

Research article

## Blood Flow Restriction Training Reduces Hemodynamic Load and Improves Cardiovascular Biomarkers in Runners with Exercise-Induced Hypertension

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### Abstract

Exercise-induced hypertension (EIH) is associated with elevated risks of arrhythmia, coronary artery disease, arterial stiffness, and sudden cardiac death. Blood flow restriction (BFR) training has been proposed as a non-pharmacological intervention. This study aimed to evaluate whether changes in cardiovascular biomarkers accompanied hemodynamic improvements following BFR training in middle-aged runners with EIH. This secondary analysis included 28 male runners with EIH (mean age:  $57.4 \pm 6.5$  years) from a prior cohort applying the same BFR training protocol. Participants exhibited a maximal systolic blood pressure  $\geq 210$  mmHg during graded exercise testing (GXT) and were assigned to a BFR training group (BFRTg,  $n = 16$ ) or a control group (non-BFRTg,  $n = 12$ ). BFR training was performed twice weekly for 20 minutes over 8 weeks. Cardiorespiratory fitness and hemodynamic response during GXT were also assessed. Cardiovascular biomarkers (endothelin-1 [ET-1], high-sensitivity C-reactive protein [hs-CRP], NT-proBNP, and nitric oxide [NO]) were measured pre- and post-intervention. In the BFRTg, ET-1, hs-CRP, and NT-proBNP levels decreased after BFR training, while maximal systolic blood pressure decreased and  $\text{VO}_2\text{max}$  increased (all  $p < .05$ ). Hemodynamic load also improved, as indicated by reductions in resting and maximal rate-pressure product (RPP) and pulse pressure during maximal exercise (all  $p < .05$ ). BFR training improved the exercise blood pressure response and cardiorespiratory fitness in runners with EIH. The reduction in hemodynamic load, reflected by decreases in RPP and PP, was accompanied by significant reductions in ET-1, hs-CRP, and NT-proBNP.

**Key words:** Blood flow restriction, exercise-induced hypertension, cardiovascular markers, endothelial function, inflammation, nitric oxide.

### Introduction

Exercise-induced hypertension (EIH) is a risk factor for cardiovascular disease. In the general population, it is associated with left ventricular hypertrophy (Gottdiener et al., 1990), an increased likelihood of developing hypertension (Singh et al., 1999), and increased cardiovascular morbidity and mortality (Schultz et al., 2013; Weiss et al., 2010). The incidence of EIH is higher in long-distance runners than in the general population (Kim et al., 2021). In this demographic, arrhythmia (Kim et al., 2021), left ventricular hypertrophy (Gwag et al., 2024), and coronary artery plaque have been reported more frequently than in runners with a normotensive exercise response (Kim et al., 2020).

A recent hypothesis suggests that in long-distance

runners, EIH chronically elevates myocardial workload during exercise. This may, in turn, increase the incidence of coronary artery disease, driven by ventricular hypertrophy, increased carotid intima-media thickness, and arterial stiffness, thereby acting as a potential risk factor for sudden death during exercise (Kim and Park, 2024). Despite these concerns, no longitudinal studies have confirmed increased mortality among runners with EIH, highlighting the need for mechanistic research.

EIH is typically defined by a systolic blood pressure  $\geq 210$  mmHg during maximal graded exercise test (GXT) (Allison et al., 1999). Although clinical guidelines for treating EIH have not yet been established, angiotensin II has been identified as a key regulator of exercise-induced blood pressure elevation (Kim et al., 2020). Pharmacological strategies targeting the renin-angiotensin system have therefore been proposed (Kokkinos et al., 2006; Warner et al., 1999), but the exploration of non-pharmacological exercise-based interventions remains limited.

The effects of blood flow restriction (BFR) training on muscle hypertrophy, muscular endurance, and cardiorespiratory fitness have been well-established (Dong et al., 2024). These effects are attributed to exercise-induced metabolic stress under transient limb ischemia, which has been shown to stimulate the expression of mitochondrial and vascular endothelial growth factors, thereby improving endothelial function (Shimizu et al., 2016). This mechanism has led to the hypothesis that BFR training may reduce blood pressure. While some studies have reported a positive impact on resting blood pressure, the majority have focused on acute reductions following a single bout of exercise (Araujo et al., 2014; Pinto and Polito, 2016). Recent systematic reviews and meta-analyses indicate that BFRT (blood flow restriction training) can influence hemodynamic responses and vascular function, although its cardiovascular effects and optimal implementation strategies remain uncertain (Huang et al., 2025; Kong et al., 2024).

Despite these mechanistic links, no studies have investigated whether BFR training can attenuate the exaggerated hemodynamic responses observed in endurance runners with EIH, nor whether improvements in blood pressure responses are accompanied by favorable changes in cardiovascular biomarkers associated with endothelial function, inflammation, and myocardial stress. Clarifying this relationship is important because endurance runners with EIH may experience repeated elevations in exercise blood pressure, potentially leading to chronic cardiovascu-

lar stress and structural remodeling (Gwag et al., 2024). Recently, the authors reported for the first time that applying BFRT in runners with EIH reduced maximal exercise blood pressure and myocardial workload (Kim et al., 2025a). Building on these previous findings, this secondary analysis sought to determine whether the observed hemodynamic improvements are accompanied by concurrent adaptations in cardiovascular biomarkers in this population.

Therefore, the purpose of this study was to examine whether an 8-week BFR aerobic training intervention in runners with EIH improves hemodynamic responses during exercise and produces favorable adaptations in cardiovascular biomarkers. We hypothesized that BFR training would reduce exercise blood pressure and hemodynamic load, and that these improvements would be accompanied by significant changes in endothelial-related and myocardial stress biomarkers, including ET-1, hs-CRP, and NT-proBNP.

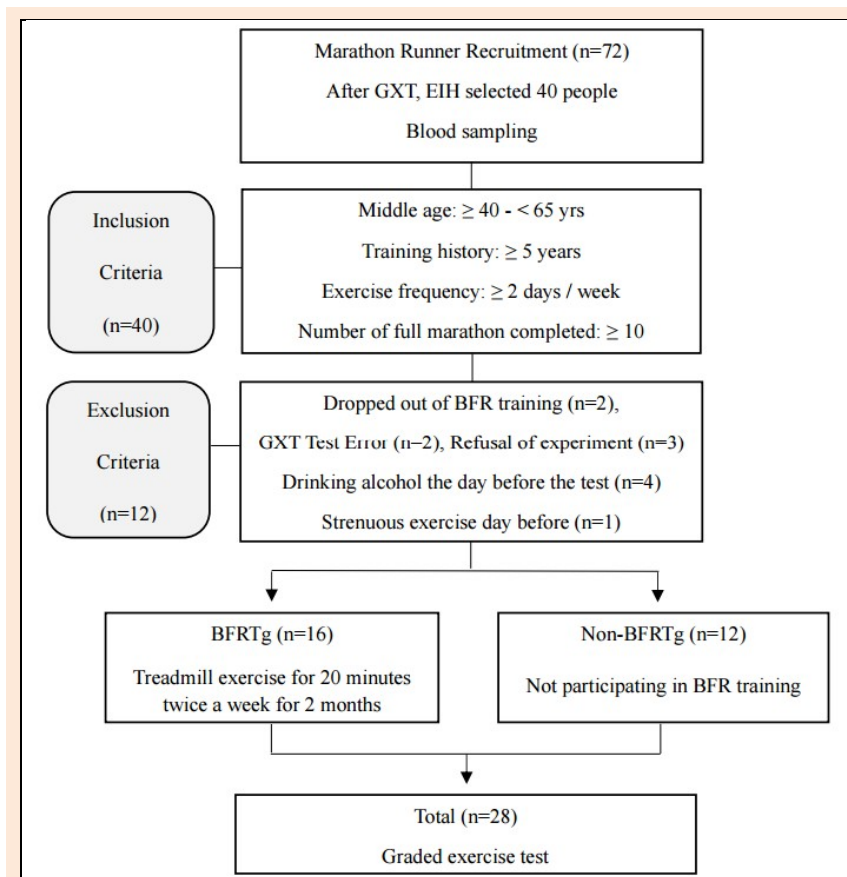
## Methods

### The study protocol and subjects

This study was conducted as a secondary analysis of a previously published intervention cohort investigating the effects of BFRT in runners with exercise-induced hypertension. The study procedure utilized GXT-based hemodynamic response data that had already been obtained from the previous study (Kim et al., 2025a) and additional blood biomarkers (endothelin-1, hs-CRP, NT-proBNP, NO) were

analyzed to comprehensively evaluate the effects of BFRT. The present investigation was therefore conducted as a secondary analysis of data from a previously published intervention study examining the effects of BFRT in runners with EIH. Initially, 72 individuals volunteered for the GXT, of whom 40 runners were identified as having EIH.

Several participants were excluded: two who dropped out during the BFR training, two with errors in GXT results, and three who declined the final test. Furthermore, five participants from the prior study were further excluded due to factors that could influence blood biomarker outcomes: four who consumed alcohol and one who performed strenuous exercise the day before testing. Consequently, a final sample of 28 participants was included for the analysis of both GXT results and blood biomarkers. Because the present study represents a secondary analysis derived from an existing cohort, the sample size was determined by the number of participants who met the additional eligibility criteria for biomarker analysis. Therefore, no additional a priori sample size calculation was performed specifically for the present study. Participants whose maximal systolic blood pressure (SBP) increased to  $\geq 210$  mmHg during the GXT were classified as having exercise-induced hypertension (Allison et al., 1999). Group allocation was not randomized. Participants who participated in the BFR exercise program were assigned to the BFR training group (BFRTg,  $n = 16$ ), whereas those who did not participate served as the control group (non-BFRTg,  $n = 12$ ) (Figure 1).



**Figure 1.** Flow chart of the study procedure. GXT; graded exercise testing; BFRTg; blood flow restriction training group; EIH; exercise-induced hypertension.

**Table 1.** Characteristics of the study participant demographics.

| Variable                          | BFRTg (n = 16) | non-BFRTg (n = 12) | p-value |
|-----------------------------------|----------------|--------------------|---------|
| <b>Physical characteristics</b>   |                |                    |         |
| Age (years)                       | 56.3 ± 5.7     | 58.8 ± 7.4         | 0.333   |
| Height (cm)                       | 172.1 ± 7.4    | 169.6 ± 4.5        | 0.314   |
| Weight (kg)                       | 69.9 ± 8.3     | 66.3 ± 8.4         | 0.280   |
| BMI (m <sup>2</sup> /kg)          | 23.6 ± 2.5     | 23.0 ± 2.6         | 0.574   |
| Disease                           | 7 (43.8%)      | 4 (33.3%)          | 0.791   |
| Hypertension                      | 5 (31.3%)      | 3 (25.0%)          | 1.000   |
| Dyslipidemia                      | 1 (6.3%)       | 1 (8.3%)           | 1.000   |
| Diabetes                          | 1 (6.3%)       | 0 (0%)             | 1.000   |
| <b>Exercise data</b>              |                |                    |         |
| Exercise history (yrs)            | 15.5 ± 6.8     | 18.2 ± 5.7         | 0.275   |
| Marathon completed (numbers)      | 65.8 ± 56.8    | 53.9 ± 38.9        | 0.539   |
| Marathon time (min)               | 233.3 ± 35.0   | 229.0 ± 37.8       | 0.754   |
| Exercise time (min/day)           | 80.6 ± 34.1    | 83.3 ± 32.0        | 0.833   |
| Exercise intensity (Borg's scale) | 14.3 ± 1.4     | 14.5 ± 0.9         | 0.791   |
| Exercise frequency (weeks)        | 4.1 ± 1.5      | 4.1 ± 1.6          | 0.947   |
| <b>GXT</b>                        |                |                    |         |
| HR <sub>rest</sub> (beats/min)    | 59.0 ± 7.7     | 57.0 ± 3.6         | 0.418   |
| SBP <sub>rest</sub> (mmHg)        | 127.1 ± 12.1   | 124.1 ± 11.2       | 0.507   |
| DBP <sub>rest</sub> (mmHg)        | 82.1 ± 8.9     | 78.7 ± 5.6         | 0.255   |
| HR <sub>max</sub> (beats/min)     | 161.6 ± 13.3   | 162.5 ± 7.1        | 0.835   |
| SBP <sub>max</sub> (mmHg)         | 223.5 ± 9.6    | 217.5 ± 7.0        | 0.080   |
| DBP <sub>max</sub> (mmHg)         | 93.8 ± 6.6     | 94.5 ± 9.2         | 0.821   |
| TET (sec)                         | 781.2 ± 117.1  | 808.3 ± 75.4       | 0.493   |
| VO <sub>2max</sub> (ml/kg/min)    | 45.5 ± 9.5     | 47.8 ± 6.6         | 0.482   |

Values are presented as mean ± SD. BFRTg: blood flow restriction training group, BMI: body mass index, GXT: graded exercise test, HR: rest heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, TET: total exercise time, VO<sub>2max</sub>: maximal oxygen uptake

Table 1 presents the baseline characteristics of the participants, including anthropometric data, exercise history, and GXT results. Participants were middle-aged men aged 40 - 65 years who met the following inclusion criteria: a minimum of 5 years of running experience, at least 5 completed marathons, and a regular exercise routine of at least 30 minutes per session performed more than twice per week for at least the past six months.

Participants were instructed to refrain from alcohol consumption for at least 24 hours prior to physiological testing and to avoid strenuous exercise on the day preceding testing. Current smokers or users of tobacco products were excluded. During the study period, participants were instructed to maintain their habitual dietary patterns. Nutritional supplement use was not specifically restricted; however, participants were asked not to initiate new supplements or change their habitual supplement intake during the intervention period. In addition, caffeine intake was restricted for at least 12 hours prior to physiological testing to minimize potential acute effects on cardiovascular responses.

The final sample consisted exclusively of male runners (n = 28) with a mean age of 57.4 ± 6.5 years, mean height of 171.0 ± 6.3 cm, mean body weight of 68.3 ± 8.4 kg, and mean body mass index (BMI) of 23.3 ± 2.5 kg·m<sup>-2</sup>. There were no significant between-group differences in anthropometric variables (age, height, weight, BMI) or in the prevalence of comorbidities such as hypertension, dyslipidemia, and diabetes. Exercise-related characteristics, including years of running experience, number of marathon completions, finishing times, daily exercise duration, and exercise intensity and frequency, were also comparable between groups. Furthermore, GXT parameters

showed no significant between-group differences in resting heart rate (HR<sub>rest</sub>), SBP<sub>rest</sub>, diastolic blood pressure (DBP<sub>rest</sub>), maximal HR (HR<sub>max</sub>), maximal SBP (SBP<sub>max</sub>), maximal DBP (DBP<sub>max</sub>), total exercise time (TET), or maximal oxygen uptake (VO<sub>2max</sub>). Participants in the control group were instructed to maintain their habitual exercise routines (≥2 sessions per week) throughout the study period but did not participate in the structured BFR training program.

This study was conducted in accordance with the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of the Korea National Sport University (20230921-091).

### Graded Exercise Test (GXT)

A maximal GXT was administered to screen runners for EIH and to evaluate their hemodynamic and cardiorespiratory responses. Testing was performed on a motorized treadmill (T170DE, hp cosmos, Traunstein, Germany) following the Bruce protocol. Each stage lasted 3 minutes, and physiological variables were collected at 2 minutes and 30 seconds into each stage.

Resting measurements of heart rate (HR) and blood pressure were obtained before the test. During exercise, HR, SBP, DBP, rating of perceived exertion (RPE; Borg scale), and oxygen uptake were assessed at each stage and at peak exertion. Cardiopulmonary variables were measured using a breath-by-breath metabolic system (Quark CPET, COSMED, Lavio, Italy). Heart rate and electrocardiogram (ECG) data were continuously monitored via a CH2000 system (Cambridge Heart, Bedford, MA, USA), and blood pressure was recorded using an automated sphygmomanometer (Tango+, SunTech Medical, Morris-

ville, NC, USA).

To ensure precise blood pressure assessment, a trained operator placed a high-fidelity microphone over the brachial artery and used headphones to auscultate during automatic measurements. All GXT procedures were performed in accordance with the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (Gibbons et al., 1997). Because all participants were experienced runners, no separate familiarization session was conducted; participants performed a brief warm-up and were instructed on the testing procedures prior to testing.

### Blood flow restriction exercise method

Runners who participated in the BFR exercise set their heart rate to 40–60% of their heart rate reserve (HRR) using data from the GXT and the Karvonen formula. Participants engaged in treadmill exercise for 20 minutes per session, twice weekly for 8 weeks with at least 48 hours between sessions to allow adequate physiological recovery and minimize cumulative physiological stress associated with BFR exercise. Adjustments to incline and speed were made to maintain the target heart rate range. All training sessions were conducted in the evening between 18:00 and 21:00 after participants had completed their daily work and dinner. To minimize potential variability due to circadian rhythms in exercise responses, participants conducted all training sessions within this consistent time window throughout the intervention period. All testing and training sessions were conducted indoors at an ambient temperature of approximately 23°C and a relative humidity of approximately 40–50%.

The exercise program applied BFR training at an intensity of 50% HRR in the first week; with a band worn on the proximal upper thigh, the 'Cycle mode (Low SKU)' function was applied for 20 minutes, involving repetitions of applying a continuous pressure load for 30 seconds followed by a 5-second pressure release to recirculate blood flow. In the second week, an intensity of 50% HRR was also applied; after applying 'Cycle mode (Medium SKU)' for 10 minutes, the protocol was converted to the 'Constant mode' method at 250 mmHg and maintained for 10 minutes without blood recirculation, performed for a total of 20 minutes. From the third to the eighth week, the training intensity was increased to 60% of HRR. The protocol

involved a single application of 'Cycle mode,' followed by 15 minutes of continuous blood flow restriction at 250 mmHg.

The 'Constant mode,' which maintains a set pressure, was limited to 20 consecutive minutes. During application of this mode, blood flow in the lower limbs was assessed by observing changes in skin color on the lower thigh above the knee after the area was firmly pressed with a thumb and then released. If the skin color did not return from white to red within 3 seconds, this indicated excessive blood flow restriction; therefore, the exercise was paused, and the cuff pressure was lowered from 250 mmHg to 230 mmHg. KAATSU training was performed using the KAATSU C3 device (KAATSU Global, Inc., Sacramento, CA, USA) with large-sized pneumatic thigh cuffs (narrow-width cuff; width  $\approx$  5 cm).

The selection of exercise intensity, session frequency, duration, pressure mode, and progression in the present protocol was based on previous BFR studies demonstrating that low-to-moderate intensity aerobic exercise with BFR improves vascular function and cardiovascular responses while minimizing cardiovascular strain (Abe et al., 2006; Hughes et al., 2017; Loenneke et al., 2012).

The intervention was conducted under continuous supervision by an experienced operator, incorporating progressive pressurization and real-time perfusion checks to minimize the risk of excessive ischemia. No adverse events were observed during the intervention period. A detailed week-by-week overview of the 8-week BFR training protocol, including target intensities, pressure modes, and progression patterns, is summarized in Table 2.

### Blood sampling & analysis

All blood samples were obtained following an overnight fast of at least 8 hours and were collected between 08:00 and 10:00. Blood was drawn from the antecubital vein into serum separator tubes (BD Microtainer® SST™). The tubes were processed for serum separation, and the resulting serum samples were stored frozen until analysis.

Nitric oxide (NO) levels were measured using an Absorbance microplate reader (Versa Max, Molecular Devices, USA) based on a colorimetric method with reagents from R&D Systems. Endothelin-1 (ET-1) was analyzed via an enzyme immunoassay (EIA) on a luminometer using

**Table 2.** Overview of the 8-Week BFR Training Protocol.

| Training Phase                       | Target Intensity (%HRR) | Session Frequency & Duration        | Pressure Mode and Progression   | Purpose and Characteristics   |
|--------------------------------------|-------------------------|-------------------------------------|---|---|
| <b>Week 1 (Adaptation)</b>           | 50 % HRR                | 2 sessions per week $\times$ 20 min | Alternating pressure–release cycles ( $\approx$ 150 $\rightarrow$ 220 mmHg). Each inflation lasted 30 s followed by 5 s reperfusion; pressure raised $\sim$ 10 mmHg per cycle.  | Preliminary acclimation stage to induce tolerance to partial occlusion and ensure safety under low load.                        |
| <b>Week 2 (Transition)</b>           | 50 % HRR                | 2 sessions per week $\times$ 20 min | Step 1: Cyclic mode 230–300 mmHg for 10 min with gradual increments (+10 mmHg per step).<br>Step 2: Constant mode $\approx$ 250 mmHg maintained for 10 min of steady occlusion. | Intermediate phase introducing moderate continuous pressure while maintaining controlled circulation cycles.                    |
| <b>Weeks 3–8 (Progressive phase)</b> | 60 % HRR                | 2 sessions per week $\times$ 20 min | Initial 5 min of cyclic loading (230–300 mmHg, one sequence of pressure increases) immediately followed by $\approx$ 15 min constant restriction at 250 mmHg.                   | Continuous treadmill walking/jogging at moderate intensity under stable occlusion to enhance vascular and metabolic adaptation. |

Human Endothelin-1 QuantiGlo ELISA Kits (R&D Systems, USA). Assay precision was based on the manufacturer's specifications; the coefficient of variation (CV) was 6.7% within a reference range of 0.401 - 2.83 pg/mL.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured on a Cobas 8000 / e602 analyzer (Roche, Germany) using an electrochemiluminescence immunoassay (ECLIA) with Roche reagents. High-sensitivity C-reactive protein (hs-CRP) was measured on a Cobas 6000/C501 analyzer (Roche, Germany) using a particle-enhanced immunoturbidimetric assay with Roche reagents. The coefficients of variation (CV) for both the NT-proBNP and hs-CRP assays were less than 5%.

### Statistical analysis

Statistical analyses were performed using SPSS Statistics (version 21, IBM Corp., Armonk, NY, USA). Data are presented as mean  $\pm$  standard deviation. Baseline differences between groups were assessed using independent-samples t-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. A two-way repeated-measures ANOVA was used to examine the main effects of time and group, as well as the Time  $\times$  Group interaction. Normality was assessed using the Shapiro-Wilk test; when violated, non-parametric alternatives (Mann-Whitney U and Wilcoxon signed-rank tests) were applied. When a significant interaction was observed, post-hoc comparisons were performed using paired- or independent-samples t-tests with Bonferroni correction. Effect sizes are reported as partial eta squared ( $\eta_p^2$ ). Statistical significance was set at  $p < 0.05$ .

### Results

Table 3 presents the changes in resting and maximal GXT

variables following BFR training in runners with EIH. There were no significant interaction effects for HR<sub>rest</sub>, SBP<sub>rest</sub>, DBP<sub>rest</sub>, HR<sub>max</sub>, DBP<sub>max</sub>, or total exercise time. However, a significant interaction effect was observed for SBP<sub>max</sub>, with the BFRTg showing a significant decrease compared to the non-BFRTg ( $p < 0.05$ ). Additionally, a significant interaction effect was found for VO<sub>2max</sub>, with the BFRTg demonstrating a significant increase compared to the non-BFRTg ( $p < 0.05$ ).

Table 4 presents the changes in RPP and PP (pulse pressure) at rest and during maximal exercise following BFR training in runners with EIH. Significant interaction effects were identified for both resting and maximal RPP, with the BFRTg demonstrating a greater reduction in myocardial workload compared with the non-BFRTg ( $p < 0.05$ ). For PP, no significant differences were observed at rest; however, a significant interaction effect was evident during maximal exercise, whereby the BFRTg exhibited significantly lower PP than the non-BFRTg ( $p < 0.05$ ).

Figures 2 - 5 illustrate the changes in cardiovascular biomarkers following BFR training in runners with EIH. For Endothelin-1 (ET-1), the BFRTg showed a significant decrease from  $1.32 \pm 0.23$  pre-intervention to  $1.14 \pm 0.33$  post-intervention ( $p < 0.05$ ), while the non-BFRTg changed from  $1.23 \pm 0.25$  to  $1.26 \pm 0.32$ , resulting in a significant Time  $\times$  Group interaction effect ( $p < 0.05$ ) (Figure 2). Regarding hs-CRP, the BFRTg experienced a significant decrease from  $0.93 \pm 0.82$  pre-intervention to  $0.39 \pm 0.23$  post-intervention ( $p < 0.05$ ), whereas the non-BFRTg changed from  $0.73 \pm 0.84$  to  $1.33 \pm 1.81$ , which yielded a significant interaction effect between the groups ( $p < 0.05$ ) (Figure 3).

For NT-proBNP, the BFRTg changed from  $32.3 \pm 27.2$  pre-intervention to  $24.0 \pm 18.6$  post-intervention,

**Table 3. Changes in maximal exercise stress test following BFR training.**

| Variables                         | Group     | Pre               | Post               | p-value ( $\eta_p^2$ )                                   |
|-----------------------------------|-----------|-------------------|--------------------|--|
| RRPP<br>(mmHg·bpm)                | BFRTg     | 132.0 $\pm$ 18.2  | 113.7 $\pm$ 17.2*§ | T: 0.004 (0.283), G: 0.688 (0.006), I: 0.003 (0.299)     |
|                                   | non-BFRTg | 124.9 $\pm$ 96.4  | 125.2 $\pm$ 15.5   |  |
| MRPP<br>(mmHg·bpm)                | BFRTg     | 362.2 $\pm$ 37.3  | 288.9 $\pm$ 35.4*§ | T: < 0.001 (0.624), G: 0.017 (0.201), I: < 0.001 (0.524) |
|                                   | non-BFRTg | 356.2 $\pm$ 20.9  | 348.7 $\pm$ 27.2   |  |
| PP <sub>rest</sub><br>(mmHg)      | BFRTg     | 45.0 $\pm$ 6.3    | 34.5 $\pm$ 10.0*   | T: < 0.001 (0.367), G: 0.355 (0.033), I: 0.394 (0.028)   |
|                                   | non-BFRTg | 45.4 $\pm$ 7.2    | 38.7 $\pm$ 10.6*   |  |
| PP <sub>max</sub><br>(mmHg)       | BFRTg     | 130.0 $\pm$ 12.0  | 95.0 $\pm$ 18.0*§  | T: < 0.001 (0.511), G: 0.023 (0.183), I: < 0.001 (0.383) |
|                                   | non-BFRTg | 124.5 $\pm$ 8.5   | 120.0 $\pm$ 16.5   |  |
| HR <sub>rest</sub><br>(beats/min) | BFRTg     | 59.0 $\pm$ 7.7    | 62.8 $\pm$ 10.8*   | T: 0.029 (0.170), G: 0.322 (0.038), I: 0.531 (0.015)     |
|                                   | non-BFRTg | 57.0 $\pm$ 3.6    | 59.1 $\pm$ 7.2     |  |
| SBP <sub>rest</sub><br>(mmHg)     | BFRTg     | 127.1 $\pm$ 12.1  | 119.2 $\pm$ 8.0*   | T: 0.204 (0.061), G: 0.611 (0.010), I: 0.057 (0.133)     |
|                                   | non-BFRTg | 124.1 $\pm$ 11.2  | 125.8 $\pm$ 12.7   |  |
| DBP <sub>rest</sub><br>(mmHg)     | BFRTg     | 82.1 $\pm$ 8.9    | 84.7 $\pm$ 7.3     | T: 0.006 (0.260), G: 0.785 (0.003), I: 0.121 (0.090)     |
|                                   | non-BFRTg | 78.7 $\pm$ 5.6    | 87.0 $\pm$ 4.5*    |  |
| HR <sub>max</sub><br>(beats/min)  | BFRTg     | 161.6 $\pm$ 13.3  | 159.1 $\pm$ 18.8*  | T: 0.881 (0.001), G: 0.500 (0.018), I: 0.303 (0.041)     |
|                                   | non-BFRTg | 162.5 $\pm$ 7.1   | 164.5 $\pm$ 7.2    |  |
| SBP <sub>max</sub><br>(mmHg)      | BFRTg     | 223.8 $\pm$ 9.0   | 182.2 $\pm$ 16.6*§ | T: < 0.001 (0.673), G: 0.002 (0.044), I: < 0.001 (0.218) |
|                                   | non-BFRTg | 219.0 $\pm$ 5.3   | 212.0 $\pm$ 14.9   |  |
| DBP <sub>max</sub><br>(mmHg)      | BFRTg     | 82.1 $\pm$ 8.9    | 84.7 $\pm$ 7.3*    | T: 0.006 (0.203), G: 0.785 (0.042), I: 0.121 (0.052)     |
|                                   | non-BFRTg | 78.7 $\pm$ 5.6    | 87.0 $\pm$ 4.5     |  |
| TET (sec)                         | BFRTg     | 781.2 $\pm$ 117.8 | 810.0 $\pm$ 118.9  | T: 0.263 (0.048), G: 0.737 (0.004), I: 0.290 (0.043)     |
|                                   | non-BFRTg | 808.3 $\pm$ 75.4  | 809.1 $\pm$ 99.2   |  |
| VO <sub>2max</sub><br>(ml/kg/min) | BFRTg     | 45.5 $\pm$ 9.5    | 49.6 $\pm$ 7.9*    | T: 0.55 (0.135), G: 0.848 (0.001), I: < .001 (0.452)     |
|                                   | non-BFRTg | 47.8 $\pm$ 6.6    | 48.1 $\pm$ 7.6     |  |

Values are presented as mean  $\pm$  SD.  $\eta_p^2$ : partial eta squared; BFRTg: blood flow restriction training group; HR: rest heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; TET: total exercise time. \*: significant difference in post for pre at  $p < .05$ , §: significant difference between BFRTg and non-BFRTg at  $p < .05$ .

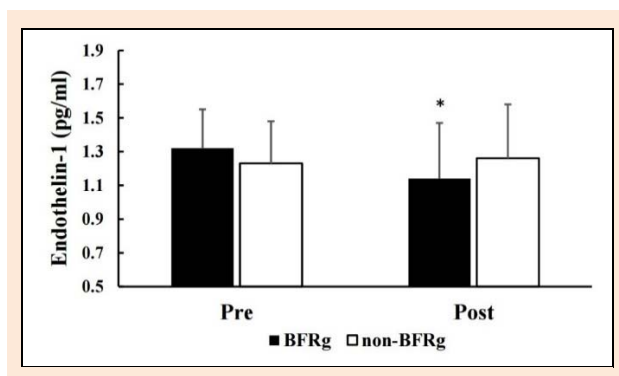
**Table 4. Changes in MRPP and PP following BFR training.**

| Variables          | Group     | Pre          | Post           | p-value ( $\eta_p^2$ )                                   |
|--------------------|-----------|--------------|----------------|--|
| RRPP<br>(mmHg·bpm) | BFRtg     | 132.0 ± 18.2 | 113.7 ± 17.2*§ | T: 0.004 (0.283), G: 0.688 (0.006), I: 0.003 (0.299)     |
|                    | non-BFRtg | 124.9 ± 96.4 | 125.2 ± 15.5   |  |
| MRPP<br>(mmHg·bpm) | BFRtg     | 362.2 ± 37.3 | 288.9 ± 35.4*§ | T: < 0.001 (0.624), G: 0.017 (0.201), I: < 0.001 (0.524) |
|                    | non-BFRtg | 356.2 ± 20.9 | 348.7 ± 27.2   |  |
| PPrest<br>(mmHg)   | BFRtg     | 45.0 ± 6.3   | 34.5 ± 10.0*   | T: < 0.001 (0.367), G: 0.355 (0.033), I: 0.394 (0.028)   |
|                    | non-BFRtg | 45.4 ± 7.2   | 38.7 ± 10.6*   |  |
| PPmax<br>(mmHg)    | BFRtg     | 130.0 ± 12.0 | 95.0 ± 18.0*§  | T: < 0.001 (0.511), G: 0.023 (0.183), I: < 0.001 (0.383) |
|                    | non-BFRtg | 124.5 ± 8.5  | 120.0 ± 16.5   |  |

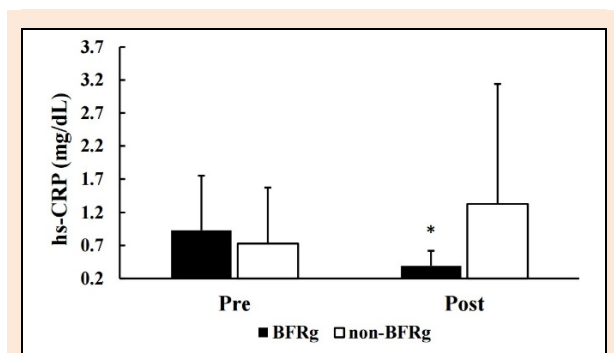
Values are presented as mean ± SD.  $\eta_p^2$ : partial eta squared; BFRtg: blood flow restriction. Tg: training group; RRPP: rest rate pressure product; MRPP: maximal rate pressure product; PP: pulse pressure; RRPP and MRPP values were divided by 100 for presentation; \*: significant difference in post for pre at  $p < 0.05$ ; §: significant difference between BFRtg and non-BFRtg at  $p < 0.05$ .

while the non-BFRtg showed a significant increase from  $20.2 \pm 15.7$  to  $38.0 \pm 39.6$  ( $p < 0.05$ ); there was a significant interaction effect between the two groups ( $p < 0.05$ ) (Figure 4). For NO, the BFRtg changed from  $78.7 \pm 59.2$  pre-intervention to  $63.9 \pm 64.6$  post-intervention, and the non-BFRtg changed from  $39.7 \pm 13.6$  to  $38.1 \pm 22.4$ ; there was no significant interaction effect (Figure 5).

induced favorable changes in cardiovascular biomarkers, including reductions in ET-1, hs-CRP, and NT-proBNP. These findings support our initial hypothesis that BFR training would attenuate exercise-induced hemodynamic stress and be accompanied by beneficial adaptations in endothelial function, inflammation, and myocardial stress.



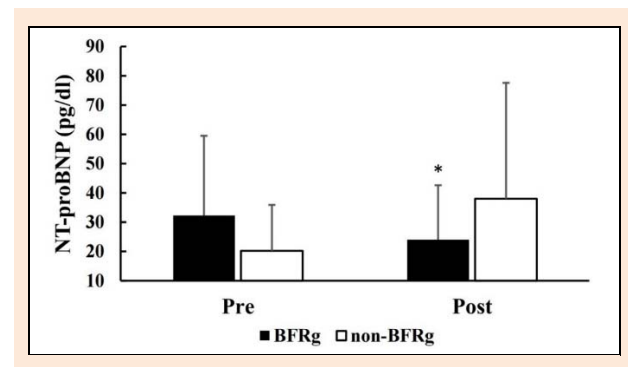
**Figure 2. Changes in endothelin-1 before and after BFR training.** BFRtg: blood flow restriction training group; \*: Significant difference from pre to post at  $p < 0.05$ ; Time × group interaction:  $p = 0.025$  ( $\eta_p^2 = 0.178$ ).



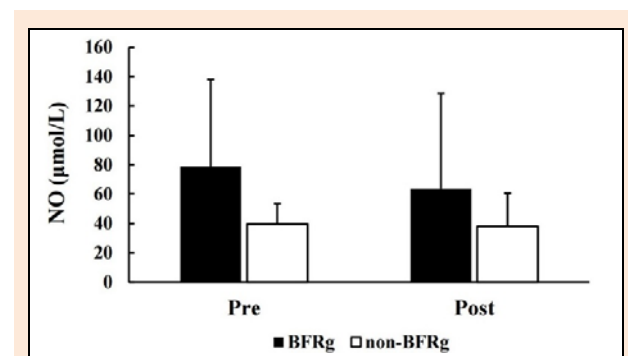
**Figure 3. Changes in hs-CRP before and after BFR training.** Hs-CRP: high sensitivity C-reactive protein; BFRtg: blood flow restriction training group; \*: Significant difference from pre to post at  $p < 0.05$ ; Time × group interaction:  $p = 0.047$  ( $\eta_p^2 = 0.143$ ).

## Discussion

The principal findings of the present study were that an 8-week BFR training program significantly reduced exercise systolic blood pressure and myocardial workload, as evidenced by decreases in SBPmax, RPP, and PP, while simultaneously improving  $VO_{2max}$  in runners with exercise-induced hypertension. In addition, BFR training



**Figure 4. Changes in NT-proBNP before and after BFR training.** NT-proBNP: N-terminal pro-brain natriuretic peptide; BFRtg: blood flow restriction training group; \*: Significant difference from pre to post at  $p < .05$ ; Time × group interaction:  $p = 0.007$  ( $\eta_p^2 = 0.250$ ).



**Figure 5. Changes in NO before and after BFR training.** NO: nitric oxide; BFRtg: blood flow restriction training group; Time × group interaction:  $p = 0.481$  ( $\eta_p^2 = 0.019$ ).

The present study was conducted as a secondary analysis of the cohort previously investigated by Kim et al., with a specific focus on cardiovascular biomarker assessment. Participants who could have influenced the blood analysis results were excluded based on predefined criteria, thereby enhancing the internal validity for interpreting biomarker responses (Kim et al., 2025b). While the fundamental GXT outcomes—maximal SBP and  $VO_{2max}$ —remained consistent with the previous findings (Table 2), the current analysis primarily aimed to determine whether

these hemodynamic improvements were accompanied by favorable biochemical adaptations. Specifically, the 8-week BFR training significantly reduced circulating levels of ET-1 and NT-proBNP, which can influence blood pressure reduction during exercise. It also lowered the systemic inflammatory marker hs-CRP, whereas no distinct changes were observed in NO concentrations.

First, ET-1 is a potent vasoconstrictor that promotes the proliferation of vascular smooth muscle cells and their migration into the intima, thereby playing an important role in the early pathophysiology of atherosclerosis (Lüscher and Barton, 2000). Furthermore, ET-1 has been shown to activate the NF- $\kappa$ B pathway, increasing the expression of inflammatory cytokines, particularly interleukin-6 (IL-6) (Dhaun et al., 2012). IL-6 is a major factor that induces the hepatic synthesis of high-sensitivity C-reactive protein (hs-CRP); thus, ET-1 indirectly mediates the elevation of hs-CRP, which in turn contributes to systemic inflammation and the progression of atherosclerosis (Ridker, 2016).

In the present study, ET-1 and hs-CRP showed a significant reduction only in the BFRTg, but not in the non-BFRTg (Figure 2 and Figure 3). This finding suggests that BFR training may have induced the expression of vascular endothelial growth factors through metabolic stress, thereby improving arterial endothelial function, reducing vascular tone, and ultimately decreasing hs-CRP (Shimizu et al., 2016).

From a physiological perspective, BFR training induces repeated cycles of ischemia and reperfusion, which increase shear stress on the vascular endothelium. This hemodynamic stimulus enhances endothelial nitric oxide synthase (eNOS) activity and improves endothelial function (Green et al., 2017). Furthermore, the accumulation of metabolic by-products such as lactate and reactive oxygen species during BFR exercise may activate intracellular signaling pathways associated with vascular remodeling and anti-inflammatory adaptations (Patterson et al., 2019; Pearson and Hussain, 2015). These mechanisms may collectively contribute to the observed reductions in ET-1 and hs-CRP, reflecting improved vascular regulation and attenuation of systemic inflammation.

We also found that in runners with EIH, BFR training led to a reduction in NT-proBNP, a marker of myocardial wall stress (Figure 4). This finding is consistent with previous research in hypertensive patients, which demonstrated that low-intensity blood flow restriction exercise lowers systolic blood pressure and improves autonomic regulation (Zhao et al., 2022). While regular exercise is known to improve endothelial function (Liang et al., 2024; Maeda et al., 2004), such general adaptations are insufficient to fully explain the present findings. Instead, BFR training provides distinct physiological stimuli, including repeated ischemia–reperfusion cycles and augmented shear stress, which may induce unique vascular adaptations beyond those induced by conventional exercise (Patterson et al., 2019; Shimizu et al., 2016). These mechanisms may have contributed to the observed reductions in ET-1 and hs-CRP, as well as the improvement in hemodynamic load in runners with exercise-induced hypertension. Given that activation of angiotensin II within the renin–angiotensin–aldosterone system (RAAS) and endothelial dysfunction

are key mechanisms underlying EIH in long-distance runners, the recovery of vascular reactivity appears to be closely linked to the reduction in NT-proBNP (Kim et al., 2020). Moreover, a meta-analysis in patients with heart failure demonstrated that regular exercise significantly reduces NT-proBNP levels (do Nascimento et al., 2022; Malandish et al., 2022).

Kim et al. reported that runners with EIH showed significantly greater increases in ET-1 and NT-proBNP after completing a marathon compared to a control group (Kim et al., 2013), and that NT-proBNP levels were also elevated following a 100-km race (Kim et al., 2012). These findings suggest that runners with EIH experience a relatively greater myocardial burden during competition, as the marked rise in blood pressure leads to an increased rate-pressure product. More recently, Kim et al. demonstrated that even a single bout of exercise in runners with EIH led to elevations in NT-proBNP and superoxide dismutase (SOD), indicating that repeated high myocardial workload during routine training may accelerate myocardial hypertrophy or atherosclerosis over time (Kim et al., 2025b). Accordingly, the observed reductions in ET-1 expression and NT-proBNP following BFR training—achieved through repeated cycles of blood flow occlusion and reperfusion that generate strong shear stress on the arterial endothelium and alter endothelial expression patterns—are unlikely to represent transient responses. Rather, they reflect adaptive alleviation of myocardial wall stress, suggesting a cardio-protective effect of BFR training in runners with EIH (Scharhag et al., 2005).

In addition to these biomarker adaptations, the present study identified significant reductions in both RPP and PP, indicating diminished myocardial oxygen demand and arterial load (Table 4). PP is strongly influenced by maximal systolic blood pressure ( $SBP_{max}$ ), and emerging evidence shows that BFR interventions in runners with EIH reduce exercise-induced SBP elevations (Kim et al., 2025a), which may partially account for the observed PP reduction. Given that elevated PP and RPP are independent predictors of cardiovascular morbidity (Agarwal et al., 2024; Jiang et al., 2023; Kim, 2023), these findings further support the hemodynamic and cardioprotective benefits of BFR training in this population.

While NO concentrations are typically expected to increase after exercise interventions (Arefirad et al., 2022), improvements in endothelial function do not necessarily coincide with elevations in basal NO levels. Brinkley et al. reported that enhancements in endothelial function occurred without significant alterations in the absolute concentrations of NO metabolites (Brinkley et al., 2009). Similarly, Allen et al. noted that plasma nitrite is rapidly oxidized to nitrate in circulation, thereby limiting its reliability as an indicator of NO production in clinical contexts (Allen et al., 2005). Furthermore, it has been suggested that improvements in endothelial function can occur independently of changes in circulating NO metabolites (Green et al., 2017). These findings are not entirely consistent across the literature, as some studies report increased NO bioavailability following exercise, whereas others show no change despite improved endothelial function. Such discrepancies may be attributed to differences in exercise

modality, intervention duration, participant characteristics, and methodological variability.

These findings support the notion that endothelial function may improve independently of basal NO concentrations—a mechanism that may underlie the observed reduction in ET-1 following BFR training. Accordingly, the significant improvements in ET-1, hs-CRP, and NT-proBNP after BFR training suggest that this intervention may enhance endothelial function, mitigate inflammation, and reduce myocardial wall stress in runners with EIH.

Although this study provides novel insights, certain limitations should be considered. This is the first study to investigate the effects of BFR training on hemodynamic load and cardiovascular-related biomarkers in runners with EIH. First, excluding participants based on factors that could influence hematological parameters (e.g., excessive exercise or alcohol consumption the day before) limits the generalizability of the findings to the broader population of EIH runners. Second, various pre-analytical and analytical variables—including the timing of blood collection, fasting duration, hydration status, medication use, and immediate post-collection handling (e.g., centrifugation delays, storage conditions)—were not fully controlled, which may have affected the interpretation of the results. Third, as this study was a secondary analysis of an existing cohort rather than a prospectively powered trial, the sample size may have been insufficient to detect small effect sizes for certain biomarkers. Therefore, non-significant findings should be interpreted with caution. Fourth, as the key biomarkers were measured within a single institution and across limited analytical batches, the possibility of inter-assay variability and batch effects cannot be entirely excluded. Fifth, NO was assessed at a single time point, which is insufficient for a precise evaluation of endothelial function; dynamic responses (e.g., post-exercise changes in NO metabolites) and additional vascular function indicators, such as flow-mediated dilation (FMD), were not included. Sixth, repeated comparisons of four biomarkers increase the risk of Type I error, underscoring the need for stricter statistical correction procedures and incorporation of additional markers in future studies. Seventh, although partial control was applied to certain lifestyle factors (e.g., alcohol intake before testing and caffeine restriction), other variables, such as hydration status, habitual dietary patterns, caloric intake (quantity and quality), supplement use, and sleep quality, were not strictly standardized during the intervention period. These factors may have influenced cardiovascular responses and physical performance and should therefore be considered when interpreting the findings. Eighth, antihypertensive medication use and blood pressure control were not strictly standardized; therefore, residual confounding related to medication use and blood pressure regulation cannot be completely excluded. Ninth, cuff pressure was not individualized to Doppler-derived arterial occlusion pressure (AOP), as recommended in current BFR guidelines (Patterson et al., 2019). Instead, a KAATSU-based protocol using fixed or progressively increased absolute pressures was applied. Although this approach may be considered a methodological limitation, similar absolute pressure ranges (150 - 260 mmHg) have been widely used in prior KAATSU studies with low

reported adverse event rates (Abe et al., 2006; Clarkson et al., 2020; Hughes et al., 2017; Loenneke et al., 2012; Suga et al., 2010; Yasuda et al., 2010), supporting the practical feasibility of the present protocol. Tenth, although both groups maintained comparable habitual training throughout the study period, exercise exposure was not strictly standardized or controlled. Therefore, the independent effects of BFR cannot be completely isolated from those of habitual endurance training.

Finally, cuff pressure was not individualized to AOP, which is recommended in contemporary BFR guidelines. However, the KAATSU-based protocol employed fixed or progressively increased pressures with real-time perfusion monitoring, and no adverse events were observed. Future studies should incorporate individualized AOP-based prescriptions to enhance methodological precision. Despite these limitations, the present findings demonstrate that BFR training may reduce hemodynamic load and improve cardiovascular-related biomarkers in runners with EIH, underscoring its potential clinical relevance.

## Conclusion

The present study showed that, in runners with EIH, an 8-week BFR training program improved exercise blood pressure response and cardiorespiratory fitness, accompanied by favorable changes in cardiovascular biomarkers, including ET-1, hs-CRP, and NT-proBNP. In addition, reductions in resting and maximal RPP and PP were indicative of decreased hemodynamic load. These findings suggest that BFR training may enhance vascular regulation, reduce inflammation, and attenuate myocardial stress in this population. However, given the study design and sample size, these findings should be interpreted with caution, and larger randomized trials are warranted to confirm these effects.

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### Key points

- Blood flow restriction (BFR) training significantly reduces maximal systolic blood pressure and myocardial workload in runners with exercise-induced hypertension (EIH).
- BFR training leads to favorable cardiovascular biomarker adaptations, including reductions in endothelin-1, hs-CRP, and NT-proBNP, reflecting improved endothelial function and reduced myocardial wall stress.
- Improvements in VO<sub>2</sub>max and hemodynamic load indicate that BFR training may serve as an effective non-pharmacological intervention for middle-aged endurance runners with EIH.
- Future studies should incorporate individualized arterial occlusion pressures and evaluate long-term vascular and cardiac adaptations to BFR training.

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