Acute Central Stiffness and Muscle Morphological Responses Following Blood Flow Restricted Resistance Exercise with Autoregulated and Non-Autoregulated Pressure Application

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Data availability statement

Data are available upon reasonable request. Requests for data sharing from appropriate researchers and entities will be considered on a case-by-case basis. Please contact Tim Werner.

ABSTRACT

Objective:

To investigate the acute effects of autoregulated (AR) and non-autoregulated (NAR) blood flow restriction (BFR) resistance exercise to volitional fatigue on indices of arterial stiffness and muscle morphology using the Delfi Personalized Tourniquet System.

Methods:

Following a randomized AR-BFR/NAR-BFR familiarization session, 20 physically active adults (23±5 years; 7 female) participated in 3 randomized treatment-order sessions with AR-BFR, NAR-BFR, and No-BFR. Participants performed 4 sets of dumbbell wall squats to failure using 20% of 1 repetition maximum. BFR was performed with 60% of supine limb occlusion pressure. Testing before and immediately post-session included an ultrasonic scan of the carotid artery, applanation tonometry, and blood pressure acquisition. Vastus lateralis cross-sectional area (CSA), and echo intensity (EI) were also assessed via ultrasound before and after each session.

Results:

CF-PWV increased in the NAR-BFR and No-BFR groups following exercise while CR-PWV increased in the No-BFR group (all $p < 0.05$). CF-PWV exhibited an interaction effect between AR-BFR and NAR-BFR in favor of AR-BFR ($p < 0.05$). There were significant main effects of treatment for CSA ($p=0.016$) and EI ($p=0.019$) with all conditions on CSA and EI, with a greater increase in NAR-BFR.

Conclusion:

AR-BFR training does not influence indices of arterial stiffness while NAR-BFR and No-BFR training increases central stiffness. Additionally, low-load resistance exercise to failure induces muscle swelling regardless of BFR. However, NAR-BFR increased CSA and EI compared to AR-BFR. These findings suggest that AR-BFR causes a lower fluid flux to the intracellular space, possibly inducing less muscle damage and swelling than NAR-BFR.

Key messages:

- **What is already known**
    - Autoregulation (AR) of applied blood flow restriction (BFR) training pressures is a device feature that may enhance the acute safety of BFR exercise.
    - AR-BFR accounts for the change in limb circumference that occurs during the different phases of muscular contraction, whereas non-autoregulation (NAR-BFR) of applied pressure does not.
    - As AR-BFR is a device-specific feature, there is currently no research investigating the acute impact of autoregulation on central arterial stiffness and muscle swelling using the Delfi Personalized Tourniquet device.
- **What this study adds**
    - AR-BFR blunts the increase in central arterial stiffness compared to NAR-BFR and No-BFR low-load resistance exercise to failure.
    - NAR-BFR exercise increased post-exercise muscle swelling compared to AR-BFR and No-BFR low-load resistance exercise to failure, indicating heightened intramuscular fluid flow and potentially greater muscle damage.
- **How this study might affect research, practice, or policy**
    - Our study supports the use of AR-BFR during BFR exercise as it prevents the exercise-induced increases in central arterial stiffness and additional muscle swelling response compared to NAR-BFR and No-BFR low-load exercise.
    - AR-BFR may be favored in populations where acute increases in central arterial stiffness may heighten the risk of cardiovascular and/or cerebrovascular events.

1.0 Introduction

Low-load resistance exercise with blood flow restriction (BFR) is becoming increasingly implemented in rehabilitation (1) because of the similar musculoskeletal benefits it confers compared to traditional heavy load strength training, including muscle hypertrophy (2) and strength (3). However, despite BFR's growth as an alternative exercise approach, there are still concerns regarding its safety profile (4–6).

A primary safety concern during BFR exercise is the potential for excessive hemodynamic and cardiovascular disturbances that likely exceed the responses produced with load-matched exercise and approach or exceed heavy load strength training (4), which can lead to serious adverse events (i.e., cerebrovascular events). Research has shown that brachial systolic and diastolic blood pressures (BP) are elevated above low-load exercise in elderly and hypertensive patients (7,8). Albeit not as elevated as populations with pre-existing conditions, similar reports have been observed in young and older normotensive populations during resistance exercise with BFR (9). Nonetheless, reports of cerebrovascular events have not been documented in the literature thus far (5), highlighting the relative safety of the intervention in multiple populations.

While peripheral hemodynamics (i.e., brachial BP measures) have been a focus of research in elucidating the safety profile of BFR resistance exercise, less is known regarding the central hemodynamic (i.e., aortic BP and stiffness measures) responses. A recent systematic review (10) highlighted significant heterogeneities that exist in the limited body of literature in this area, including differences in BFR prescriptive factors and repetition schemes, as well as the absence of the "gold standard" pulse wave velocity (PWV) assessment, for arterial stiffness in acute resistance exercise investigations. PWV measures the difference in time delay of the systolic waveform between a central (i.e., aorta) and peripheral (i.e., radial or femoral artery) site

and provides a measure of stiffness associated with the central arterial apparatus (11). Significantly stiffer arteries may predispose exercisers to a higher risk of cardiovascular events (11) during acute bouts of exercise and are associated with higher PWVs.

Evidence indicates that chronically elevated PWV independently predicts the presence of cardiovascular risk factors (i.e., atherosclerosis) (11) and hypertension (12), as well as morbidity and mortality (13). As such, it is prudent to understand the impact that an acute resistance exercise session with BFR may play on PWV, particularly as BFR is becoming more utilized in populations with hypertension (8), obesity (14), and heart failure (15).

While research on PWV appears to indicate a deleterious effect on health when chronically elevated, acute measures of central arterial stiffness (including PWV) following resistance exercise appear to vary based on whether the exercise was performed with the upper or lower body (16), the contraction type (i.e., concentric versus eccentric) (17), the repetition scheme used (18), the exercise cadence employed (19), and the load used (i.e., 30% 1-rep max versus 70-80% 1-rep max) (20). Arterial stiffness measures tend to increase acutely and a rule of thumb is that chronic PWV elevations of 1 m/s increases all-cause mortality (21), although the relative importance of acute increases is less established, particularly in the BFR literature. Therefore, understanding the impact of resistance exercise with BFR on acute measures of arterial stiffness is important but currently understudied.

As BFR becomes more widely implemented in different practice settings (1), the availability of BFR equipment for consumer purchase has increased. However, there is a dearth of research available on the different types of BFR devices used, as well as particular features marketed to enhance its safety during application (22). One of those features is autoregulation, whereby the applied pressure to the exercising limb from the BFR cuff is kept relatively constant

compared to a manually inflatable (non-autoregulated) cuff that does not adjust and, therefore, may heighten cardiovascular and perceptual exercise responses (23). A recent study (24) highlighted the potential for autoregulation to enhance the safety of BFR exercise as compared to non-autoregulated cuff applications. Jacobs (24) showed a 3x risk reduction in minor adverse events (i.e., lightheadedness) in the autoregulated compared to the non-autoregulated cuff condition when performing the same exercise series. This study provided the first direct evidence that autoregulation may enhance the acute safety profile of BFR exercise. However, the hemodynamic (i.e., brachial blood pressures) and perceptual responses (i.e., rate of perceived exertion/discomfort) to exercise between conditions were largely the same, indicating the influence of other factors not measured. A potential factor may be the acute change in arterial stiffness. Thus, much is unknown regarding the impact of autoregulation on arterial stiffness.

Last, as muscle swelling may play a role in the long-term adaptive response to resistance exercise (25), it is important to understand the potential acute differences that arise from the type of applied BFR pressure. No evidence currently exists reporting acute muscle swelling differences between the same exercise performed with and without autoregulation compared to the same exercise without BFR. Therefore, it is unknown whether this feature may impact the swelling response and, thus, the long-term adaptive potential.

This study aimed to assess the acute impact of autoregulation on arterial stiffness and muscle swelling in a cohort of healthy, physically active adults during wall squat exercise to volitional fatigue. We hypothesized that no differences in arterial stiffness or muscle swelling would be observed between the autoregulated or non-autoregulated BFR cuff conditions or between low-load resistance exercise without BFR.

2. Methods

2.1 Participants

Twenty-five physically active individuals were recruited on the Salisbury University campus via a flyer and e-mail outreach. Physically active was characterized as consistently exercising for greater than 6 months of ≥ 1,000 MET/min/week. Participants were initially screened by TW for study eligibility (Table 1) and if they met inclusion criteria and did not display any exclusion criteria, they were scheduled for a familiarization session. Each participant signed an informed consent document in accordance with the Declaration of Helsinki acknowledging potential risks and harms.

Inclusion Criteria	Exclusion Criteria
• Age 18-40 years old	• Resting BP > 140/90 mmHg
• Physically active (> 6 months) of ≥ 1,000 MET/min/wk	• BMI > 40 kg/m2
• Weight stable for previous 6 months (±2.5 kg)	• Diabetes
• Female subjects reported regular menstrual cycles for the last 2 years	• Recent surgery (< 2 months)
[redacted]	• Past or current history of CHD, stroke or major CVD events. Reported sleep apnea.
	• Active renal or liver disease

Table 1. Inclusion and exclusion criteria. BP, blood pressure. MET, metabolic equivalent. BMI, body mass index. CHD, chronic heart disease. CVD, cardiovascular disease.

2.2 Study Design

This intervention assessed differences in arterial stiffness and muscle swelling responses following lower body blood flow restriction (BFR) in exercise performed to volitional fatigue using two different applied pressure settings (autoregulated [AR-BFR] versus non-autoregulated [NAR-BFR]) in a sample of healthy, physically active participants. In this crossover, randomized-controlled study, each participant reported to the lab for four sessions. During the

initial session (familiarization), each participant was randomized to AR-BFR or NAR-BFR using a randomization software (www.random.org/lists) and the exercise protocol was performed without assessing outcomes. Following the familiarization session, each participant was randomized into AR-BFR, NAR-BFR or No-BFR by the same software and performed the identical exercise protocol as in the familiarization session (Figure 1), but with outcome variables assessed.

****Insert Figure 1 Here****

Each session was separated by at least 7 days to reduce the potential impact on exercise performance and recovery. Participants were instructed to continue their normal training activities while avoiding exercise-related activities and caffeine and alcohol 24 hours before each session. Subjects reported within ±1 hour to minimize diurnal variations in responses. All measurements were conducted in the Exercise Physiology Research Lab at Salisbury University after a 4-hour fast between 0600 to 1200 hours. The study was approved by the ethics committee of Salisbury University (approval number 7) and pre-registered at clinicaltrials.gov.

2.3 Patient and public involvement

Participants were not involved in designing the research question or conducting the research. However, participants were surveyed regarding the occurrence of adverse events during and following performance of the protocol. Upon request, participants were informed of the results of the study.

2.4 Equity, diversity, and inclusion statement

Our author group is mixed gender and nationalities, and our population cohort studied included females (n=7; 35%). The author group is composed of junior, mid-career, and senior researchers

from different disciplines, including physical therapy and exercise science. Due to the cohort studied (university population), we acknowledge that participants likely were not from lower socioeconomic statuses, and thus, our results may not be generalizable to that population.

2.5 Testing Protocol

Initially, participants had their one repetition maximum (1-RM) determined and then underwent a familiarization session to acclimate them to the sequencing of data collection and the BFR stimulus. In all sessions, 4 sets to volitional fatigue of dumbbell wall squats were performed using ~20% 1-RM (to the nearest 5-pound increment) with- (AR-BFR) or without (NAR-BFR) autoregulation of applied pressures, in addition to a No-BFR condition. Dumbbells were held with arms fully extended and the shoulder flexed at 0˚. Due to the synthetic ice pad (Snipers Edge, Minneapolis, MN) mounted on the wall, drag was minimized during the upward and downward phase of each repetition. Rest between sets was 1 minute. Cadence was monitored via a metronome (Seiko, Mahwah, NJ) for a 2 second concentric and a 2 second eccentric phase, with range of motion set to 90˚ of knee flexion at the bottom and full extension at the top. Volitional fatigue for each set was determined as the inability to perform the technique to specifications (i.e., maintaining back flat against the wall), inability to maintain appropriate cadence, and/or desire to stop. A verbal warning was given upon the first technique violation, and then the set was stopped with a second violation.

Ultrasonography of the carotid artery, applanation tonometry, BP acquisition, and ultrasonography of the vastus lateralis were completed before and immediately following all training sessions except the familiarization session, where baseline data was only collected before the exercise. Rate of perceived exertion (RPE), rate of perceived discomfort (RPD), and a subjective measure of participant enjoyment of the session were assessed immediately post-

exercise in all training sessions, as well as adverse events monitored. In addition, total training volume and repetitions were recorded for all trials.

2.5.1 BFR settings – autoregulation and limb occlusion pressure

For the AR-BFR or NAR-BFR familiarization and BFR exercise trials, two 11.5cm variable contour pneumatic BFR cuffs (Delfi Personalized Tourniquet Systems, Vancouver, Canada) were placed around the most proximal portion of each thigh. Following a 10-minute supine rest, limb occlusion pressure (LOP) was determined and subsequently set at 60% LOP for the duration of exercise. To minimize potential discrepancies, each participant used 34" length cuffs. The Delfi Personalized Tourniquet device has been previously validated for its accuracy in determination of LOP compared to doppler ultrasound (26) and has the capacity to adjust the applied pressure (i.e., autoregulate) and cuff diameter to the exercising limb to maintain a relatively consistent pressure despite changes in muscle volume during exercise using a pulse pressure sensor (23). Conversely, during NAR-BFR training, the cuff diameter does not adjust to the phase of muscle contraction during exercise. BFR was applied continuously in both conditions, inflating prior to the first set, and deflating after completion of the 4th set following subjective assessments. Total time under tension was recorded for both BFR sessions. Participants were blinded to the presence of autoregulation for all trials but were not blinded when exercising in the No-BFR condition as no cuffs were applied to the exercising limbs.

2.5.2 No-BFR Exercise

A No-BFR training session utilizing the same failure scheme and load but without the pneumatic cuffs applied to the legs was also performed in a randomized order.

2.5.3 Familiarization Session

A maximal dumbbell wall squat strength test (1-RM) was completed prior to the familiarization session at Maggs Recreational Center at Salisbury University in accordance with the guidelines from the National Strength and Conditioning Association (27). All 1-RMs were determined within 5 attempts. Afterwards, participants walked to the laboratory and sat quietly with legs uncrossed for 10-minutes prior to seated BP measurements. Height, weight, and body composition assessment via BODPOD followed. Participants then rested supine on the examination table for 10-minutes. Ultrasound scans of the vastus lateralis were recorded followed by supine BP measurements. Lastly, carotid ultrasound scans and arterial tonometry were performed, which completed all pre-training assessments. For all central arterial assessments and muscle ultrasound, the examiners were not blinded to the group condition due to limitations in personnel. Participants were then provided instructions on RPE, RPD, and shown a 1-10 Likert scale assessing likelihood of performing the training again during the familiarization session. Participants were informed that these would be assessed immediately post-exercise during sessions 2-4. Each participant was then randomized into AR-BFR or NAR-BFR and performed the exercise protocol as described above.

2.6 Outcome Measures

2.6.1 Anthropometrics

Total body mass and height were measured during the familiarization session on a medical scale and stadiometer (Detecto 439 Physician Beam Scale) accurate to ± 0.1 kg and stadiometer between 0600 and 1200 after a void and 12-hour fast. Participants wore standard shorts and t-shirts at the time of weighing. Air displacement plethysmography (BOD POD) (Cosmed Metabolic Company, Rome) measured fat and fat-free body mass. Participants wore tight clothing and sat quietly inside the BOD POD during three sequential measurements.

2.6.2 Brachial Blood Pressure

Seated and supine brachial BP measurements were taken under quiet, ambient (~24℃) conditions. All BP measurements adhered strictly to American Heart Association guidelines (28). After a 5-10 minute rest period, both seated and supine measurements were auscultated from the right brachial artery using an automated sphygmomanometer (Welch, Allyn, New York). Systolic (SBP) and diastolic (DBP) BPs were recorded every 2 minutes, and average SBP and DBP readings were tabulated using 3 sequential measurements within 6 mmHg of each other.

2.6.3 Carotid Artery Ultrasonography

A doppler ultrasound machine probe (Terason t3300, Burlington, MA) was placed approximately 2 cm distal from the carotid bulb after a 10-minute supine rest. Longitudinal B-mode images of the right common carotid artery were measured in triplicate and averaged. The distance between the apical surface of the tunica media of the near and far wall was used to determine systolic (maximal) and diastolic (minimal) diameters.

2.6.4 Arterial Applanation Tonometry

Using a high-fidelity transducer (Complior Analytic Tonometer, Alam Medical, Vincennes, France), right carotid arterial pressure waveforms and amplitudes were recorded after a 10-minute supine rest. The right brachial supine SBP and DBP (explained above) and carotid waveforms were used to equate carotid SBP (cSBP), DBP (cSBP), and mean arterial pressure (cMAP) through a proprietary transfer function. All tonometry recordings were taken by the same experienced researcher (TW) with excellent reproducibility ($r>0.90$; $p<0.05$) for β-stiff, pulse wave velocity (PWV), and arterial compliance (AC).

2.6.5 Pulse Wave Velocity

After a 10-minute supine rest, three high-fidelity tonometers (Complior Analytic Tonometer, Alam Medical, Vincennes, France) simultaneously recorded and averaged 10 waveforms from the right-sided carotid, radial, and femoral arterial sites with the strongest pulse palpation. Distances between the arterial sites were measured in the supine position with a caliper to the nearest 0.5 cm. Carotid-femoral pulse wave velocity (CF-PWV) and carotid-radial pulse wave velocity (CR-PWV) were calculated by dividing the distance between arterial sites by the foot-to-foot time delay between arterial waveforms (PWV = D (m)/Δt (sec)).

2.6.6 β Stiffness Index and Arterial Compliance

β-stiff is an index of arterial stiffness independent of acute changes to BP (11). It was calculated as β = ln (SBP/DBP) / [(systolic diameter-diastolic diameter)/diastolic diameter] and expressed in arbitrary units. Carotid systolic and diastolic diameters, cSBP and cDBP, were factored in the β-stiff calculations. Arterial compliance (AC) is an indice of arterial stiffness and is sensitive to acute BP changes (29). AC was calculated as (π(systolic diameter^2 – diastolic diameter^2) ÷ 4(SBP-DBP)) using carotid diameters and pressures.

2.6.7 Vastus Lateralis Ultrasonography

Participants' muscle cross-sectional area (mCSA) and echo intensity (EI) of the vastus lateralis (VL) muscle was assessed using a brightness mode (B-mode) of the ultrasound imaging system (Terason t3300, Burlington, MA) and a multi-frequency linear-array probe (Model 15L4 Smart Mark 4-15 MHz). All ultrasonic scans were conducted on the participants' right leg to measure the mCSA and EI of the VL. Each participant was positioned on their left side at a knee flexion angle of 110° with the hips positioned in 0° of flexion. The VL measurements were obtained

from the right leg at 50% of the distance between the greater trochanter and lateral edge of patella. Location of measurement was marked with indelible ink at every session to ensure scans were taken at the same area for both pre- and post-measurements. All ultrasound pre- and post-training scans were taken by an experienced individual (MM) with appropriate intra-class correlation coefficient (ICC) and standard error of the measurement (SEM) for both mCSA (ICC = 0.97, SEM = 1.02 cm^2) and EI (ICC = 0.98, SEM = 1.02 au).

2.6.8 Perceptual Experience Assessments

Immediately following completion of the final set and with the cuffs still inflated, participants were requested to provide their RPE and RPD and rate the likelihood that they would perform the same exercise again. Participants were asked to anchor their response based on the entire exercise session. Three- 8-inch x 10-inch charts were held in front of the participant by the same administrator (TW) in the following order: RPE, RPD, and a 1-10 Likert scale. RPE and RPD scales were read to the participant in accordance with a previous validation study (30). Likelihood to perform this exercise again was assessed with the question "on a scale of 1-10, how likely would you perform the same exercise again? 10 being very likely and 0 being not likely at all."

2.6.9 Performance

Performance was evaluated by total exercise volume and repetitions to failure in each condition.

2.6.10 Safety – Adverse Events

Participants were asked to report any adverse responses in conjunction with the performance of each exercise bout. Any responses gathered were classified according to a recently published review (5).

2.7 Statistical Analysis

G*Power (Kiel University, Germany) software 3.1.9.7 calculated a sample size of 20 participants to detect an effect size of 0.35 using repeated measures analysis of variance (ANOVA) at $\alpha = 0.05$ & $\beta = 0.80$. To account for the expected attrition rate of 20%, 25 individuals 18-40 years of age of all races and ethnic backgrounds meeting the inclusion and exclusion criteria (Table 1) were recruited for the study. Statistical Package for the Social Sciences (IBM SPSS version 28, SPSS Inc., Chicago IL) was used for both descriptive and inferential statistical analyses. Paired sample t-tests assessed baseline differences. Two-way ANOVAs were used to examine the effects of treatment and the treatment-order interaction on variables of interest. Post hoc analysis (Tukey HSD) was performed on variables with significant F-ratios. Findings with a $p < 0.05$ were considered significant, and all data are presented in means ± standard deviation (SD) unless otherwise stated**.** Effect sizes (Cohen's *d*) were defined as: 0.2, small; 0.5, moderate; and ≥ 0.8, large (31).

3. Results

3.1 Participants

Participant characteristics are listed in Table 2. Thirteen males and 7 females (22.6±4.9 years, 7 females) completed the study. Attrition of five individuals occurred for various reasons, including time constraints, missed appointments, acute illness, and loss of contact (Figure 1). No injuries or adverse events related to the treatments were reported. There were no significant baseline differences in arterial stiffness and cardiovascular (Table 3)**,** muscle morphology (Table 3) or performance (Table 4) variables among any of the randomized sessions.

Variable	Mean±SD
Age, yr	22.6±4.9
Height, cm	175.2±9.7
Weight, kg	79.7±15.9
BMI, kg/m^2	25.6±4.9
Body Fat, %	15.9±8.9
Fat Mass, kg	12.7±8.5
Fat Free Mass, kg	66.8±14.3
Seated SBP, mmHg	124±10
Seated DBP, mmHg	74±7
Seated MAP, mmHg	90±7
Dumbbell wall squat 1 RM, kg	99.4±38.1
Right leg LOP, mmHg	205±17
Left leg LOP, mmHg	189±12
MET · min^{-1} · wk^{-1}	2966±1400

Table 2. Baseline participant characteristics. SD, standard deviation. Yr, year. SBP, systolic blood pressure. DBP, diastolic blood pressure. MAP, mean arterial pressure. 1 RM, one-repetition maximum. LOP, limb occlusion pressure. MET, metabolic equivalents.

3.2 Hemodynamics

Several hemodynamic changes were identified (Table 3). Central SBP increased (mean difference (MD) = 7±12 mmHg, 95% confidence interval (CI) (2-13), p = 0.004, effect size (ES) = 0.65), central pulse pressure (PP) (MD = 7±12 mmHg, 95% CI (1-13), p = 0.012, ES = 0.55), and central mean arterial pressure (MAP) (MD = 3±7 mmHg, 95% CI (1-6), p = 0.029, ES = 0.45) in No-BFR. Compared to AR-BFR, HR, SBP, and RPP were significantly higher immediately following exercise in NAR-BFR (MD HR: 8±12 bpm, p=0.01, 95% CI (2-13), ES = 0.63; MD RPP: 1297±1973 au, p<0.01, 95% CI (373-2219), ES = 0.66), and No-BFR (MD HR: 8±14 bpm, 95% CI (2-14), p = 0.01, ES = 0.58; MD SBP: 6±9 mmHg, 95% CI (1-10), p = 0.01, ES = 0.58; MD RPP: 1773±2074 au, 95% CI (819-2726), p<0.01, ES = 0.87). All groups experienced a significant increase in supine heart rate (HR) and rate pressure product (RPP) following treatment (all p<0.05). Additionally, NAR-BFR and No-BFR experienced a significantly greater increase in supine HR (MD NAR-BFR:4±9 bpm, 95% CI (1-8), p = 0.046, ES = 0.41; MD No-BFR: 7±9 bpm, 95% CI (3-11), p = 0.002, ES = 0.79) and supine RPP (MD NAR-BFR: 560±1215 au, 95% CI (26-1146), p = 0.030, ES = 0.46; MD No-BFR: 1066±1391 au, 95% CI (396-1736), p = 0.002, ES = 0.76) compared to AR-BFR.

3.2 Central Arterial Stiffness Measures

Following the intervention, CF-PWV significantly increased in NAR-BFR (MD = 0.57±1.12 m/s, 95% CI (0.05 - 1.09), p = 0.017, ES= 0.51) and No-BFR (MD = 0.63±1.42 m/s, 95% CI (+0.04-1.3), p = 0.032, ES = 0.44) **(Table 3).** Compared to AR-BFR, NAR-BFR experienced a greater increase in CF-PWV (MD = 0.70±1.60 m/s, 95% CI (0.05-1.44), p = 0.034, ES = 0.43) (**Table 3**). CR-PWV significantly decreased after the intervention in No-BFR (MD = -0.82±1.51

m/s, 95% CI (0.09-1.54), p = 0.015, ES = 0.54). No significant time effects or interactions were detected in β-stiffness and AC (Table 3) (all p>0.05) with the interventions.

3.3 Muscle Swelling

VL CSA increased in AR-BFR (MD = 2.34±1.23 cm^2, 95% CI = 1.82-2.88, p<0.01, ES = 2.08), NAR-BFR (MD = 2.53±0.79 cm^2, 95% CI (2.16-2.91), p<0.01, ES = 3.18), and No-BFR (MD = 2.18±1.14 cm^2, 95% CI (1.64-2.72), p<0.01, ES=1.91) following the intervention (Table 3). VL EI was also increased in AR-BFR (MD = 2.35±3.46 au, 95% CI (0.73-3.97), p<0.01, ES = 0.68), NAR-BFR (MD = 4.84±7.74 au, 95% CI (1.22-8.46), p<0.01, ES = 0.63), and No-BFR (MD = 3.21±4.89 au, 95% CI (0.93-5.50), p<0.01, ES = 0.66) after the intervention (Table 3). Additionally, there was a significantly greater increase in CSA (MD = 0.61±1.03 cm^2, 95% CI = 0.13-1.09, p<0.01, ES = 0.59) and EI (MD = 5.84±8.89 au, 95% CI (1.67-9.99), p<0.01, ES = 0.66) in NAR-BFR compared to AR-BFR following exercise training.

	AR-BFR		NAR-BFR		No-BFR		Baseline Difference p values
Variable	PRE	POST	PRE	POST	PRE	POST	
CF-PWV, m/s	7.05±1.40	7.12±1.43	7.12±1.15	7.69±1.65*‡	6.87±1.04	7.51±1.41*‡	0.757
CR-PWV, m/s	9.33±3.07	8.33±2.66	9.35±2.50	9.33±2.51	8.91±1.74	8.36±2.18*	0.775
Central SBP, mmHg	117±15	119±16*	117±15	119±14*	115±12	122±13*	0.629
Central DBP, mmHg	67±8	65±9	67±8	67±11	67±8	68±9	0.840
Central PP, mmHg	50±12	54±13*	50±15	53±13	48±12	55±13*	0.641
Central MAP, mmHg	83±9	83±10	84±8	84±10	83±8	86±9*	0.713
β-SI, *U*	6.02±2.04	5.42±1.44	5.99±2.31	5.85±1.60	6.45±2.33	6.08±2.93	0.738
AC, $mm^2/mmHg \times 10^{-1}$	1.41±0.40	1.41±0.44	1.44±0.68	1.30±0.38	1.31±0.42	1.38±0.58	0.593
Supine SBP, mmHg	121±10	128±12*	121±8	129±15*	122±9	131±12*	0.629
Supine DBP, mmHg	67±8	65±9	67±8	67±11	67±8	68±9	0.840
Supine PP, mmHg	55±7	63±10*	54±8	63±10*	55±9	63±12*	0.791
Supine MAP, mmHg	85±8	86±9	85±7	87±11	85±7	89±9*	0.642
Supine HR, bpm	63±9	79±13*	65±10	83±12*‡	62±11	85±13*‡	0.316
Supine RPP, au	7409±1426	9474±1966*	7625±1156	9910±1766*‡	7051±1026	10415±1749*‡	0.070
CSA, cm^2	27.38±6.78	29.73±7.18*	27.81±6.91	30.34±7.33*‡	27.58±6.74	29.76±7.05*	0.221
EI, au	65.30±10.51	67.66±10.54*	68.64±10.17	73.49±11.04*‡	67.57±9.57	70.78±10.95*	0.187

Table 3. Arterial stiffness, central hemodynamics and muscle swelling responses pre- and post-intervention. Values expressed as mean ± SD; C, carotid; R, radial; F, femoral; PWV, pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; β-SI, β stiffness index; AC, arterial compliance; HR, heart rate; RPP, rate pressure product; CSA, cross sectional area; EI, echo intensity. * P<0.05 Time Effect; ‡ P<0.05 Interaction with AR-BFR.

3.4 Performance

Total reps and training volume were significantly lower in AR-BFR (reps: -29.6±13.9, 95% CI (-23.11-36.08), p<0.01, ES=2.13; volume: -1331±855, 95% CI (-931-1731), p<0.01, ES=1.55) and NAR-BFR (reps: -31.0±17.9, 95% CI (-22.59-39.40), p<0.01, ES=1.73; volume: -1426±999, 95% CI (-958-1893), p<0.01, ES=1.42) compared to No-BFR (Table 4). Time under tension was not different between BFR conditions (452±87 s vs. 444 ± 74 s in AR-BFR and NAR-BFR, respectively). RPD was significantly greater in AR-BFR (1.2±1.4, 95% CI (0.5-1.9), p<0.01, ES = 0.86) and NAR-BFR (1.6±1.3, 95% CI (1.0-2.2), p<0.01, ES =1.2) compared to No-BFR (Table 4). RPE and the 1-10 Likert scale assessing the likelihood of performing the training again was not different between any condition (all p>0.05).

3.5 Safety – occurrence of adverse events

No adverse events occurred during- or following any session, including the familiarization.

Variable	AR-BFR	NAR-BFR	No-BFR
Total Reps	53±20‡	52±17‡	83±27
Volume	2436±1263‡	2341±1020‡	3767±1771
TUT, sec	452±87	444±74	N/A
RPE	8.2±0.8	8.5±1.0	8.2±1.2
RPD	6.2±2.3‡	6.6±2.2‡	5.0±2.4
Perform again	6.85±2.39	6.95±2.61	7.50±2.50

Table 4. Reps, repetitions; TUT, time under tension; RPE, rating of perceived exertion; RDP, rating of perceived discomfort; Perform again, 10-point Likert scale assessing desire to perform exercise again. ‡ P<0.05 Between difference with No-BFR.

4. Discussion

This is the first study to examine the acute responses between AR-BFR, NAR-BFR, and No-BFR exercise on arterial stiffness and muscle morphological changes in a lower body resistance protocol to volitional fatigue using a frequently studied BFR training device in healthy, physically active adults. The main findings are (1) AR-BFR blunts exercise-induced central arterial stiffness compared to NAR-BFR and No-BFR, (2) NAR-BFR induces higher post-exercise muscle swelling than AR-BFR, and (3) no differences were observed between perceptual outcomes or volume performed between AR-BFR and NAR-BFR; however, both produced greater discomfort than No-BFR.

4.1 Arterial stiffness, central and peripheral hemodynamics

AR-BFR blunted the increase in carotid-femoral pulse wave velocity (CF-PWV) compared to NAR-BFR 10 minutes post-exercise with between-group differences of ~0.70 m/s with a small to moderate effect. We also observed that No-BFR increased CF-PWV 0.63 m/s, although between-group differences with AR-BFR did not reach significance. In addition, supine RPP following

exercise was elevated in both NAR-BFR and No-BFR trials above AR-BFR, indicating heightened myocardial workload (32). We also observed negligible or no between-group differences in central hemodynamics (central SBP/DBP/PP/MAP) and changes in β-stiffness or AC. Explaining the potential reasons why these results may have occurred is challenging, and likely not due to performance- or perceptual-related factors, as total volume, time under tension, and RPE/RPD were similar between BFR conditions. Moreover, the increase in post-exercise CF-PWV occurred in No-BFR, where participants performed ~34% more volume, lowering the likelihood that volume modulates the CF-PWV response. As this was the first study of its kind, no direct comparisons can be made with the existing body of BFR literature. However, our findings support that AR-BFR reduces the post-exercise central arterial stiffness and myocardial workload compared to NAR-BFR and No-BFR, although the relative importance of such differences are debatable based on the acute nature of the trial and the health of the participants.

Central arterial stiffness is an important variable to consider when implementing resistance training programs, given its association with morbidity and mortality in those with cardiovascular risk factors and the direct impact it has on myocardial workload (33). A recent review (10) highlighted the absence of investigations utilizing CF-PWV and, therefore, an uncertainty in elucidating the acute relative cardiovascular risk of performing low-load BFR exercise despite the benefits observed from long-term training programs (2). The absence of evidence in this area of BFR safety is concerning, considering the expansion of this technique into rehabilitation settings where individuals may have a greater likelihood to be older, have medical conditions, and/or musculoskeletal ailments (34). As these populations tend to exhibit stiffer arteries at rest, it is prudent to understand the potential impact on acute measures of CF-

PWV in healthy populations before BFR exercise prescription in at-risk patients becomes ubiquitous.

Prior research has shown that an acute moderate-high-intensity resistance exercise session (≥ 65% 1-RM) increases measures of CF-PWV immediately post-exercise in healthy, young adults (35) with long-term interventions showing negligible or even a reduced CF-PWV (20). Other studies have shown differing acute autonomic responses to upper- versus lower-body exercise performed at a similar percentage of 1-RM (30% 1-RM) in older adults (36) despite longitudinal resistance exercise programs lowering resting BP, increasing muscle mass and strength, and improving body composition (20). Determining the threshold at which increases in CF-PWV becomes deleterious, as well as the relevance of mitigating acute post-exercise central stiffness and myocardial workload during- and following exercise is unknown. This is an important area of future research.

The only two BFR resistance training studies (37,38) that assessed PWV lasted 4-6 weeks and utilized leg extension exercise to failure three times per week in both young (37) and older (38) adults. Both measured PWV peripherally from the femoral artery to the posterior tibial artery, providing insight into the long-term impact of BFR on peripheral arterial stiffness. The limited evidence from these studies suggests that older adults are more likely to experience peripheral arterial stiffness following low-load BFR exercise than younger adults. While both studies had participants exercise to failure, some important differences prevent comparisons with our study. As neither study assessed arterial stiffness via CF-PWV, it is unknown whether a longitudinal lower body low-load BFR resistance exercise program impacts central arterial stiffness in a similar manner as traditional moderate-high intensity resistance exercise prescriptions (i.e., negligible impact or slight increases). Secondly, both studies used a single-

joint leg extension exercise, whereas ours used a multi-joint squat exercise. Thirdly, peripheral PWV sampling occurred 2-4 days post-intervention in both trials, whereas ours occurred 10 minutes post-exercise. Thus, comparisons between the existing body of literature are difficult.

Prior research has hypothesized that the acute increases in central stiffness markers following high-intensity resistance exercise may be due to the unique hemodynamics of strenuous exercise (35). Pierce et al. (35) proposed that large fluctuations in BP and the use of the Valsalva maneuver mechanically compress the vasculature, leading to a heightened pressor response and acute stiffening of the arteries. However, over time (i.e., weeks to months), the central arterial apparatus adapts, leading to negligible changes in central stiffness (20). In support of the adaptation capacity of the arterial system, Hunt et al. (39) observed that similar to other bodily tissues, arteries undergo adaptation following resistance exercise with BFR. Their investigation into the time course of arterial adaptations highlighted that over six weeks, the calf arteries first exhibited increases in flow-mediated dilatation followed by an augmentation of maximal conduit artery diameter and a return to baseline flow-mediated dilatation capacity (39). Therefore, acute assessments may not provide a reliable means to determine the adaptation potential and long-term safety of an intervention.

Nonetheless, while the relevance of the magnitude of acute changes in CF-PWV speeds are uncertain, the current body of evidence indicates that changes of +1m/s increase age-, sex-, and risk-factor adjusted cardiovascular events, mortality, and all-cause mortality between 14-15% (40). As our study evidenced acute increases of 0.6-0.7 m/s in both NAR-BFR and No-BFR, practitioners seeking to minimize adverse events during BFR exercise may choose AR-BFR as it prevented increases in central arterial stiffness. Although it is important to note that no adverse events were recorded in any group throughout our entire study..

4.2 Muscle swelling

The results showed that the AR-BFR, NAR-BFR, and No-BFR conditions significantly increased vastus lateralis (VL) CSA regardless of using BFR. These results confirmed previous findings and contributed additional evidence demonstrating acute hypertrophic response following low-load BFR exercise (41). However, NAR-BFR significantly increased VL and CSA compared to AR-BFR. Since acutely increased muscle size post-exercise can result from muscular damage or edema, measuring muscle quality, as indicated by ultrasound echo intensity (EI), has been recommended to evaluate the potential influence of muscular edema or damage (42). Our findings indicated that the low-load wall squats to failure significantly increased EI values for all conditions regardless of BFR. However, the NAR-BFR condition showed a significantly greater increase in EI compared to the AR-BFR condition.

It has been previously established that ultrasound EI values can also be used to evaluate muscle quality (43) and to indicate intramuscular water and glycogen content (44). Lower ultrasound EI values are associated with higher intramuscular water and glycogen content, resulting in hypoechoic ultrasonic images (45,46). Previous research investigating the sensitivity of EI suggested that increased intramuscular water and glycogen concentrations are strongly related to decreasing ultrasound EI values (44,47). In the present study, there is a possibility that the increased muscle CSA and EI was influenced by muscular edema and damage. The increased EI values indicated decreased intramuscular water and glycogen levels following each exercise session to volitional fatigue. These findings suggest autoregulated pressure in AR-BFR can cause a lower fluid flux to the intracellular space and possibly less muscle damage and swelling, as indicated by lower CSA and EI, compared to NAR-BFR. However, there was a lack of sufficient data for further analyses to test this hypothesis. Future studies are needed to compare the effects

of AR-BFR and NAR-BFR on muscle size and quality using ultrasound measures, as well as intramuscular water and glycogen concentrations in long-term (> 6 weeks) trials.

4.3 Performance, perceptual responses, and safety

In this study, AR-BFR and NAR-BFR did not display differences in any of the performance or perceptual measurements assessed. Both displayed similar total repetitions, volume, time under tension, RPE, and RPD. In comparison, No-BFR performed significantly more repetitions and total volume than both BFR conditions with less RPD. These results align with the overall body of literature on No-BFR versus BFR exercise on reducing exercise performance (48), as we observed a volume reduction of approximately 34% in both BFR conditions. However, this partially conflicts with a recent meta-analysis on perceptual demands (49) that indicated RPE/RPD was similar between No-BFR as long as exercise was taken to volitional fatigue. Our study reported high RPD in both BFR conditions compared to No-BFR with equal RPE. Lastly, our results conflict with a recent study investigating autoregulation of applied pressures using another commercially available BFR training device (24), indicating that acute responses to a BFR training program with autoregulation are likely device-specific (22).

In the only other study directly comparing the impact of AR-BFR on exercise performance with cuffs of similar size, Jacobs et al. (24) had 56 participants perform a series of fixed and failure leg extension BFR exercise protocols in a randomized order using 20% 1-RM. Using the Smartcuffs™ device (cuff width 10.16 cm) capable of performing both AR-BFR and NAR-BFR, it was observed that during failure protocols, AR-BFR condition performed significantly more volume than NAR-BFR with similar RPE and less RPD (albeit not likely clinically relevant). Interestingly, no clinically relevant differences were observed in heart rate

and brachial BP responses between conditions, leaving unanswered questions regarding what could be responsible for the observed differences. In contrast, our study with the Delfi Personalized Tourniquet device did not show performance or perceptual differences between the AR-BFR and NAR-BFR conditions. This observation may be attributable to differences in device autoregulation responsiveness. The Delfi has a greater ability to dynamically adapt to the changing limb circumference as compared to the Smarttools™ cuff, leading to a negligible loss of performance or perceptual differences between conditions.

In addition, it is important to note that no adverse events were reported in our study despite all exercise sessions (including the familiarization session) being conducted to failure, whereas Jacobs et al. (24) reported an adverse event in 7.14% of trials (n = 16 total) with a risk difference of 7% between NAR-BFR and AR-BFR in favor of AR-BFR. It is challenging to understand why the occurrence of adverse events was higher given our study protocol had BFR exercise performed to failure in all trials, whereas Jacobs et al. (24) had participants perform a fixed repetition scheme more indicative of recommended practice (48) before performing a failure routine. More research is needed to understand the participant-, device- and protocol-specific ways to minimize the occurrence of adverse events during BFR exercise.

4.4 Limitations

This is the first study investigating the arterial stiffness and muscle morphological responses to an acute exercise session to volitional fatigue with and without the presence of autoregulation of applied BFR pressures, but it is not without limitations. First, we sought to include both males and females to have a better representative sampling of healthy, physically active young adults. However, our study was likely not adequately powered to assess between-sex differences.

Recognizing the potential for different responses between sexes, we performed a between-sex analysis. We noted divergent responses in CR-PWV in the NAR-BFR condition in females, as well as a reduced overall volume of exercise performed in all conditions, compared to males. However, nothing else reached significance (Supp Table 1). Therefore, we cannot say with certainty that the responses between sexes are identical, warranting more research that uses a sample size adequately powered to detect between-sex differences. Secondly, due to not having a leg press, we utilized a wall squat. As this type of exercise is not confined to a predetermined range of motion, there is likely a greater skill component than a traditional leg press and different muscle activation patterns. In addition, participants performed the wall squat leaning into a minimal friction wall, which may have altered the load moved by the lower body. To control for this we included a familiarization session identical to the one performed in data collection. This likely allowed for some motor learning to occur and potentially reduced the impact of the novel wall squat exercise. Thirdly, indirect markers such as creatine kinase and myoglobin were not assessed, limiting our ability to assert that the additional swelling in NAR-BFR post-exercise was indicative of a greater muscle damage response. Future research should pair blood sampling with ultrasonic assessments to determine whether the presence of autoregulation blunts some of the exercise-induced muscle damage responses to BFR exercise. Lastly, as participants were healthy, one cannot extrapolate the findings to clinical populations without a degree of caution.

4.5 Clinical Implications

With more devices available for consumer purchase, it is prudent for research to investigate whether certain features, such as autoregulation, impact the acute response to BFR exercise. Our study provides three main takeaways. The primary takeaway is that autoregulation of applied pressures has the potential to limit the exercise-induced increases in CF-PWV in healthy,

physically active men and women. This may have relevance for increasing the safety of BFR exercise as non-autoregulated pressures, as well as low-load exercise to failure, increased CF-PWV to a similar degree. Secondly, our results on performance and perceptual responses diverge from a recent study on autoregulation using a different device (24), supporting that autoregulation is a device-specific feature that may have varying impact on the acute- and potentially long-term responses to BFR exercise. As such, autoregulation is an important feature that warrants consideration in practice and future research, particularly with respect to at-risk populations where attenuating the central stiffness responses may be desired. Lastly, non-autoregulated pressures increased the muscle swelling response to exercise, potentially indicating the presence of greater muscle damage. The use of autoregulation may, therefore, also serve a protective role in mitigating adverse responses to BFR exercise.

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Contributions

TW is responsible for the overall content as guarantor. NR conceived of the study. TW and MM performed data collection and statistical analyses. NR, TW, and MM wrote the first draft of the manuscript. NR, NL, MM, LM, JM, BF and TW critically appraised and revised the manuscript and approved its final form.

Competing Interests

NR is the founder of the BFR PROS and teaches BFR training workshops to fitness and rehabilitation professionals using a variety of BFR training devices.

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Figure Captions

Figure 1. Schematic of study protocol. AR-BFR, Autoregulated BFR pressures; NAR-BFR, Non-autoregulated BFR pressures; No-BFR, Low-load exercise without BFR.

Figure 2. Schematic of all treatment sessions. CSA, cross sectional area; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPE, rating of perceived exertion; RDP, rating of perceived discomfort; Perform again, 10-point Likert scale assessing desire to perform exercise again; HR, heart rate; RPP, rate pressure product.

Supplementary Table 1

	Male (n=13)			Female (n=7)		
Variable	AR-BFR	NAR-BFR	No-BFR	AR-BFR	NAR-BFR	No-BFR
CF-PWV, m/s (mean difference)	-0.22±1.09	1.00±1.07	0.70±1.31	0.04±0.69	-0.22±0.73	0.50±1.73
CR-PWV, m/s (mean difference)	-1.23±2.85	0.56±2.40	-0.53±1.46	-0.59±2.30	-1.10±1.79‡	-0.60±2.61
β-SI, *U* (mean difference)	-0.44±2.02	-0.61±2.09	0.33±3.26	-0.91±1.82	0.74±1.83	-1.69±2.62
AC, $mm^2/mmHg \times 10^{-1}$ (mean difference)	-0.01±0.06	-0.00±0.05	-0.01±0.05	0.01±0.05	-0.04±0.05	0.04±0.06
CSA, cm^2 (mean difference)	2.59±1.19	2.74±0.83	2.33±1.22	1.91±0.91	2.15±0.62	1.92±1.01
EI, au (mean difference)	1.70±2.50	4.75±8.79	2.75±4.41	3.57±4.77	5.02±5.95	4.07±5.95
Total reps	51±15	50±14	80±22	56±28	54±23	87±36
Volume, load x reps	2797±1273	2696±927	4325±1732	1766±1000‡	1682±891‡	2729±1413‡
Volume relative to weight, volume x body weight $(kg)^{-1}$	69.18±29.54	67.77±27.47	107.92±43.56	53.37±28.71	48.64±23.72	75.67±15.19
Volume relative to FFM, volume x FFM $(kg)^{-1}$	79.68±33.93	77.16±28.21	123.10±45.11	69.67±39.52	62.88±30.73	98.63±66.84
RPE	8.07±0.76	8.23±1.01	8.3±0.94	8.29±0.95	8.86±0.90	8.00±1.52
RPD	6.23±2.59	6.31±2.50	5.15±2.88	6.14±1.77	7.14±1.68	4.71±1.38

Perform again	7.08±2.47	7.62±2.63	7.54±2.44	6.43±2.37	5.71±2.21	7.43±2.82

Table S1. Male and female vascular, muscular and performance pooled analysis. C, carotid; R, radial; F, femoral; PWV, pulse wave velocity; β-SI, β stiffness index; AC, arterial compliance; CSA, cross sectional area; EI, echo intensity; reps, repetition; RPE, rating of perceived exertion, RDP, rating of perceived discomfort; Perform again, 10-point Likert scale assessing desire to perform exercise again. ‡ $P<0.05$ Interaction with males