.27 ± 2.68	25.18 ± 1.76	36

Table 3. Comparison of SBP, DBP, as well as Serum NO and ET-1 Levels in the Three Study Groups Before and After the Intervention

Variable	Time	Con	BFR	BFR	F	p (intergroup)
Systolic blood pressure	Pre-test	136.58 ± 2.94	138.22 ± 4.49	137.01 ± 3.48	21.091	0.001
	Post-test	136.45 ± 2.85	130.5 ± 3.51	134.84 ± 4.07		
	Change (%)	0.095	5.58	1.58		
	P (within-group)	0.14	0.03*	0.001*		
Diastolic blood pressure	Pre-test	84.71 ± 4.44	83.3 ± 1.93	84.56 ± 2.57	16.730	0.001
	Post-test	82.2 ± 2.63	81.78 ± 1.39	81.78 ± 1.39		
	Change (%)	2.96	3.28	2.72		
	P (within-group)	0.054	0.039*	0.001*		
NO (pg/ml)	Pre-test	127.23 ± 7.27	14.11 ± 2.66	118.71 ± 3.93	16.807	0.001
	Post-test	127.28 ± 2.27	137.59 ± 9.72	142.92 ± 5.19		
	Change (%)	0.039	20.57	20.39		
	P (within-group)	0.57	0.002*	0.000*		
ET-1 (pg/ml)	Pre-test	54.71 ± 8.52	62.74 ± 3.62	57.34 ± 8.54	27.116	0.001
	Post-test	54.64 ± 7.2	52.72 ± 4.43	46.78 ± 7.81		
	Change (%)	0.127	15.97	18.41		
	P (within-group)	0.093	0.000*	0.000*		

P < 0.05 was considered statistically significant.

In examining inter-group differences with pre-test values controlled as covariates, the ANCOVA results revealed significant differences among the groups for all variables. For SBP, the F-statistic was 21.091 ($p \leq 0.001$), with a partial eta squared effect size of 0.439. For DBP, the F-statistic was 16.730 ($p \leq 0.001$), with a partial eta squared of 0.383. For serum NO levels, the F-statistic was 16.807 ($p \leq 0.001$), with a partial eta squared of 0.384. For ET-1, the F-statistic was 27.116 ($p \leq 0.001$), with a partial eta squared of 0.501.

The results of the Bonferroni post hoc test for pinpointing inter-group differences revealed that systolic and diastolic blood pressure ($p \leq 0.001$) and ET-1 levels ($p = 0.003$) were significantly lower in both training groups (with and without BFR) compared to the control group. Furthermore, NO levels were significantly higher in both training groups compared to the control group ($p \leq 0.001$). However, no significant differences were observed between the two resistance training protocols (with and without BFR) for any variable ($p > 0.05$). The 95% confidence intervals for mean differences were calculated for all comparisons. Additionally, post hoc power analysis based on the obtained effect sizes confirmed adequate statistical power (≥ 0.80) for all variables.

Discussion

The primary objective of the present study was to compare the effects of eight weeks of high-intensity resistance training (without blood flow restriction) and low-intensity resistance training combined with BFR on hemodynamic variables and serum biomarkers in men with prehypertension. The findings of the present study demonstrated that both training modalities significantly reduced SBP and DBP at rest. Furthermore, significant reductions in serum ET-1 levels and significant increases in NO levels were observed compared to the control group. However, inter-group comparisons revealed no significant differences in the efficacy of the two training protocols. In this vein, post hoc power analysis for the primary variables indicated adequate statistical power (> 0.80). Moreover, given the absence of participant attrition during the intervention, the final analysis results completely matched those of the intention-to-treat (ITT) analysis. It should also be noted that the blood pressure reductions observed in this study pertain exclusively to assessments carried out at rest.

The significant reduction in blood pressure at rest observed in the present study is consistent with findings from the relevant literature (36-38) reporting hypotensive effects of resistance training. However, in contrast to the findings of Lopes et al. (39), who reported that BFR training was more effective than high-intensity resistance training in reducing blood pressure, the absence of such a pronounced difference in the present study may be attributable to differences in the protocols. In the present study, attempts were made to match total volume load across the three groups as closely as possible. This meticulous control of training variables, combined with the participants' baseline vascular status (pre-hypertensive), likely contributed to both interventions eliciting comparable physiological responses across the assessed variables.

To explain the observed similar responses and positive changes in serum biomarkers, it is necessary to consider the roles of shear stress and metabolic

stress. Endothelial function is largely dependent on the balance between vasodilatory factors (such as NO) and vasoconstrictive factors (such as ET-1) (4, 5, 10). Increased NO production may contribute to reduced peripheral vascular resistance by decreasing the tonicity of vascular smooth muscle, thereby aiding in the regulation of blood pressure at rest. It is hypothesized that high-intensity resistance training (without BFR) increases shear stress on the vessel wall through powerful muscle contractions and post-contraction reactive hyperemia, thereby stimulating endothelial nitric oxide synthase (eNOS) and ultimately leading to NO production (13, 40).

In contrast, low-intensity training combined with BFR compensates for the absence of heavy mechanical loads by increasing metabolic stress (10, 41). Blood flow restriction leads to the accumulation of metabolites, such as hydrogen ions. On the other hand, cuff release following each exercise set induces a reactive hyperemic response, which appears to impose sufficient shear stress on the vascular wall, comparable to that of high-intensity training, thereby contributing to favorable changes in NO and ET-1 secretion (42). Therefore, it is plausible that both training modalities, through distinct pathways (mechanical stress dominance versus metabolic stress dominance), have successfully achieved adequate stimulation over the eight-week intervention period. Nevertheless, caution is warranted when interpreting changes in these serum biomarkers as necessarily indicative of complete, structural vascular improvements (e.g., alterations in vessel wall thickness or elasticity). Furthermore, given that direct indices of endothelial function, arterial stiffness, or peripheral blood circulation were not measured in the present study, these explanations should be interpreted as potential mechanisms.

Limitations

One limitation of the present study concerns the method used to determine cuff pressure during BFR training. According to the latest methodological standards, the most accurate approach to ensuring precise blood flow restriction is to apply a specific percentage of arterial occlusion pressure (AOP) measured by Doppler ultrasound (29). In the present study, due to equipment constraints, an alternative approach was employed using 80% of systolic blood pressure (SBP) at rest. Although this pressure is hemodynamically sufficient to achieve complete venous occlusion and partial arterial restriction (thereby inducing metabolic and shear stress), it may not correspond to an equivalent percentage of blood flow restriction (AOP) across all participants. Another limitation of the present study pertains to the sample size and study population. Despite conducting a power analysis to determine the minimum required number of participants, the final sample size was relatively small (n = 36), owing to the nature of the preliminary clinical trial (pilot), stringent inclusion criteria, and potential participant attrition.

Furthermore, restricting the study population to men aged 30- 45 years limits the generalizability of the findings to other age groups and women. An additional limitation relates to dietary control. Precise daily dietary monitoring was not feasible throughout the entire eight-week intervention period; therefore, dietary control was limited to a 24-hour dietary recall prior to blood sampling. The final limitation is the absence of post-intervention follow-up to assess the sustainability of effects. Owing to the timeframe of the study, evaluating long-term effects following training cessation (follow-up) was not feasible.

Recommendations

To address the limitations of the present study and to enrich the existing literature, researchers are advised to heed the following suggestions for future investigations. First, to overcome the constraint of sample size and enhance the generalizability of findings, studies should be designed and conducted with larger samples drawn from more diverse populations, including women and older age groups. In addition, to address the limitation related to BFR equipment, future clinical trials should employ Doppler ultrasound to precisely determine and standardize cuff pressure based on arterial occlusion pressure (AOP). More rigorous control of confounding variables is likewise warranted, which can be achieved by closely monitoring and recording participants' dietary intake through daily food diaries throughout the intervention period. Furthermore, to evaluate the sustainability of the observed vascular effects, follow-up assessments ranging from 1 to several months should be conducted after completion of the training intervention. Finally, direct assessment of functional and structural vascular indices — such as flow-mediated dilation (FMD) and intima-media thickness (IMT) — should be incorporated alongside biomarker evaluation, as this would provide clearer insight into the underlying physiological mechanisms.

Conclusion

The findings of the present study demonstrated that eight weeks of resistance training — whether high intensity training (without BFR) or low intensity training combined with BFR — was associated with

significant positive changes in endothelial-related biomarkers (increased NO and decreased ET-1), as well as reductions in blood pressure at rest in men with prehypertension. Comparison of the two training modalities revealed no significant differences, with both interventions producing comparable changes in the assessed variables at rest.

Based on the results, low-intensity resistance training combined with BFR may be considered a potential exercise option to help regulate blood pressure at rest. This training modality may be particularly applicable for individuals who, due to clinical conditions, injury, or joint weakness, are unable to tolerate heavy training loads. However, prescribing this type of training for populations with cardiovascular disorders requires strict adherence to safety principles, initial screening, and direct supervision by qualified professionals.

Acknowledgments

We thanks all appreciate all the individuals who participated in and assisted this research at various stages.

Authors' Contribution

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Funding

This study, based on a secondary analysis of part of the data extracted from the Ph.D. thesis in Exercise Physiology by Ali Yari (Ethics Code: IR.IAU.KSH.REC.1402.068 and IRCT Registration Code: IRCT20220501054712N1), was prepared without financial support.

Conflict of Interest

The authors did not have a conflict of interest.

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