LOW-LOAD RESISTANCE EXERCISE COMPLETED TO VOLITIONAL FAILURE DECREASES PAIN PERCEPTION POST-EXERCISE IN FEMALES AND MALES

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Abstract:

Exercise-induced hypoalgesia (EIH) is the acute pain reduction post-exercise. Typically, high-intensity and/or long-duration exercise is required to elicit EIH. Alternatively, low-load resistance exercise with blood flow restriction (LL+BFR) may elicit EIH. However, there is conflicting evidence regarding the necessary repetitions and volume load. This study evaluated EIH after 75 repetitions (1×30, 3×15) (BFR-75) and four sets to volitional failure (BFR-F) protocols. Twenty-six participants completed unilateral knee extensions at 30% of maximal strength using a BFR-75 and BFR-F protocol. Pain pressure threshold (PPT) of the rectus femoris was assessed before and after exercise. Repetitions completed, volume load, occlusion time, and PPT were analyzed. Participants completed more repetitions (91.4±30.5), volume load (5,204.9±2,367.0 Nm), and had a longer occlusion time (345.8±76.2 seconds) during BFR-F compared to BFR-75 (73.2±3.7 repetitions, 4,451.1±1,498.1 Nm, 300.5±52.2 seconds, respectively). Collapsed across sex, PPT increased from pre- (3.24±1.91 kgf) to post-exercise (3.76±2.27 kgf) for BFR-F but not for BFR-75 (3.51±1.67 to 3.68±2.04 kgf). The results indicated that BFR-F, but not BFR-75, elicited EIH, as assessed by an increase in PPT. Lower loads used during LL+BFR may be a clinically relevant alternative to high-intensity and/or long-duration exercise in populations that may not tolerate high-intensity or prolonged exercise to induce EIH.

Key words: *exercise-induced hypoalgesia, pain pressure threshold, blood flow restriction, muscle pain, resistance exercise, pain measurement*

Introduction

Pain and pain-related musculoskeletal conditions are among the leading causes of non-communicable disease-related disability burden globally (Hay, et al., 2017). In the United States of America, an estimated 126.1 million adults have experienced pain in the previous three months, and of those, 25.3 million adults report experiencing pain daily (Nahin, 2015). Furthermore, pain is frequently cited as a reason why individuals avoid exercise or movement, which can lead to comorbidities and decreased quality of life (Luque-Suarez, Martinez-Calderon, & Falla, 2019). There is a wide range of available treatments for pain, including pharmaceuticals and clinic-based pain management modalities, however, exercise has also been shown to acutely and chronically reduce pain (exercise-induced hypoalgesia [EIH]) (Koltyn, 2002). Exercise has the unique benefit of inducing positive health adaptation, including improving quality of life (Hart & Buck, 2019; Shailendra, Baldock, Li, Bennie, & Boyle, 2022), with a low risk of adverse side effects (McCartney, 1999). The combination of improved quality of life and potential attenuation of pain suggests that exercise may be a clinically useful intervention for clinicians and practitioners.

The underlying mechanisms of EIH have not been fully elucidated, but EIH has been observed following a variety of exercise interventions (Micalos & Arendt-Nielsen, 2016; Samuelly-Leichtag, Kodesh, Meckel, & Weissman-Fogel, 2018; Vaegter, Handberg, & Graven-Nielsen, 2014), including resistance training (Baiamonte, et al., 2016). It has been suggested that the magnitude of EIH is related to the intensity and duration of the exercise session (Rice, et al., 2019; Vaegter & Jones, 2020), although high intensity (>67% of 1 repetition maximum [1RM]; Haff, et al., 2016) and/or long durations may not be well tolerated by all populations, specifically in populations with physical limitations, including post-surgical, clinical, or elderly populations. For example, in healthy men and women, pain pressure threshold (PPT) of the quadriceps increased (16.8% ± 16.9%) following a 3-minute wall squat (Vaegter, et al., 2019). Alternatively, EIH has been observed following low-intensity resistance exercise (30-40% 1RM) combined with blood flow restriction (BFR) (Hughes & Patterson, 2020). Thus, low-load resistance training with BFR (LL+BFR) may be a viable alternative to high-intensity or long-duration exercise to achieve EIH.

Although EIH has been observed following LL+BFR exercise, there is limited available evidence that has utilized objective measures (i.e., PPT) to assess the occurrence and scale of EIH following LL+BFR. Furthermore, previous investigations (Hughes & Patterson, 2020; Song, Kataoka, et al., 2022a; Song, Yamada, et al., 2022b) have observed EIH following different exercise designs. Specifically, EIH has been observed following 75 repetitions (1×30, 3×15 [BFR-75]) (Hughes & Patterson, 2020) and after four sets of exercise with each set to volitional failure (BFR-F) (Song, Kataoka, et al., 2022a). These two protocols are the most commonly used during BFR exercise, although it has been suggested that completing sets to failure may not be recommended for all populations (Patterson, et al., 2019); however, no previous investigation has directly compared the magnitude of EIH following BFR-75 and BFR-F. Therefore, the purpose of this investigation was to directly compare the prevalence and magnitude of EIH following BFR-75 and BFR-F. Based on previous investigations (Hughes & Patterson, 2020; Song, Kataoka, et al., 2022a), we hypothesized that EIH would be similar in the two conditions.

Methods

Twenty-six participants (female, *n* = 13; male, *n* = 13) volunteered to participate in this investigation (Table 1). An *a priori* power analysis was conducted based on previous investigations (Focht & Koltyn, 2009; Hughes, Grant, & Patterson, 2021; Hughes & Patterson, 2020; Korakakis, Whiteley, & Giakas, 2018) that examined EIH following LL+BFR and reported effect size. The analyses were completed using G*Power (Faul, Erdfelder, Buchner, & Lang, 2009) with power set to 0.8 and an alpha of 0.05. The results indicated that a sample size of 8 to 16 was sufficient; therefore, 13 females and 13 males were recruited to have two full samples to allow for sex-based comparisons. All participants within the dataset were classified as tier one (recreationally active) and 150-300 minutes of moderate-intensity activity or 75-150 min of vigorous-intensity activity a week (McKay, et al., 2022). The participants provided written informed consent before participating in the study and completed a medical history questionnaire. Participants were excluded from the study if they had a history of blood clots, were currently pregnant, or had been diagnosed with a muscular, metabolic, pulmonary, or cardiovascular disease. Menstrual cycle and pharmaceutical contraceptives were not controlled for in the present study due to the nature of the study (single time point) and inconsistent evidence regarding the relationship between pain perception, acute exercise performance, and menses (Colenso-Semple, D'Souza, Elliott-Sale, & Phillips, 2023; Iacovides, Avidon, & Baker, 2015; Romero-Parra, et al., 2021). This investigation was approved by the University Institutional Review Board for Human Subjects and conducted in accordance with the ethical standards of the Declaration of Helsinki (2013).

Table 1. Demographic information

	n	Age	Height (cm)	Weight (kg)
Females	13	22 ± 3	160.3 ± 8.8	68.8 ± 14.5
Males	13	23 ± 4	178.2 ± 7.6	77.9 ± 10.6
Combined	26	23 ± 4	170.4 ± 10.1	74.5 ± 13.0

Protocol

This investigation used a randomized, counterbalanced, within-subject crossover design. Each participant completed BFR-75 (1 × 30, 3 × 15) and BFR-F (four sets to volitional failure) in a randomized order during the same visit, separated between legs, and by approximately 20 minutes of rest. There is limited and conflicting evidence regarding the duration of EIH (Hughes & Patterson, 2020; O'Leary, Falla, Hodges, Jull, & Vicenzino, 2007), but this response typically dissipates 15 minutes post-exercise (Koltyn & Arbogast, 1998; Naugle, Fillingim, & Riley, 2012). To ensure that no systemic effects or order effects occurred, analyses were first completed by exercise protocol order, then by exercise protocol. Participants completed both protocols (BFR-75 and BFR-F) which consisted of unilateral, isokinetic, concentric-eccentric knee extension muscle actions at $120°s^{-1}$ on an isokinetic dynamometer (Biodex Medical Systems, Inc., Shirly, New York, US). The order in which the protocols were completed (BFR-75 vs. BFR-F) was randomized, as was the leg (right vs. left). After a 20-minute rest period, the opposite leg completed the other exercise protocol (BFR-75 or BFR-F) following the same procedures. All repetitions were performed through a 90° range of motion (90° to 180° of knee extension) at 30% of maximal voluntary isometric contraction (MVIC) peak torque and 30 seconds of rest were allotted between sets. To determine MVIC, participants completed three

MVIC (3-s contraction at a 90° angle with the leg perpendicular to the ground) knee extension muscle actions separated by one minute. The highest MVIC peak torque value was used to determine exercise load. MVIC, rather than concentric peak torque, was used to determine exercise load based on previous research that has shown concentric peak values may be reduced at higher contraction speeds (Yoon, Park, Kang, Chun, & Shin,1991).

Blood flow restriction

To determine total arterial occlusion pressure, an 11-centimeter-wide cuff (SC10D, Hokanson Inc., Belleview, WA, USA) connected to a Hokanson rapid cuff inflator device (Hokanson Inc., Belleview, Washington, US) was applied to the most proximal aspect of the upper leg while the participants laid supine on a padded table. The cuff was slowly inflated and deflated while blood flow through the posterior tibial artery was visually monitored using Doppler ultrasound (GE Logiqe, General Electric Medical Systems, Milwaukee, WI, USA) and a linear array probe (L4-12t, 4.2–13.0 MHz, 38.4-mm field of view, GE Healthcare, Milwaukee, WI, USA). Water-soluble transmission gel was applied to the posterior aspect of the medial malleolus to enhance acoustic coupling and the posterior tibial artery was located. Blood flow through the posterior tibial artery was monitored using the color flow mode. Total arterial occlusion pressure was defined as the lowest pressure required to completely occlude the posterior tibial artery. The procedure to determine total arterial occlusion pressure was then repeated on the opposite leg. During exercise, BFR was applied at 60% of the total arterial occlusion pressure for each limb, which is at the center of the recommended occlusion pressure range of 40%-80% of the total arterial occlusion pressure for blood flow restricted exercise and is within the range of previous investigations (Hughes & Patterson, 2020; Patterson, et al., 2019; Song, Yamada, et al., 2022b).

Pain pressure threshold

To assess PPT, a pressure algometer (Wagner FPX, Greenwich, CT, USA) with a 1 cm^2 flat rubber tip was applied perpendicular to the rectus femoris muscle at 50% of the distance between the anterior superior iliac spine and the superior aspect of the patella. Force was applied at approximately 1 kgf/s, and participants were asked to identify when the force applied was "slightly uncomfortable". PPT was assessed by the same research team member for each participant. The corresponding force (kg) at which this occurred was recorded and the procedure was completed three times with approximately 30 seconds between each trial. The means of the three trials were used for statistical analysis.

Rating of perceived exertion

The OMNI resistance exercise scale (0-10) was used to assess rating of perceived exertion (RPE) (Lagally & Robertson, 2006). Before exercise, participants were familiarized with the OMNI Resistance Exercise Scale and given standard instructions (Robertson, et al., 2003). After each set of exercise, participants were presented with an image of the scale, including anchoring points, and instructed to rate their effort, strain, or exertion for the exercise (not the discomfort of the blood flow restriction cuff or isokinetic dynamometer).

Statistical analysis

The Shapiro-Wilk test was used to check the normality of the data. Total repetitions completed, exercise volume load (repetitions × load [peak torque of each repetition]), and total occlusion time between the conditions were analyzed using a one-way paired sample *t*-test to quantify potential differences between the two protocols that may affect EIH responses. To check for an exercise order effect, a 2 (Order [first bout, second bout]) × 2 (Time [pre-exercise, post-exercise]) repeated measures ANOVA was performed. Following the non-significant effect for exercise order, a second 2 (Sex [female, male]) × 2 (Condition [BFR-75, BFR-F]) × 2 (Time [pre-exercise, post-exercise]) mixed factor repeated measures ANOVA was performed to assess the effect of condition. RPE was assessed using a 2 (Condition [BFR-75, BFR-F]) × 4 (Time [set 1-4]) repeated measures ANOVA. Significant interactions were decomposed using follow-up pairwise comparisons. Greenhouse-Geisser corrections were applied when sphericity was not met according to Mauchly's test of sphericity. Cohen's *d* was calculated for each *t*-test and partial eta-squared effect sizes (η_p^2) were calculated for each ANOVA. To interpret Cohen's *d* small (d = 0.2), medium (d = 0.5), and large (d = 0.8) were used, and small (0.01), medium (0.06), or large (0.14) for partial eta-squared (Cohen, 1988). An alpha of $p \leq .05$ was considered statistically significant for all comparisons. All statistical analyses were performed using IBM SPSS v. 28 (IBM, Armonk, NY, USA).

Results

Total repetitions

Participants completed significantly (p=.002, Cohen's d = -0.621) more repetitions during BFR-F (91.4 ± 30.5) compared to BFR-75 (73.2 ± 3.7) (Figure 1A).

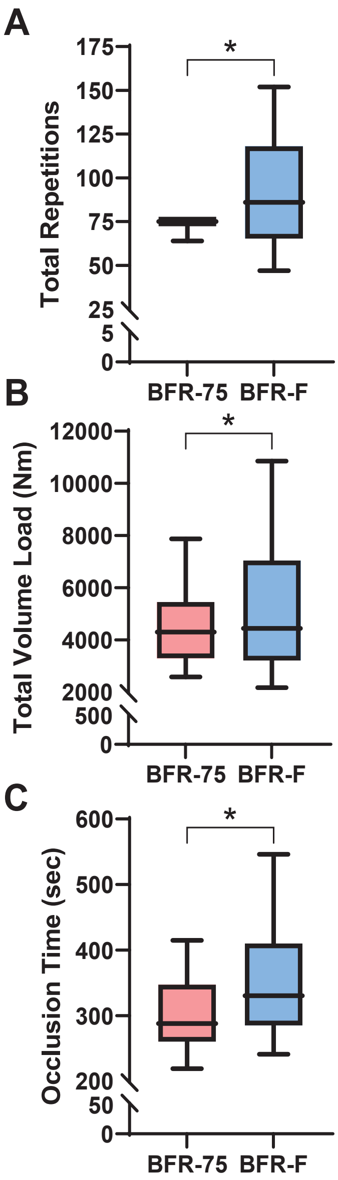

*Figure 1. Box and whisker plots for A. Total repetitions completed, B. Total volume load (Nm), and C. Occlusion time (seconds) for the 75 repetitions (1×30, 3×15 [BFR-75]) and 4-sets to volitional failure (BFR-F) of isokinetic, concentric-eccentric knee extension muscle actions. * Denotes a significant (p<.05) difference between BFR-75 and BFR-F.*

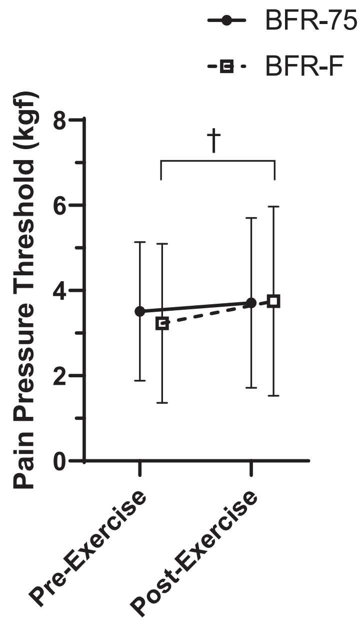

Figure 2. Mean and standard deviation responses for pain pressure threshold (PPT) before and after 75 repetitions (1×30, 3×15 [BFR-75]) and 4-sets to volitional failure (BFR-F) protocols. † Denotes a significant (p<.05) difference between pre- and post-exercise PPT for BFR-F only.

Exercise volume load

There was a significant ($p=.045$, Cohen's d = -0.354) difference in exercise volume load between BFR-F (5,204.9 ± 2,367.0 Nm) and BFR-75 (4,451.1 ± 1,498.1 Nm) (Figure 1B).

Total occlusion time

Occlusion time was significantly ($p=.003$, Cohen's d = -0.618) greater during BFR-F (345.8 ± 76.2 seconds) compared to BFR-75 (300.5 ± 52.2 seconds) (Figure 1C).

Exercise order PPT

There was no significant ($p=.776$, $\eta_p^2 = 0.004$) Order × Time interaction.

Condition PPT

There was no significant ($p=.081$, $\eta_p^2 = 0.132$) three-way Sex × Condition × Time interaction or two-way Sex × Condition ($p=.364$, $\eta_p^2 = 0.038$) or Sex × Time ($p=.505$, $\eta_p^2 = 0.020$) interaction. There was, however, a significant two-way Condition × Time interaction ($p=.027$, $\eta_p^2 = 0.204$). Follow-up pairwise comparison, collapsed across Sex, indicated no significant ($p=.144$) difference between pre- and post-exercise ($p=.827$) between BFR-F and BFR-75. However, for BFR-F, the post-exercise PPT (3.76 ± 2.27 kgf) was greater ($p=.013$, $CI_{95\%} = 0.127 - 0.955$) than the pre-exercise PPT (3.24 ± 1.91 kgf). There was no significant (p.336, $CI_{95\%}$ = -0.529–0.189) difference for BFR-75 between post-exercise (3.68 ± 2.04 kgf) or pre-exercise (3.51 ± 1.67 kgf) (Figure 2).

Discussion and conclusions

The purpose of this investigation was to directly compare the prevalence and magnitude of EIH following the two most commonly used LL+BFR protocols, BFR-75 and BFR-F. We hypothesized that both protocols would elicit EIH due to increased neuromuscular, cardiovascular, and metabolic stress; however, the results of the present study indicated that BFR-F, but not BFR-75, elicited a significant increase in PPT (0.80±1.31Δ kgf) post-exercise. Participants completed significantly more repetitions and volume load during BFR-F (91.6 ± 31.1 repetitions; 5,204.9 ± 2,367.0 Nm, respectively) compared to BFR-75 (73.2 ± 3.7 repetitions; 4,451.1 ± 1,498.1 Nm, respectively) (Figure 1A, 1B).

Furthermore, occlusion time was longer during BFR-F (345.8 ± 76.2 seconds) than during BFR-75 (300.5 ± 52.2 seconds) (Figure 1C). These findings suggested that BFR-F induced EIH following a single bout of low-load resistance (30% 1RM) with BFR (AOP 60%), while BFR-75 did not (Figure 2).

The results of the present study were in agreement with previous investigations (Song, et al., 2021; Song, Yamada, et al., 2022b) that examined EIH following acute LL+BFR exercise. For example, in healthy men and women, PPT increased by approximately 0.6 kg/cm^2 5-minutes post-exercise following four sets of unilateral concentric-eccentric knee extension muscle actions performed to failure at 30% 1RM (80% AOP) (Song, Yamada, et al., 2022b). Furthermore, in healthy men and women, PPT increased by 0.28 kg/cm^2 following four sets of 2-minute isometric handgrip contractions at 30% of maximum strength with BFR (50% AOP) (Song, et al., 2021). There were, however, AOP-specific PPT responses that increased to a greater extent at 80% AOP (+3.72 ± 2.24 kgf) than 40% AOP (+2.43 ± 1.60 kgf) among recreationally active men and women following 75 repetitions (1×30, 3×15) of unilateral leg press muscle actions at 30% of 1RM (with 40% and 80% AOP) (Hughes & Patterson, 2020). Interestingly, unlike EIH responses that typically dissipate 5-30 minutes post-exercise following non-occluded resistance exercise (Naugle, et al., 2012), PPT remained elevated 24-hours post-exercise indicating the presence of EIH following BFR exercise (Hughes & Patterson, 2020). Collectively, the results of the present study, in conjunction with previous investigations (Hughes & Patterson, 2020; Song, et al., 2021; Song, Yamada, et al., 2022b) suggested that LL+BFR can induce EIH following exercise.

There is limited available evidence that has evaluated the underlying physiological responses that may mediate the EIH response following LL+BFR, although several mechanisms have been proposed. Specifically, EIH may be related to increased blood pressure and/or baroreceptor stimulation, recruitment of higher-order motor units, noxious stimulation, metabolite accumulation, and/or hypoxia (Hughes & Patterson, 2019; Koltyn, Brellenthin, Cook, Sehgal, & Hillard, 2014; Vaegter & Jones, 2020). These theoretical mechanisms may be influenced by muscle groups activated (Hughes & Patterson, 2020), AOP utilized (Hughes & Patterson, 2020), exercising to fatigue vs. non-fatigue (Song, et al., 2021), and exercise duration and/or occlusion time (Song, Yamada, et al., 2022b). For example, in the present study, PPT was unaffected following BFR-75, which was shorter in duration and utilized a non-fatigue design, resulting in fewer repetitions and a lower volume load. The increased repetitions, volume load, and occlusion time during the BFR-F condition may have resulted in greater motor unit recruitment and subsequent stimulation of the motor cortex. It has been hypothesized that increased activity in the motor cortex may alter the processing or perception of pain in connected regions of the brain, such as the thalamus, resulting in hypoalgesia (Farina, Tinazzi, Le Pera, & Valeriani, 2003; Hughes & Patterson, 2019). Additionally, unlike the present study, Hughes and Patterson (2020) reported an increase in PPT following BFR-75, which may reflect larger muscle mass involved during a leg press exercise (multi-joint exercise) compared to a knee extension exercise (single-joint exercise), which could have resulted in greater motor unit recruitment and motor cortex activity. For example, LL+BFR exercise has been associated with an increase in metabolite accumulation (Lauver, Cayot, Rotarius, & Scheuermann, 2017; Lauver, Cayot, Rotarius, & Scheuermann, 2020) and increased/early recruitment of type II muscle fibers compared to non-occluded conditions (Fatela, Mendonca, Veloso, Avela, & Mil-Homens, 2019). Thus, our findings, in conjunction with previous investigations (Hughes & Patterson, 2020; Song, et al., 2021; Song, Yamada, et al., 2022b), suggest that one or more of the theoretical mechanisms mediate BFR-induced EIH.

During non-occluded exercise, EIH is typically related to the intensity and duration of exercise (Vaegter & Jones, 2020), with high-intensity and long-duration exercise necessary to induce EIH. For example, in healthy men and women, the time duration between the onset and cessation of a pain-inducing stimulus (Forgione and Barber strain gauge simulator; Forgione & Barber, 1971) increased by 15 seconds when measured 5-minutes after a 45-minute whole-body resistance training session (bench press, leg press, pull downs, and arm extensions) using heavy loads/ higher intensity (70% of 1RM) compared to six minutes of exercise with 30% of MVIC in the present study. However, the effect was temporary and no longer present 15 minutes after exercise (Koltyn & Arbogast, 1998). Alternatively, LL+BFR may elicit similar acute EIH responses compared to a high-intensity exercise approach and may be present up to 24 hours after exercise, which has not been observed following non-occluded exercise (Hughes & Patterson, 2020). Furthermore, LL+BFR has also been shown to elicit positive muscular adaption, including increased strength and muscle hypertrophy (Cook, Murphy, & Labarbera, 2013; Jessee, et al., 2018; Loenneke, Wilson, Marín, Zourdos, & Bemben, 2012). Together, the acute hypoalgesic effect of LL+BFR, as well as its effectiveness as a training modality, supports the potential application of LL+BFR in various populations (e.g., healthy, elderly, post-surgical, or other clinical populations).

The present study was completed with healthy men and women which may limit the generalizability of the findings to other populations. Future investigations should seek to expand the understanding of EIH following LL+BFR by including acute or sub-acute pain populations that may benefit from EIH following exercise, including post-surgical, clinical, or elderly populations. Furthermore, the assessments used to quantify pain in the present investigation reflect the minimal mechanical somatosensory threshold related to pain in the region assessed which may not reflect other forms of somatosensory perception or other regions of the body.

The results of the present study indicated that BFR-F elicited a significant acute increase in PPT, suggesting that BFR-F can be used to induce EIH. In contrast, BFR-75 was not associated with changes in PPT, and BFR-75 performed fewer repetitions, had lower exercise volume load, and shorter occlusion time than BFR-F. Thus, during LL+BFR, the EIH response may be mediated, in part, by repetitions, volume load, and/or occlusion time. Regardless, the lower loads and longer EIH associated with LL+BFR may be clinically relevant for populations that may not tolerate high intensities (> 67% 1RM) or prolonged exercise to induce EIH.

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