

Acute and delayed muscle damage following blood flow restriction resistance training in healthy adults

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Abstract:

Introduction: Low-load resistance exercise with blood flow restriction (LLBFR) has potential influence local physiological responses. For this training method to be appropriately prescribed, not only should the volume and intensity must be considered, but also specific variables such as the applied cuff pressure and time under blood flow restriction. **Material and Methods:** This randomized cross-over trial was conducted within 6 visits, at the same time of day, separated at least 72 and no more than 96 h and examined the acute and delayed indirect muscle damage after LLBFR in healthy adults. Twelve recreationally active healthy males completed performed a 45-degree leg press exercise (30 + 15 + 15 + 15 repetitions at 20% 1RM) in two conditions: free-flow resistance training (FFRT) and blood flow restriction resistance training (BFRRT). Indirect markers of muscle damage, including creatine kinase (CK) and visual analog scale of muscle soreness (VAS-soreness) were assessed at baseline and 24 h post-exercise. Lactate (LAC) was measured to compare internal load at baseline and 5 min post-exercise. All participants were instructed not to perform any type of exercise during the entire experimental protocol period (approximately 1.5 weeks). **Results:** Were observed a higher statistically CK and VAS-soreness at 24 h post-exercise compared to baseline for BFRRT ($p < 0.05$). LAC was significantly increased in BFR-RT compared to FFRT ($p < 0.05$). **Conclusion:** Adding BFR to non-failure 20% 1 RM leg press at 50% arterial occlusion pressure does provide a slight alteration of indirect markers of muscle damage and lactate compared to performing the same exercise with free blood flow in healthy participants.

Key Words: strength exercise; hypoxia; creatine kinase; muscle soreness.

Introduction

Increasing strength and muscle hypertrophy are essential for sports performance (Lum & Barbosa, 2019; McGuigan et al., 2012) and health (García-Hermoso et al., 2018; Benatti & Pedersen, 2015). For this to occur, resistance training (RT) has been recommended to be performed with moderate (between 60 to 79%) or high loads ($\geq 80\%$) of one repetition maximum (1RM) (American College of Sports Medicine, 2009; Lopez et al., 2021).

However, it appears essential to manipulate training variables (e.g., volume and intensity) to avoid stagnation and overtraining (Plisk & Stone, 2003). An alternative to traditional approaches, involves performing low-load RT combined with blood flow restriction (LLBFR), a method that promotes strength and muscle hypertrophy using loads between 20 and 50% 1RM (Slysz et al., 2016).

For this LLBFR training method to be appropriately prescribed to increase strength and muscle mass, not only should the volume and intensity must be considered, but also specific variables such as the applied cuff pressure and time under blood flow restriction (BFR) (Patterson et al., 2019). Although the dose-response of exercise volume (Martín-Hernández et al., 2013), cuff pressure (Lixandrão et al., 2015; Kim et al., 2017), and exercise load (Slysz et al., 2016) have already been studied in leg extension and leg press RT exercise, metabolic responses under BFR remains to be extensively studied (Lixandrão et al., 2018).

One of the mechanisms responsible for increasing strength and muscle mass through this training method is linked to the reduction of oxygen supply to the muscle (Takarada et al., 2000). Consequently, this condition promotes heightened metabolic stress, which, in turn, stimulates the increased secretion of growth hormone (GH) (Gosselink et al., 1998), the synthesis of anabolic growth factors such as the mammalian target of rapamycin (mTOR) protein (Fujita et al., 2007), heat shock proteins (HSP) (Kawada et al., 2005), nitric oxide synthase-1 (Christiansen et al., 2019) (Larkin et al., 2012) (20,21), decreased myostatin expression (Laurentino et al., 2012), and recruitment of fast-twitch fibers (Moritani et al., 1992).

Another crucial phenomenon for increasing muscle mass is exercise-induced muscle damage (EIMD), a condition caused by the mechanical overload of exercise, leading to various structural changes such as the rupture of proteins in the cytoskeleton, sarcolemma, basal lamina, and connective tissue (Vierck et al., 2000).

This condition manifests symptoms such as an increase in plasma muscle proteins (CK, LDH, myoglobin), reduction in muscle strength and/or power, delayed onset muscle pain (DOMS), an increase in inflamed markers, and muscle swelling caused by edema (Tee et al., 2007). It has already been demonstrated that LLBFR stimulates fast-twitch muscle fibers early (Moritani et al., 1992). These muscle fibers have a greater capacity to produce muscle strength and, therefore, are more susceptible to EIMD (Schoenfeld, 2012). In this condition, muscle structures are ruptured (Vierck et al., 2000), and although it can induce an inflammatory condition and acutely reduce muscle performance, it plays an essential role in increasing muscle mass as it triggers an organic disorder capable of activating satellite cells crucial for repair and muscle growth (Schoenfeld, 2012; Vierck et al., 2000). Despite that, the literature presents conflicting results regarding the effects of LLBFR on muscle damage (Sieljacks et al., 2016; Neto et al., 2018; Takarada et al., 2000; Alvarez et al., 2020). For instance, some studies failed to identify changes in indirect markers of muscle damage, while other studies showed significant changes within 24-48 hours after exercise (Sieljacks et al., 2016; Alvarez et al., 2020).

According to (de Queiros et al. 2021), the magnitude of changes in indirect measures of muscle damage induced by TFRFS is influenced by the individual's training status, the group of muscles exercised, exercise load, repetition volume (muscle failure vs. non-failure), and contraction rhythm execution. Therefore, varying degrees of muscle damage occur when using different protocols and samples (Queiros et al. 2021).

A previous review study stated that low-intensity exercise in combination with BFR demonstrated minimal effect on muscle function, no prolonged muscle swelling, no prolonged muscle soreness, and no increases in blood markers suggestive of muscle damage (Loenneke et al., 2014). In contrast, a first-time bout of BFR exercise using five sets of unilateral knee extensions to volitional failure with 30% of 1 RM with a continuously applied cuff pressure of 100 mmHg throughout the exercise session induced similar muscle damage as high-intensity eccentric exercise (e.g., less muscle voluntary contraction, elevated serum activity of intramuscular enzymes and increased muscle soreness) (Sieljacks et al., 2016).

In contrast, a study using a similar protocol to the aforementioned but with three sets (compared to five) demonstrated that delayed onset muscle soreness (DOMS) was significantly greater for the nonoccluded leg (Wernbom et al., 2009). These studies highlight the potential for muscle damage markers to be elevated following BFR RT particularly when taken to volitional fatigue. However, it is not clear if LLBFR influences these responses or if it is the volume of exercise, or both. Therefore, the objective of this study was to investigate the acute and delayed responses of indirect marker of muscle damage responses after low-load resistance training with and without BFR in healthy adults. We hypothesize that BFR-RT would elicit greater indirect markers of muscle damage compared to FF-RT.

Material & methods

Experimental Approach

This randomized cross-over trial was conducted within 6 visits, at the same time of day, separated at least 72 and no more than 96 h. All participants were able to complete the exercise interventions and were instructed not to perform any type of exercise during the entire experimental protocol period (approximately 1.5 weeks). The first visit consisted of signing the informed consent form, completing questionnaires to assess the level of physical activity (IPAQ—short version), physical and health condition (PAR-Q), stratification risk for thromboembolism (Motykie et al., 2000), and use of medications and food supplements that could affect muscle performance. In addition, at the same visit, they were evaluated by an experienced cardiologist. The cardiologist performed a resting electrocardiogram and an ankle-brachial index (ABI) test to verify the presence of peripheral vascular disease (Aboyans et al., 2012). Furthermore, 45-degree leg press 1 RM was evaluated in the first session. Finally, participants were familiarized with the visual analogue scale of soreness (VAS-soreness) (Price et al., 1983). During the second visit, participants performed a 1 RM retest, and once again were familiarized with VAS-soreness. In addition, a BFR familiarization exercise session was performed with 30 repetitions at 20% 1RM using 50% arterial occlusion pressure in a 45-degree leg press.

In visits 3 and 5, the exercise protocol sessions were carried out in one of the two conditions (FF-RT and BFR-RT) described below. Interventions were conducted in a randomized cross-over design by picking a protocol inside of sealed randomization envelope. Visits 4 and 6 occurred 24 hours after visits 3 and 5, respectively where measures of indirect muscle damage were assessed.

The exercise was performed in the 45-degree leg press (PowerTech, Rigueto, Campinas, Brazil) and consisted of 4 sets (30—15—15—15 repetitions), with a load at 20% 1RM, 45-s rest interval between sets, and rhythm of 1-s for concentric and 1-s for eccentric (controlled by a metronome). Thus, the exercise duration was approximately 5 min. Participants were comfortably positioned on the equipment and instructed to maintain the alignment between ankles, knees, and hips. In addition, during the exercise, re-searchers used colored adhesive tapes to visually delimit the range of motion (90° of knee flexion in the eccentric phase and almost complete extension—approximately 20° of flexion—during the concentric phase). All participants performed the exercise under two conditions: In FF-RT, exercise was performed without BFR. In BFR-RT, cuffs were inflated at the beginning of the exercise and remained inflated until the end of the last series (including the rest intervals). The interval between protocols was a minimum of 72 and a maximum of 96 h and participants reported to the lab at similar times of day to minimize diurnal variations.

In BFR-RT, BFR was induced by a pair of inflatable cuffs with 20 cm width x 42 cm length (Missouri-Mikatos, São Paulo, Brazil) that were placed on the proximal part of the thighs (as close as possible to the inguinal crease) with 50% of the total arterial occlusion pressure (AOP). Indirect measures of muscle damage (creatinine kinase and VAS-soreness) were collected at baseline and after 24 h of recovery. To measure internal load, blood lactate (LAC) was collected at baseline, immediately after and 5 min after exercise.

Subjects

Twelve healthy and physically active male participants were recruited for the study. All participants were informed about the purpose, practical details, and possible risks associated with the experiment and, before the collections began, gave their consent by signing a consent form. The study was approved by the Ethics and Research Committee of the Catholic University of Brasília, CAAE 39652920.4.0000.0029 and was conducted according to the Declaration of Helsinki. Exclusion criteria were individuals with any of the following conditions: musculoskeletal injuries in the lower limbs, continuous use of medication and/or nutritional supplement, resting blood pressure $\geq 140 \times 90$ mmHg, heart disease, peripheral vascular disease, diabetes, BMI ≥ 30 , one or more risk factors for thromboembolism. Thus, none of the recruited participants were excluded from the study.

One Repetition Maximum Test (1RM)

The test started with five minutes of general warm-up performed on a treadmill (Imbrasport Millenium ATL, Imbramed, Porto Alegre, Brazil) at low intensity ($\leq 85\%$ heart rate reserve). Afterwards, they performed three static stretching exercises for the hamstrings, hips, and quadriceps (1 series of 10-s). After that, the participants were positioned in the 45-degree leg press (PowerTech, Rigueto, Campinas, Brazil), maintaining the alignment of the ankle, knee, and hip joints to perform the specific warm-up and the test itself, according to recommendations by Brown and Weir (2001). The 1 RM values for each participant were obtained after no more than five attempts (separated by 3 min of interval recovery).

The load adjustment was aided by the Brzycki equation (Oliveira et al., 2010). During the eccentric phase, participants were instructed to perform 90° of knee flexion and in the concentric phase, extend the knee (approximately 20°) to near full extension. To have greater precision in the result, after a period of 96 h, a load confirmation test (re-test) was performed, which was conducted in the same way as the first test, but the first attempt was started with the 1RM found. For the value of 1 RM, the weight of the leg press platform (i.e., 40 kg) was considered. During all attempts, at least two re-searchers were present to offer spotting and safety to minimize risk of accidents.

Indirect Measures of Muscle Damage

Creatine Kinase (CK)

Creatine kinase measurements were performed in a portable Reflotron Plus® biochemical analyzer (Roche diagnostics, Mannheim, Baden-Württemberg, Germany). For this, the participants rested for five minutes, and after performing asepsis of the finger with 70% alcohol, a 30 μ L blood sample was collected in a capillary tube. After that, blood was aspirated using a P200 pipette (Gilson, Villiers-le-Bel, France) and then applied to reactive zone of Reflotron® CK strip (Roche diagnostics, Mannheim, Baden-Württemberg, Germany).

Muscle Soreness—Visual Analog Scale (VAS soreness)

The muscle soreness was evaluated using the Visual Analog Scale, where values represent 0–2 (mild pain), 3–7 (moderate pain), and 8–10 (severe pain) (Price et al., 1983). Before answering, the participants were instructed to perform a half squat to notice any amount of muscle soreness caused by exercise in the lower limbs. Soon after, they responded based on the following instruction: “We want you to answer how much soreness you are feeling right now in your leg muscles. Remember that it’s an exercise-related soreness, feeling sore muscles. So, what value from zero to 10 do you assign? Zero being no soreness and ten the worst muscle soreness you have ever felt” (Brown et al., 2001).

Lactate

Was measured using a YSI 2700 biochemical analyzer (Yellow Springs, OH, USA). After asepsis of the earlobe with 70% alcohol, a 25 μ L blood sample was collected in a heparinized capillary tube. Then, the blood sample was placed inside an Eppendorf tube containing 50 μ L of 1% sodium fluoride as previously reported (Oliveira et al., 2010). The entire contents of the tube were mixed for 10 s on a vortex mixer (EVLAB EV03, Londrina, PR, Brazil). Soon after, 25 μ L of the mixture was aspirated by the biochemical analyzer. Once the collected blood was diluted in two parts of sodium fluoride, the given value was multiplied by 3 (Moriggi et al., 2015).

Arterial Occlusion Pressure (AOP)

With the participant seated on the 45-degree leg press, measurements were taken on each leg (feet on the platform). A pair of inflatable cuffs 20cm width x 42cm length (Missouri-Mikatos, São Paulo, Brazil) were placed on the proximal part of the thighs (as close as possible to the inguinal crease). A small amount of water-based conductive gel (Mercur, Santa Cruz do Sul, RS, Brazil) was placed in the portable vascular doppler probe (DV 610B, Medmega, Franca, SP, Brazil), and this was positioned perpendicularly with minimal pressure on the dorsalis pedis artery. The AOP was determined when the arterial pulse was interrupted according to previous studies (Lixandrão et al., 2015).

Statistical Analysis

Data are expressed as means and SD (standard deviation). The Shapiro–Wilk test was applied to check for normality. Thus, a paired t-test was run to determine statistic difference of pre – post and an unpaired t-test was used to compare statistical difference on intervention on CK, VAS-soreness and lactate, respectively. For Cohen’s d effect size, the following conventions were adopted: $d < 0.35$ (trivial), $d = 0.35–0.80$ (small), $d = 0.80–1.50$ (medium) and $d > 1.5$ (large) (Rhea MR et al.,2004). An alpha level of ≤ 0.05 was considered significant. In addition, Graphpad Prism 8.0 software (San Diego, CA, USA) and G*power 3.1 (Faul et al.,2007) were also used.

Results

Characteristics of participants are shown in Table 1.

Table 1. Characteristics of participants. Values described as mean $\pm$ standard deviation.

Age (years)	22.75 $\pm$ 3.36
Body mass (Kg)	70.66 $\pm$ 9.28
Height (cm)	175.96 $\pm$ 5.35
BMI (Kg/m ²)	22.80 $\pm$ 2.69
Body fat (%)	12.57 $\pm$ 7.33
1 RM (Kg)	310.42 $\pm$ 51.28
Cuffs pressure (mmHg)	71.79 $\pm$ 6.79

BMI: body mass index; 1 RM: 1 repetition maximum; mmHg: millimeters of mercury.

There was a statistically higher CK was observed at post-exercise 24 h compared to baseline for BFR-RT (figure1).

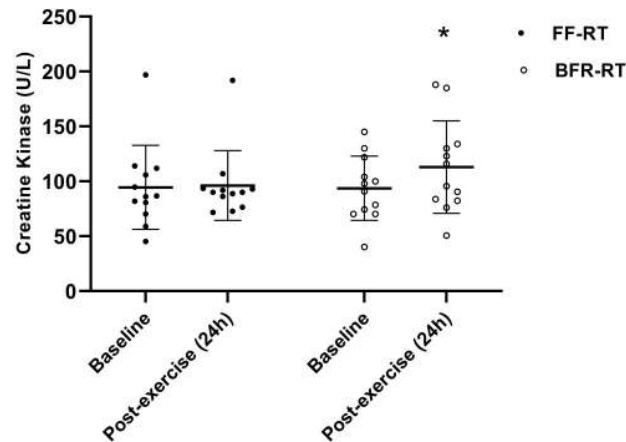


Figure 1. Creatine kinase results. U/L: units per liter; * Significant difference from baseline moment; Significance level $p \leq 0.05$.

A statistically higher VAS-soreness was observed at post-exercise 24 h compared to baseline for BFR-RT ($p < 0.05$) (figure 2).

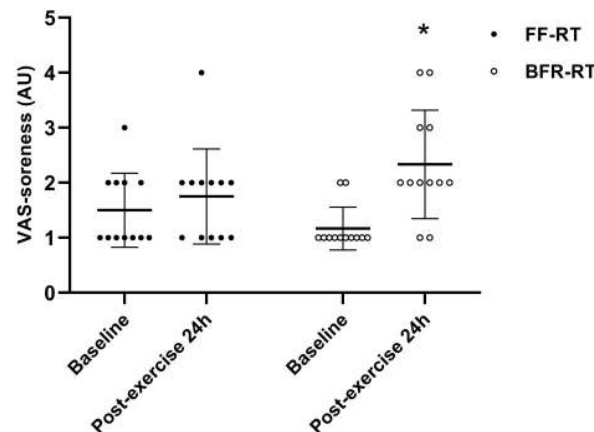


Figure 2. VAS-soreness results. AU: arbitrary units; * Significant difference from baseline moment. Significance level $p \leq 0.05$.

At the post-exercise, BFR-RT displayed a higher lactate level compared to FF-RT ($p \leq 0.05$). A statistically higher lactate levels were observed at post-exercise compared to baseline for all groups ($p \leq 0.05$).

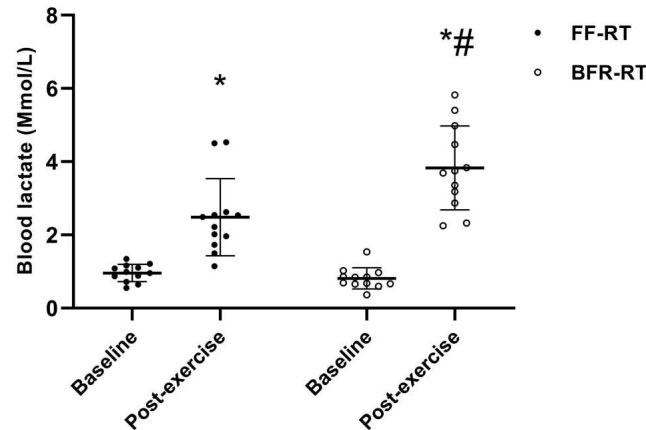


Figure 3. Blood lactate results. Mmol/L: millimoles per liter; *Significant difference from baseline moment; #Significant difference from FF-RT at the same time point. Significance level $p \leq 0.05$.

Considering values between groups, table 2 displayed effect size for CK, VAS-soreness and blood lactate.

Table 2. Values of effect size for main effect of time.

Parameters	FF-RT	BFR-RT
	<i>d</i>	<i>d</i>
CK	0.04 (Trivial)	0.66 (Small)
VAS-soreness	0.43 (Small)	2.75 (Large)
Blood lactate	7.50 (Large)	10.00 (Large)

d = effect size; FF-RT: free flow resistance training; BFR-RT: blood flow restriction resistance training; CK: creatine kinase; VAS: visual analog scale

Discussion

The aim of this study was to investigate the acute and delayed indirect muscle damage after LL-BFR. The main findings were that indirect markers of muscle damage (CK and VAS-soreness) displayed higher values on BFR-RT compared to FF-RT.

Measures of intramuscular protein and muscle pain have been used as indirect markers of exercise-induced muscle damage (EIMD) (Warren et al., 1999; Damas et al., 2016; Damas et al., 2018). EIMD is a condition caused by several factors such as mechanical overload from eccentric contractions or excessive calcium ion influx (Damas et al., 2018). However, the results of our study displayed no influence of time under BFR during the leg press on EIMD.

A previous study displayed that a first-time bout of BFR exercise using five sets of unilateral knee extensions to volitional failure with 30% of 1 RM induced similar muscle damage as high-intensity eccentric exercise (e.g., less muscle voluntary contraction, elevated serum activity of intramuscular enzymes and increased muscle soreness) (Sieljacks, et al., 2016). A contrast result using a protocol similar to the previous one but with three sets of unilateral knee extension with 30% of 1 RM, but not executed to volitional failure. It was demonstrated that delayed-onset muscle soreness (DOMS) was significantly greater for the nonoccluded leg.

The literature has been somewhat divergent about muscle damage caused by LL-BFR. Some studies have shown an increase in indirect markers of muscle damage (Sieljacks, et al., 2016; dos Santos et al., 2020; Umbel et al., 2009; Wernbom et al., 2012), while others have shown no difference (Karabulut et al., 2013; Shiromaru et al., 2019; de Queiros et al., 2021). A variable that appears relevant for increasing indirect markers of EIMD is exercise volume (de Queiros et al., 2021). Studies have shown increases in EIMD when exercise is performed until concentric failure (130 to 150 total repetitions) (Sieljacks, et al., 2016; Wernbom et al., 2012; Yasuda et al., 2015). On the other hand, non-failure studies (4 sets totaling up to 75 repetitions) have showed no difference in EIMD (Neto et al., 2018; Karabulut et al., 2013; Shiromaru et al., 2019). Thus, the absence of change in EIMD during both LL-BFR protocols in the present study can also be explained using a fixed number of repetitions, which did not induce the participants to concentric failure.

It may be considered that changes in the indirect markers of EIMD may have been observed if the time course of measurements was extended to beyond 24 h. However, a pronounced decline in muscle voluntary contraction and increased VAS soreness was seen 24 h post-exercise in a previous study using high-load training

and exercise to volitional failure with BFR (Sieljacks, et al., 2016). In that same study, CK levels for BFR and eccentric training increased similarly after 4 days (Sieljacks, et al., 2016), and the same increments are frequently observed when downhill running or high force eccentric exercise are used (Clarkson et al., 2002). These findings reinforce that higher-volume training and exercise performed to volitional failure (de Queiros et al., 2021) might be important variables in production of EIMD during BFR training, although it is noted that the repeated bout effect has also been observed following one session of LL-BFRT (Sieljacks, et al., 2016).

Blood lactate is an indirect marker of metabolic acidosis and represents the internal exercise load (Loenneke et al., 2010; Yasuda et al., 2010). Our results showed that post-exercise lactate was significantly higher in BFR-RT compared to FF-RT. This demonstrates that increments of lactate are because blood vessels are likely occluded, preventing the egress of metabolites as previously reported. In addition, it appears that the lactate levels are elevated with increasing levels of external compression (Yasuda et al., 2010).

Some limitations of the present study should be mentioned. Cross-over designs may face problems with carryover effects and possible systematic differences between EIMD responses during the later compared to the earlier sessions. The use of signal-intensity analysis from magnetic resonance imaging could have provided additional insights to what occurs in the entire muscle after different times under BFR. It is worth noting that the present results should not be extrapolated to different exercises (e.g., use of small muscle groups in combination with different exercise intensities), pressure cuff conditions (e.g., different combinations of occlusion pressure), and cuff widths. Moreover, the high CV reported for the leg press in this study should be considered; however, the within-subjects design employed ensured a similar load for each participant. Furthermore, while participants performed a work-matched protocol, performing sets until concentric failure could make the results more exaggerated since the fixed volume of repetitions might not be enough to cause muscle damage or induce significant physiologic stress.

Conclusions

In conclusion, adding BFR to non-failure 20% 1 RM leg press at 50% arterial occlusion pressure does provide a slight alterations of indirect markers of muscle damage and lactate compared to performing the same exercise with free blood flow in healthy participants. Based on the results of the present study, LLBFR under the conditions conducted may be an interesting alternative for conducting training in individuals with musculoskeletal injuries or even athletes in pre-competitive periods. It is suggested that studies be conducted to investigate muscle damage in special populations such as the elderly and those with rheumatic diseases.

Conflicts of interest - The authors declare no conflicts of interest.

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