Blood flow restriction attenuates eccentric exercise-induced muscle damage without perceptual and cardiovascular overload

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Summary

The aim of this study was to evaluate the acute effects of high-intensity eccentric exercise (HI-ECC) combined with blood flow restriction (BFR) on muscle damage markers, and perceptual and cardiovascular responses. Nine healthy men (26 ± 1 years, BMI 24 ± 1 kg m⁻²) underwent unilateral elbow extension in two conditions: without (HI-ECC) and with BFR (HI-ECC+BFR). The HI-ECC protocol corresponded to three sets of 10 repetitions with 130% of maximal strength (1RM). The ratings of perceived exertion (RPE) and pain (RPP) were measured after each set. Muscle damage was evaluated by range of motion (ROM), upper arm circumference (CIR) and muscle soreness using a visual analogue scale at different moments (pre-exercise, immediately after, 24 and 48 h postexercise). Systolic (SBP), diastolic (DBP), mean blood pressure (MBP) and heart rate (HR) were measured before exercise and after each set. RPP was higher in HI-ECC+BFR than in HI-ECC after each set. Range of motion decreased postexercise in both conditions; however, in HI-ECC+BFR group, it returned to pre-exercise condition earlier (post-24 h) than HI-ECC (post-48 h). CIR increased only in HI-ECC, while no difference was observed in HI-ECC+BFR condition. Regarding cardiovascular responses, MBP and SBP did not change at any moment. HR showed similar increases in both conditions during exercise while DBP decreased only in HI-ECC condition. Thus, BFR attenuated HI-ECC-induced muscle damage and there was no increase in cardiovascular responses.

Introduction

Resistance exercise combined with blood flow restriction (BFR) was initially performed in Japan, and has been studied in the last 40 years as KAATSU training, or simply KAATSU (Sato, 2005; Vieira et al., 2015). BFR training consists of a exercise with a restrictive pressure surrounding the proximal end of the exercising limb which can vary depending on the restrictive devices used (Figueroa & Vicil, 2011) and the width of the pneumatic cuffs (Rossow et al., 2012). It has been reported that resistance exercise combined with BFR results in faster increase in muscle hypertrophy and muscle strength (Laurentino et al., 2012; Heitkamp, 2015; Pearson & Hussain, 2015). Furthermore, beneficial cardiovascular responses as postexercise hypotension have also been observed when BFR is applied (Takano et al., 2005; Maior et al., 2015).

Eccentric muscle actions (i.e. lengthening of muscle while producing force) have certain advantages over concentric actions (i.e. shortening of muscle while producing force) such as the development of greater torque and strength (Sudo et al., 2015). On the other hand, high-intensity eccentric resistance exercise (HI-ECC) also induces greater mechanical disruption of muscle fibre and thus postexercise inflammatory process (ACSM, 2009; Sieljacks et al., 2015; Spranger et al., 2015). These effects result in skeletal muscle functional loss, such as decreased range of motion (ROM), increased limb circumference (CIR) and increased exercise-induced muscle soreness which can last until 4 days after exercise, and consequently, longer rest period is necessary for repeated training session (Hirose et al., 2004; Damas et al., 2016). In addition, HI-ECC is more effective in increasing muscle hypertrophy (ACSM, 2009).
Blood flow restriction (BFR) effects over pain and muscle damage has been studied mainly after low-intensity (LI, i.e. 20–50% of 1RM) resistance exercise. It has been shown that resistance exercise combined with BFR shows higher rating of perceived exertion (RPE) and pain (RPP) (Vieira et al., 2015; Neto et al., 2016). Also, the hypoxic condition and metabolite accumulation caused by BFR can increase muscle protein synthesis during exercise recovery (Fry et al., 2010; Laurentino et al., 2012) without inducing muscle damage (Thiebaud et al., 2013, 2014; Sieljacks et al., 2015).

However, none is known about the effectiveness of BFR during HI-ECC. Only one in animal model study has attempted to address this question (Sudo et al., 2015). Sudo et al. (2015) showed that BFR decreased muscle fibre damage induced by HI-ECC using histochemical analysis (maximal eccentric contractions of the tibialis anterior muscle). The authors observed increased protein synthesis simultaneously to muscle damage attenuation, showing also a hypertrophic factor following HI-ECC combined with BFR. Thus, hypertrophy may result from protein synthesis even when muscle damage is attenuated (Hirose et al., 2004; Damas et al., 2016).

The ECC is a strong stimulus to induce muscle damage, and no one has evaluated the effects of BFR to prevent or attenuate muscle damage induced by HI-ECC. Thus, the purpose of this study was to evaluate whether BFR could attenuate HI-ECC-induced muscle damage and to study perceptual and cardiovascular responses to BFR.

**Methods**

**Participants**

Nine healthy young men, who had been involved in regular resistance exercise for at least 1 year and at least 3 days per week, were enrolled in this study. All participants completed the Physical Activity Readiness Questionnaire (PAR-Q) and signed an informed consent according to the Declaration of Helsinki on human experimentation of 1975, as revised in 2013. The study was approved by the local ethics committee (nº. 1.518.807, CAAE: 52895716/9-0000-5060), and all participants were informed of the inherent risks and benefits before signing a written informed consent term. The following exclusion criteria were adopted: (i) use of drugs that could affect cardiorespiratory responses; (ii) bone-, joint- or muscle-diagnosed problems that could limit the execution of elbow flexor; (iii) systemic hypertension (≥140/90 mmHg or use of antihypertensive medication); (iv) metabolic disease; and (v) use of exogenous anabolic–androgenic steroids, toxic drugs or medication with potential effects on physical performance. Participants were instructed to refrain from strenuous activities at least 72 h before the exercise sessions and to avoid the use of any pain-relieving medications (anti-inflammatory drugs), and maintained their normal food intake and lifestyle habits throughout the study.

**Experimental design**

The present study used a balanced, randomized crossover design to perform the exercise protocol. Eccentric exercise session was performed in two experimental conditions: (i) without BFR (HI-ECC) and (ii) combined to BFR (HI-ECC+BFR).

This experimental design was performed in the sequence of exercise counterbalanced by arm dominance (Newton et al., 2013). Each participant performed the exercise using the dominant and non-dominant arms. Muscle damage markers were evaluated at the following moments: pre-exercise, immediately after, 24 and 48 h after the exercise (pre-exercise, post-0 h, post-24 h and post-48 h, respectively). Cardiovascular and perceptual responses were analysed during and immediately after exercise protocol.

**Determination of the blood flow restriction pressure**

Subjects were asked to lie on a supine position while resting comfortably. A vascular Doppler probe (DV-600, Martec, Ribeirão Preto, SP, Brazil) was placed over the radial artery to determine the BFR pressure (mmHg). A standard BP cuff (width 14 cm; length 52 cm) attached to the proximal portion of arm was inflated up to the point in which the auscultatory pulse of the radial artery was interrupted. The BFR pressure was maintained constant throughout the exercise session. The cuff pressure used during the training protocol was determined as 80% of the necessary pressure for complete blood flow restriction in a resting condition (Laurentino et al., 2012). The dominant and the non-dominant arms had occlusion pressures of 121 ± 7 and 122 ± 4 mmHg, respectively (Table 1).

**Familiarization session**

Three days prior to one-repetition maximum test (1RM), participants were familiarized with the eccentric resistance exercise of elbow flexors, with 1RM testing procedure and to BFR.

### Table 1 Characteristic of the participants (n = 9).

<table>
<thead>
<tr>
<th>Anthropometry</th>
<th>Characteristic of arms</th>
<th>Dominant</th>
<th>Non-dominant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26 ± 1</td>
<td>21 ± 8</td>
<td>22 ± 4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178 ± 1</td>
<td>120 ± 8</td>
<td>121 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 ± 2</td>
<td>67 ± 2</td>
<td>35 ± 5</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>24 ± 1</td>
<td>120 ± 2</td>
<td>122 ± 3</td>
</tr>
<tr>
<td>Free fat mass (kg)</td>
<td>21 ± 1</td>
<td>35 ± 6</td>
<td>35 ± 5</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SEM.

BMI, body mass index; BFR pressure, blood flow restriction pressure; 1RM, one-repetition maximum test; ROM, range of motion; CIR, upper arm circumference.
This familiarization session consisted of one set of 10 repetitions for both dominant and non-dominant arms, with 50% of their estimated 1RM load, according to individual experience of resistance exercise (Laurentino et al., 2012).

**One-repetition maximum test**

The procedures adopted for one-repetition maximum test (1RM) for unilateral elbow flexor muscle were followed the recommendations described by Brown & Weir (2001). In short, participants ran for 5 min on a treadmill at 9 km h\(^{-1}\), followed by upper limb light stretching exercises and two warm-up sets of unilateral elbow flexor exercise. In the first set, individuals performed eight repetitions with a load correspondent to 50% of their estimated 1RM obtained during the familiarization sessions. In the second set, they performed three repetitions with 70% of their estimated 1RM. A 2-min interval was allowed between warm-up sets. After the completion of the second set, participants rested for 3 min and then had up to five attempts to achieve their 1RM with 3-min interval enforced between attempts. The 1RM strength on the elbow flexor muscles was recorded and reproduced throughout the study. Tests were conducted by an experienced researcher, and strong verbal encouragement was provided during the attempts. Both dominant and non-dominant arms were tested in a randomized order.

**Exercise protocol**

All participants \((n = 9)\) performed two bouts of HI-ECC of the elbow flexor muscles (unilateral elbow extension exercise): one using the dominant arm and another using the non-dominant arm. The arms were randomly chosen to perform the exercise in one of the two conditions: without or with BFR (HI-ECC and HI-ECC+BFR conditions, respectively), and counterbalanced such that each condition included both dominant and non-dominant arms. For the experimental session, participants performed three sets of 10 repetitions of HI-ECC or HI-ECC+BFR (130% of 1RM) of unilateral elbow extension in the Scott bench using free weights (dumbbells). The participants were allowed to rest 1 min between each set. The cadence of eccentric action was 3 s between the initial position (elbow flexed) and full extension of the elbow, while the concentric action was performed passively by the staffs returning the dumbbell at the top of the movement so that only the eccentric action was performed. The experimental session with the contralateral arm was performed at the same day, after 30 min.

**Rating of perceived exertion and pain**

Immediately after each set, the subjects were asked to report their rating of perceived exertion (RPE) and pain (RPP) using Borg’s CR-10 scale (1–10), similar to recent studies (Vieira et al., 2015; Neto et al., 2016), while 0 corresponding to ‘no exertion and pain’ and 10 corresponding to ‘extreme/maximal exertion and pain’. Participants received standardized instructions for each measure using this scale prior of exercise session.

**Markers of muscle damage**

Markers of muscle damage were measured before, immediately after, 24 and 48 h after each exercise bout (pre-exercise, post-0 h, post-24 and post-48 h, respectively). The details of the markers are shown below.

**Upper arm circumference (Thiebaud et al., 2013, 2014)**

The upper arm circumference (CIR) was assessed at five sites from the middle point between the acromial process and lateral epicondyle of the humerus using a standard tape measure (Sanny, São Bernardo do Campo, Brazil). It was measured the circumference in the middle portion, and also the circumferences in portions 1 and 2 cm above and 1 and 2 cm below the middle point. The mean value of the five measurements was used for the analysis.

**Range of motion (Thiebaud et al., 2013, 2014)**

The elbow joint angles for the fully extended and flexed positions were measured using a goniometer (Sanny) positioned in the distal forearm, while participants were asked to extend and flex the elbow as much as they could. The range of motion (ROM) was defined as the difference between the extended and flexed elbow joint angle.

**Muscle soreness upon palpation (Tanabe et al., 2015; Damas et al., 2016)**

The magnitude of muscle soreness was assessed using a visual analogue scale (VAS) consisting of a 100-mm line representing ‘no pain’ at one end (0 mm) and ‘very, very painful’ at the other (100 mm). Participants were asked to report the soreness level on the line when an investigator palpated their upper arm over the biceps brachial. All measurements were taken three times by same investigator, of similar manner in all participants, and mean values of the three measurements were used for further analysis.

**Cardiovascular responses**

Haemodynamic responses were evaluated according to the American Heart Association Guidelines (Pickering et al., 2005). Systolic (SBP), diastolic (DBP), mean blood pressure (MBP) and heart rate (HR) were monitored using an automatic blood pressure monitor (model HEM-705CP; OMROM). The cuff was placed in the contralateral arm that was performing the exercise, completely relaxed and extended. The measures were evaluated at different moments of the exercise session: before
(pre-exercise) and immediately after each set (post-set 1, post-set 2 and post-set 3). The MBP was calculated using the equation: $\text{MBP} = \text{SBP} + \left(\frac{2 \times \text{DBP}}{3}\right)$ (Neto et al., 2015).

**Statistical analysis**

Values were expressed as the mean ± standard error of the mean (mean ± SEM) for all variables. Statistical analyses were performed by two-way ANOVA with repeated measures (trials [without and with BFR] × time). When the ANOVA showed a significant interaction effect, a Tukey’s post hoc test was used to locate differences between conditions. Perceptual responses were also analysed via multiple-factor repeated-measures ANOVA for condition (HI-ECC and HI-ECC+BFR). Correlation between dominant arm versus non-dominant arms (1RM, ROM, CIR and BFR pressure), and between RPE versus RPP (HI-ECC and HI-ECC+BFR conditions) in post-set 1, post-set 2 and post-set 3, was examined through Pearson coefficients. The statistical analyses were performed using Prism software (Prism 5, GraphPad Software, Inc., San Diego, CA, USA). A value of $P < 0.05$ was regarded as statistically significant.

**Results**

**Population characteristics and arm comparison**

Table 1 shows the characteristics of the participants. As we have used both dominant and non-dominant arms in our exercise protocol, we first compared the absolute values of one-repetition maximum test (1RM), blood flow restriction (BFR) pressure, range of motion (ROM) and upper arm circumference (CIR) between arms. There were no significant differences for 1RM, ROM and CIR between arms (Table 1).

Figure 1 shows the Pearson correlation of 1RM (Fig. 1a), BFR pressure (Fig. 1b), ROM (Fig. 1c) and CIR (Fig. 1d) of the elbow flexors from dominant and non-dominant arms. Strong and significant correlation for 1RM (Fig 1a, $r = 0.968$, $P < 0.001$), BFR pressure (Fig. 1b, $r = 0.932$, $P < 0.001$), ROM (Fig. 1c, $r = 0.949$, $P < 0.001$) and CIR (Fig. 1d, $r = 0.962$, $P < 0.001$) was observed between dominant and non-dominant arms. Therefore, no differences were observed between the dominant and non-dominant arms, which allow us to use either arm from the participants.

**Rating of perceived exertion and perceived pain**

Figure 2 shows the absolute scores of rating of perceived exertion (RPE, Fig. 2a) and pain (RPP, Fig. 2b) after each set. HI-ECC increased RPE score post-set 3 versus post-set 1 while no significant differences were observed in the HI-ECC+BFR condition. No significant differences were observed between HI-ECC+BFR and HI-ECC conditions at any moment. Regarding RPP, after the first set (post-set 1) both conditions reported scores around 6 and 7 in Borg scale, classified as ‘very intense’. Also, at post-set 2 and post-set 3, both conditions showed a significant increase in RPP scores compared to post-set 1. However, HI-ECC+BFR condition showed significant higher values...
for RPP at all moments (post-set 1, 2 and 3) compared to HI-ECC condition.

Figure 3 shows the Pearson correlation between the scores of RPE and RPP for HI-ECC (Fig. 3a) and HI-ECC+BFR (Fig. 3b). There was no significant correlation between RPE and RPP scores in both conditions (Fig. 3).

**Markers of muscle damage**

Figure 4 shows the Δ values of muscle soreness (Fig. 4a), ROM (Fig. 4b) and CIR (Fig. 4c) at different moments (pre-exercise, post-0 h, post-24 h and post-48 h). Figure 4a shows that there were no differences between conditions in the muscle soreness. However, only the HI-ECC+BFR showed post-48 h muscle soreness score was significantly lower than that of post-0 h. Figure 4b shows that both conditions similarly decreased ROM immediately after exercise (post-0 h: HI-ECC, $-12.3\pm 3^\circ$; HI-ECC+BFR, $-11.1\pm 3^\circ$). However, it should be noted that only in HI-ECC condition, the ROM remains significantly reduced even 24 h after the exercise session (post-24 h: $-7.0\pm 3^\circ$, $P<0.05$), while ROM in HI-ECC+BFR condition had already returned to pre-exercise levels. Finally, Fig. 4c shows the CIR. Immediately after exercise, only the HI-ECC condition showed significant increase in CIR versus pre-exercise (post-0 h: $0.6\pm 0.3$ cm, $P<0.05$). At post-24 h and post-48 h, there was no difference on CIR in both conditions.

**Cardiovascular responses**

Figure 5 shows the haemodynamic responses (MBP, SBP, DBP and HR) evaluated after each set (pre-exercise, post-set 1, post-set 2 and post-set 3). There were no differences in MBP (Fig. 5a) and SBP (Fig. 5b). DBP (Fig. 5c) showed a significant decrease of 11 mmHg after the second set only in the HI-ECC condition (pre-exercise, $69.8\pm 3$ mmHg, $P<0.05$). HR (Fig. 5d) increased in both HI-ECC and HI-ECC+BFR conditions after set 3 with no differences between conditions.

**Discussion**

The main findings of our study were as follows: although BFR increased the rating of perceived pain, it attenuated muscle damage induced by HI-ECC and did not magnify cardiovascular responses induced by exercise. Thus, muscle damage marker responses of the elbow flexor muscles after HI-ECC were attenuated by BFR in trained men. These findings suggest that...
BFR has preventive effects on eccentric exercise-induced muscle damage indirect responses.

Both dominant and non-dominant arms were exercised in our study. We compared 1RM, ROM, CIR and BFR pressure from both arms to avoid the possibility of differences among them. Cornwell et al. (2012) evaluated maximal voluntary handgrip strength and observed that dominant arm had higher muscle strength when compared with non-dominant arm. On the other hand, Newton et al. (2013) observed no significant differences between arms for isometric torque, ROM and CIR. We observed no differences between arms when compared the values for strength in 1RM test, ROM and CIR. These results can be explained by our volunteers being regular practitioners of resistance exercise for at least 1 year. According to recent studies (Cornwell et al., 2012; Botton et al., 2016), the difference between arms decreases after training, equaling the strength and anthropometric characteristics between limbs. We also compared the BFR in both arms and no difference was observed. These data are important to avoid resulting in misinterpretation due to differences in the characteristics of participants’ arms. Also, there was no study that compared the BFR pressure between dominant versus non-dominant arms.

The RPE and RPP was analysed after each set of the HI-ECC. Our results showed similar responses between conditions for RPE after each set, but with a significant increase after exercise to HI-ECC condition. On the other hand, the RPP score increased in both groups after each set, but higher response was observed when combined with BFR. Previous studies have evaluated RPE and RPP scores to high intensity (HI, i.e. >70% of 1RM) without BFR versus LI (30–50% of 1RM) with BFR in resistance exercise performed until muscular failure (Vieira et al., 2015; Neto et al., 2016) and no differences were observed. However, for similar exercise loads, BFR group showed higher RPE and RPP (Rossow et al., 2012; Fitschen et al., 2014; Vieira et al., 2015). Recent studies showed greater accumulation of metabolic products (e.g. blood lactate) (Takano et al., 2005; Fry et al., 2010; Pearson & Hussain, 2015) and hormonal responses (e.g. increases in serum growth hormone, adrenaline, noradrenaline, insulin-like growth factor, testosterone and cortisol concentrations) (Takano et al., 2005; Kon et al., 2012; Neto et al., 2016) with BFR. It has been suggested that this accumulation of metabolic subproducts stimulates type IV fibres (nociceptors, pain receptors), leading to enhanced perceived pain (Spranger et al., 2015; Vieira et al., 2015). Therefore, as shown in our results and also in other studies (Rossow et al., 2012; Fitschen et al., 2014; Vieira et al., 2015), resistance exercise with BFR increases the RPP.

Exercise-induced muscle damage has been evaluated by several studies (Thiebaud et al., 2013, 2014; Damas et al., 2016) using indirect muscle damage markers such as muscle soreness, ROM and CIR. These markers may remain changed even 48–72 h after HI-ECC (Thiebaud et al., 2013; Sieljacks et al., 2013)
Our results show that after HI-ECC muscle damage, markers were lower in HI-ECC + BFR condition. Furthermore, we observed that after 48 h, muscle soreness of HI-ECC + BFR was lower than immediately after exercise, while no differences were observed in HI-ECC. Thiebaud et al. (2013) evaluated the effect of eccentric resistance exercise at 30% of the 1RM on muscle damage. They observed that ECC combined to BFR promoted increase in muscle soreness immediately after exercise and recovering their basal values following 24 h. However, the volunteers were not regular practitioners of any exercise training. Sieljacks et al. (2015) investigated the effects of low-intensity ECC with BFR. They observed no changes on muscle damage markers when BFR was applied. Our study is the first to examine the effects of HI-ECC combined with BFR on muscle damage markers. Furthermore, we evaluated subjects that have been enrolled in regular resistance exercise programme for at least 1 year. In summary, for trained individuals, the HI-ECC combined with BFR is less harmful compared to condition without BFR. Lower muscle damage in HI-ECC + BFR can be explained by 1) the increase in \([\text{Ca}^{2+}]_i\) (Zhang et al., 2012), 2) accumulation of intramuscular metabolites (Fry et al., 2010; Suga et al., 2010; Neto et al., 2016) and 3) increase in fibre recruitment (Loenneke et al., 2010; Suga et al., 2010; Karabulut & Perez, 2013). Also, it is shown that circulating neutrophils are involved in muscle damage by migrating into the muscle tissue and inducing inflammation (Kawanishi et al., 2016), and BFR could reduce the infiltration of neutrophils and the muscle inflammation.

Classically, muscle growth mechanisms are triggered after initial muscle damage producing increase in protein synthesis to support tissue repair (Moore et al., 2005). Recently, molecular relationship between muscle protein synthesis and muscle damage following ECC with BFR in animal model was studied (Sudo et al., 2015). The authors observed a large occurrence of muscle damage following ECC, which was not observed when exercise was combined with BFR. However, it was still observed hypertrophic signalling molecules and augmented muscle mass following ECC combined with BFR. Damas et al. (2016) showed that muscle damage does not necessarily correlate with increased protein synthesis and consequently muscle hypertrophy. The authors observed that muscle hypertrophy was the result of accumulated intermittent changes in muscle protein synthesis, which coincides with progressive attenuation of muscle damage by training.

It is well described the cardiovascular response during ECC (Hortobágyi & Devita, 2000; Meyer et al., 2003; Vallejo et al., 2006) is lower compared to conventional resistance exercise. In our results, HI-ECC decreased post-set 2 DBP only when performed without BFR, while there were no differences between conditions for SBP and HR. The decreased DBP can be explained by the decrease in peripheral vascular resistance.

![Figure 5](image-url)
during the exercise. Resistance exercise increases nitric oxide synthase which promotes vasodilatation and reductions in peripheral vascular resistance (Queiroz et al., 2013). Furthermore, systemic and regional resistance are decreased below pre-exercise values by increases in body temperature with cutaneous vasodilatation and consequently distribution of blood to the periphery (Macdonald, 2002). Also, studies have showed that resistance exercise combined with BFR increases noradrenaline and adrenaline circulating (Takano et al., 2005; Madarame et al., 2013) and consequently leads to higher peripheral vascular resistance than without BFR. Despite increasing the RPP, it was observed that the BFR did not cause increases in BP. Thus, our results strengthen that BFR is safe and can be well tolerated.

In summary, we have analysed HI-ECC-induced muscle damage with BFR. We showed that BFR attenuated indirect muscle damage markers of the elbow flexor muscles and increased rating of perceived pain while it did not increase rating of perceived exertion and cardiovascular responses after HI-ECC in trained men. Future experiments are still required to analyse the safety and efficiency of this technique in limited populations, and whether these responses occur only on indirect muscle damage markers.

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Conflict of interest

No conflict of interests, financial or otherwise, are declared by the authors.

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