



The systemic myokine response of decorin, interleukin-6 (IL-6) and interleukin-15 (IL-15) to an acute bout of blood flow restricted exercise

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Abstract

Purpose Blood flow restricted resistance exercise (BFR-RE) is an emerging hypertrophy training modality. A complete profile of its mechanisms of action has yet to be elucidated. Cytokines are universal intercellular messengers. Recent research has implicated certain cytokines (termed “myokines”) in skeletal muscle hypertrophy pathways; however, little research has been conducted on the systemic myokine response to BFR-RE as potential hypertrophic biomarkers. Therefore, this project was conducted to determine any differences in the systemic myokine response between BFR-RE and control conditions.

Methods The appearance of systemic myokines interleukin-6 (IL-6), interleukin-15 (IL-15), and decorin were measured following acute bouts of low-load resistance exercise, BFR-RE, and high-load resistance exercise in physically active young males to determine if BFR-RE modifies the exercise-induced systemic myokine response.

Results No measurable levels of IL-6 were observed during the project. No significant effects were observed for IL-15. A significant time (11.91% increase pre to post exercise; $p < 0.05$) but no condition or condition by time effect was observed for decorin.

Conclusion These findings suggest that BFR-RE does not modify the systemic myokine appearance of IL-6, IL-15, or decorin when compared to control conditions.

Keywords Exercise immunology · Weight lifting · KAATSU · Cell signalling · BFR

Abbreviations

ABPI Ankle–brachial pressure index
ANOVA Analysis of variance
APMHR Age-predicted maximum heart rate

BFR-RE Blood flow restricted resistance exercise
EDTA Ethylenediaminetetraacetic acid
ELISA Enzyme-linked immunosorbent assay
HL-RE High-load resistance exercise
HRR Heart rate reserve
IL-6 Interleukin-6
IL-15 Interleukin-15
LL-RE Low-load resistance exercise
NSAID Non-steroidal anti-inflammatory drugs
PAR-Q+ Physical activity readiness questionnaire plus
RHR Resting heart rate
STAT3 Signal transducer and activator of transcription 3

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Introduction

Research on BFR-RE has increased over the last decade. BFR-RE can be described as applying a pressurized cuff around the most proximal portion of an exercising limb (arm or leg), inflating the cuff to a predetermined restrictive

pressure such that venous return is restricted (while arterial flow is unimpeded), and completing a low load, high repetition, low rest period training protocol under the condition of mild vascular restriction (Pope et al. 2013).

Under more conventional settings, resistance training protocols designed to elicit skeletal muscle hypertrophy in novice to intermediate trainees typically include a loading scheme between 70 and 85% 1-repetition maximum (1RM) (Ratamess et al. 2009), 1–3 total sets per exercise with 6–12 repetitions per set (Hedrick 2012; Ratamess et al. 2009), and 1–2 min of rest between each set (Ratamess et al. 2009). In contrast, commonly prescribed BFR-RE protocols include a loading scheme between 20 and 40% 1RM, one set of 30 repetitions followed by three additional sets of 15 repetitions, and 30 s of rest between each set (Scott et al. 2015). Despite this disparity in training protocols, both methods have been shown to produce a similar level of skeletal muscle hypertrophy, perhaps indicating that exercise protocols of various intensity and repetition ranges are capable of producing a similar level of skeletal muscle hypertrophy (Martín-Hernández et al. 2013; Ratamess et al. 2009). Furthermore, BFR-RE results in superior hypertrophic adaptations when compared to volume matched low-load resistance exercise (LL-RE) without blood flow restriction (Loenneke et al. 2012; Takarada et al. 2004).

Cytokines are a large family of polypeptides and proteins which act as intercellular messengers. While their primary function is typically associated with an immune response, many cytokines also appear to exhibit functional pleiotropy. A single cytokine may confer different mediating effects depending upon the initial stimuli, target cell, or additional cytokines released in conjunction (Peake et al. 2015). Skeletal muscle has been found to secrete cytokines in response to muscular contraction. These cytokines (termed “myokines”) act both locally or systemically through release into the circulation (Pedersen and Febbraio 2012). The strength of an individual myokine response appears to vary based on exercise mode, volume, and intensity (Peake et al. 2015).

Resistance exercise stimulates the systemic appearance of myokines IL-6, IL-15 and decorin (Kanzleiter et al. 2014; Mitchell et al. 2013; Riechman et al. 2004). IL-6 stimulates the proliferation and mobilization of myogenic stem cells within myofibers via the signal transducer and activator of transcription 3 (STAT3) pathway (Serrano et al. 2008). Furthermore, systemically measured IL-6 has been correlated with levels found in skeletal muscle biopsies taken at 4, 24, 72, and 120 h following a muscle damaging exercise protocol ($R^2=0.89$) (Mckay et al. 2009) and is also correlated with skeletal muscle hypertrophy ($r=0.48$) (Mitchell et al. 2013). Additionally, in vivo models reported that IL-15 stimulates myosin-heavy chain accumulation in fully differentiated myocytes (Furmanczyk and Quinn 2003; Quinn et al. 1995). Finally, in vitro models have reported that decorin

binds to myostatin, a negative regulator of skeletal muscle hypertrophy (Lee 2004), within the extra-cellular matrix. This process reduces the inhibitory effects of myostatin on skeletal muscle hypertrophy (Guiraud et al. 2012; Miura et al. 2006).

Despite increased research activity, a complete profile of the mechanisms of action associated with BFR-RE induced skeletal muscle hypertrophy has yet to be elucidated. Further, there appears to be a lack of research exploring the potential role that myokines play in BFR-RE induced skeletal muscle hypertrophy. Compared to baseline measurements, Takarada et al. (2000) showed a significant increase in circulating levels of IL-6 measured 30, 60, 90, and 120 min following a blood flow restricted exercise protocol in active young males. Paterson et al. (2013) showed a similar response in older males, observing a significant increase in circulating levels of IL-6 comparing measurements taken 30 and 60 min following blood flow restricted resistance exercise.

The purpose of this research project was to measure if BFR-RE modifies the exercise-induced myokine response by comparing the appearance of systemic myokines IL-6, IL-15, and decorin after acute bouts of LL-RE, BFR-RE, and high-load resistance exercise (HL-RE). We hypothesized that the systemic myokine response would be greater in BFR-RE and HL-RE when compared to LL-RE.

Materials and methods

Institutional ethics approval was obtained and informed consent was provided by all the participants. This study utilized a randomized crossover design in which participants were randomly assigned to one of three acute-exercise conditions (LL-RE, BFR-RE, or HL-RE). Participants then completed one exercise condition per week (over the course of three successive weeks) in randomized order until all three exercise conditions had been completed.

Participants

Ten physically active participants were recruited for the study. These participants were young men (age range 18–35 years) with at least 1 year of resistance training experience and were recruited from a local university campus via recruitment poster advertisement. For the purposes of this study, resistance training experience was defined as 2–4 bouts of resistance training per week, utilizing a loading scheme of 70–85% 1RM with 1–3 sets per exercise, 6–12 repetitions per set, and rest periods between 1 and 2 min (Ratamess et al. 2009).

Inclusion and exclusion criteria

Participants in the study were required to have at least 1 year of resistance training experience and must not have engaged in any form of blood flow restricted exercise within 1 month of the present study to ensure adequate detraining from potential hypertrophic BFR-RE stimulus (Kubo et al. 2010; Yasuda et al. 2015). Furthermore, participants must have abstained from resistance training their lower body for at least 48 h prior to all required exercise sessions. Finally, all participants were cleared for exercise via completion of a Physical Activity Readiness questionnaire-plus (PAR-Q+) by answering “no” to all the questions posed in the questionnaire.

Participants were excluded if they presented with any musculoskeletal injury or limitation which could have interfered with correct placement of the blood flow restriction apparatus or completion of exercise. Participants were also excluded if they were currently taking non-steroidal anti-inflammatory drugs (NSAIDs) or any potentially anti-inflammatory supplements (e.g. omega-3 fatty acid or curcumin supplements). Finally, participants were excluded if they presented with hypertension, had used tobacco regularly within the last 6 months, or had risk factors for cardiovascular disease, heart disease, lower limb vascular conditions, or an ankle–brachial pulse index (ABPI) ratio of <0.9.

Familiarization and 1RM testing

All data collection was conducted within the same clinical exercise laboratory setting by the same research technician. Upon initial meeting, written informed consent was obtained from all participants for the project. Participant resting heart rate (RHR), ankle and brachial blood pressures (Omron Series 7 Model BP761CAN, Omron Corporation, Lake Forest, IL, USA) and basic anthropometric characteristics (height, weight, waist circumference, and BMI) were then measured. Blood pressure measurements were taken twice and the mean of the two measurements was used as each participant’s resting blood pressure. Participant ABPI was calculated by dividing their ankle blood pressure by their brachial blood pressure. Participants then warmed up on a cycle ergometer for 10 min at 50% of their heart rate reserve (HRR) as calculated using the age-predicted maximum heart rate (APMHR) Karvonen method (Jeffreys 2008; Reuter and Hagerman 2008):

$$\text{HRR} = (([\text{APMHR}] - \text{RHR}) * \% \text{Intensity}) + \text{RHR}.$$

Participant bilateral knee extension (Precor DPL0560, Precor Inc., Woodinville, WA, USA) 1RM was determined by completing the National Strength and Conditional Association’s 1RM testing protocol (Harman and Garhammer

2008). Finally, participant estimated arterial occlusion pressure was calculated by incrementally increasing KAATSU air-band restrictive pressure at the thigh until the ankle pulse (via palpation) was no longer detectable. All participants reached the maximum restrictive pressure capabilities of the KAATSU device without experiencing complete vascular occlusion. Thus, 50% of the maximum restrictive pressure (200 mmHg) was utilized for all participants during the experiment.

Resistance training bouts

Participants completed their trials at the same time of day for the duration of the study. Participants were instructed to abstain from alcohol, caffeine, or other stimulant consumption for at least 8 h prior to the familiarization and resistance training sessions. Participants were also asked to abstain from exercise until completion of the 24-h post-exercise blood draw.

Participants completed a general warm-up by riding a cycle ergometer for 10 min at 50% of their HRR. Upon completion, participants were fitted with 5-cm wide KAATSU air-bands (KAATSU Nano; KAATSU-Global, Huntington Beach, CA, USA). Air-bands were applied to the most proximal portion of the participant’s thighs, immediately distal to their gluteal fold. Cuff placement adhered to guidelines from a recent BFR-RE review (Scott et al. 2015). External pressure applied by the KAATSU air-bands prior to inflation was held at 0 mmHg.

During the BFR-RE trial, restrictive pressure during exercise was set at 200 mmHg. Immediately prior to exercise, the air-bands were inflated to from 0 to 50 mmHg and held for 20 s. They were then released for 5 s before being re-inflated to 100 mmHg for another 20 s. This pattern of inflation and deflation continued in 50 mmHg increments until four total waves had taken place and the total restrictive pressure applied reached 200 mmHg. Restrictive pressure then remained set at 200 mmHg to properly stimulate vascular restriction (but not occlusion) during each exercise bout. Participants then completed a bout of bilateral knee extension exercise following a 1:0:1 (concentric, pause, eccentric) exercise tempo assisted via metronome (iPhone Application “Pro Metronome”, EUMLab, Hangzhou, China). The exercise bout included one set of 30 repetitions, followed by three additional sets of 15 repetitions, with 30 s of rest allotted between sets. Total load was set to 30% 1RM as measured during the familiarization session. The KAATSU air-bands remained inflated for the duration of the exercise bout (including rest periods) and were released immediately upon completion of the prescribed exercise bout.

Both LL-RE and HL-RE interventions replicated the procedures utilized during the BFR-RE intervention. However, these trials proceeded without the influence of blood

Table 1 Exercise intervention details

Intervention	Load	Repetitions	Rest (s)	Applied pressure (mmHg)
LI-RE	30% 1RM	75 (30, 15, 15, 15)	30	0
BFR-RE	30% 1RM	75 (30, 15, 15, 15)	30	200
HI-RE	80% 1RM	28 (7, 7, 7, 7)	60	0

Exercise tempo proceeded with a 1-s concentric, 0 s pause, and 1-s eccentric pace as assisted by metronome

LI-RE low intensity resistance exercise, *BFR-RE* blood flow restriction resistance exercise, *HI-RE* high intensity resistance exercise

flow restriction. The KAATSU air-bands were applied to the most proximal portion of the participant's thighs but remained deflated for the duration of the intervention to act as a control. Furthermore, exercise parameters during the HI-RE intervention were modified to reflect a high-load setting. The HI-RE exercise bout included four sets of 7 repetitions with 1 min of rest allotted between sets. Total load was set to 80% 1RM as measured during the familiarization session. These parameters were selected to most accurately adhere to guidelines for skeletal muscle hypertrophy training while also equating the closest possible total exercise volume between all exercise interventions (Hedrick 2012; Ratamess et al. 2009). Exercise intervention details can be found in Table 1.

Blood sampling and analysis

Participants had blood samples drawn immediately pre-exercise, immediately post-exercise, 1-h post-exercise, and 24-h post-exercise during each intervention arm. A certified phlebotomist drew approximately 10 mL of blood from the antecubital vein using a venous blood collection needle. Blood was drawn into a vacutainer coated with ethylenediaminetetraacetic acid (EDTA). Next, collected samples were centrifuged for 15 min at 4 °C and 3000 RPM. Upon completion, separated plasma from EDTA tubes was aliquoted using a transfer pipette and placed into a microtube. The microtubes were placed in a –80 °C storage freezer and remained there until analysis.

Blood samples were analyzed in duplicate for plasma IL-6, IL-15, and decorin content by utilizing an enzyme-linked immunosorbent assay (ELISA) technique specific to manufacturer's instruction (Human IL-6 ELISA Kit KHC0061, Thermo Fisher Scientific, Waltham, WA, USA; Human IL-15 Quantikine ELISA Kit D1500, R&D Systems Inc., Minneapolis, MN, USA; Human Decorin ELISA Kit EHDCN, Thermo Fisher Scientific, Waltham, WA, USA).

Statistical analysis

A sample size analysis was completed to determine an appropriate number of participants. With α set to 0.05, β set to 0.90, and data on the appearance of systemic IL-6 in response to an acute bout of BFR-RE from Takarada et al. (2000) (Takarada et al. 2000), a sample size of nine participants provided adequate statistical power.

A two-factor (group \times time) repeated measures analysis of variance (ANOVA) was used to determine significant within-group differences for each dependant variable. A p value of ≤ 0.05 was used to determine significance. A post hoc Bonferroni adjustment was made to the p value based upon the number of comparisons to be made if statistically significant differences were found. All calculations were made using Statistica Academic version 13 (StatSoft, Tulsa, OK, USA) statistical analysis software.

Results

All participants successfully completed the required sets and repetitions. Participant descriptive details and anthropometric data are summarized in Table 2. One participant was removed from analysis due to adverse reaction to blood drawing procedures (dizziness) and thus analysis was completed on the remaining nine participants ($n=9$).

Blood samples were thawed and analyzed for plasma concentrations of IL-6, IL15, and decorin via ELISA technique. Myokine data are reported in Table 3. Analysis of blood samples for plasma concentrations of IL-6 showed no detectable levels of IL-6 for any participant during any intervention or time point. Analysis of blood samples for plasma concentrations of IL-15 showed no statistically significant condition [$F(2, 24)=0.049$, $p=0.952$], time

Table 2 Participant anthropometric characteristics

Characteristic	Mean \pm SD	Range
Age (years)	25.78 \pm 3.56	20–30
Height (m)	1.75 \pm 0.07	1.63–1.86
Weight (kg)	79.74 \pm 8.82	68.4–91
Waist circumference (cm)	84 \pm 4.85	76–91
BMI (kg/m ²)	25.93 \pm 2.22	22.3–28.9
RHR (bpm)	57.56 \pm 5.25	50–64
Brachial systolic BP	120.11 \pm 12.15	97–131
Ankle systolic BP	136 \pm 7.45	123–148
ABPI	1.14 \pm 0.10	1.01–1.30
Knee extension 1RM (lbs)	254.44 \pm 47.40	215–370

BMI body mass index, *RHR* resting heart rate, *BP* blood pressure, *ABPI* ankle–brachial pressure index (ankle systolic BP/brachial systolic BP), *1RM* 1-repetition maximum

Table 3 Numerical data for systemic myokine concentrations

Variable	Pre-exercise (mean ± SD)	Post-exercise (mean ± SD)	1 h post-exercise (mean ± SD)	24 h post-exercise (mean ± SD)
LI-RE IL-15 (pg/mL)	0.78 ± 0.69	0.78 ± 0.65	0.72 ± 0.69	0.76 ± 0.65
BFR-RE IL-15 (pg/mL)	0.65 ± 0.54	0.73 ± 0.59	0.67 ± 0.63	0.74 ± 0.73
HI-RE IL-15 (pg/mL)	0.83 ± 0.68	0.81 ± 0.70	0.77 ± 0.66	0.76 ± 0.62
LI-RE decorin (pg/mL)	2016.10 ± 1250.94	2195.20 ± 1362.85	2117.57 ± 1387.60	1895.50 ± 1182.22
BFR-RE decorin (pg/mL)	1901.19 ± 1144.05	2121.24 ± 1189.63	1996.01 ± 1196.53	1909.76 ± 1187.80
HI-RE decorin (pg/mL)	1939.47 ± 1142.65	2237.72 ± 1446.64	1983.09 ± 1323.87	1883.66 ± 1090.47

SD standard deviation, *LI-RE* low intensity resistance exercise, *BFR-RE* blood flow restriction resistance exercise, *HI-RE* high intensity resistance exercise, *IL-15* interleukin-15

[$F(3, 72) = 0.647, p = 0.588$], or condition by time [$F(6, 72) = 0.458, p = 0.837$] effects. Analysis of blood samples for plasma concentrations of decorin showed a statistically significant time [$F(3, 72) = 12.022, p = 0.000002$] but no condition [$F(2, 24) = 0.008, p = 0.992$] or condition by time [$F(6, 72) = 0.596, p = 0.733$] effect. Measurements taken for decorin immediately post-exercise were 11.91% greater than measurements taken immediately pre-, 1-h post-exercise, and 24-h post-exercise. No significant differences were found for any other time point.

Discussion

This study demonstrated a statistically significant increase in the concentration of decorin, but not IL-6 or IL-15, in the systemic circulation immediately following LL-RE, BFR-RE, and HL-RE interventions. This observation is novel because few studies have examined decorin concentrations *in vivo* following resistance exercise.

The results of the present study are in agreement with those published by Kanzleiter et al. (2014). Both experiments reported a statistically significant increase in plasma decorin measured immediately post-exercise which rapidly declined towards baseline within the first hour of recovery (Kanzleiter et al. 2014). The magnitude of change was greater during the protocol used by Kanzleiter et al. (2014) (an approximate 30% increase in circulating decorin over baseline) measured immediately post-exercise when compared to this project (11.91% increase); however, the overall exercise volume was substantially greater as well. Kanzleiter et al. (2014) utilized seven exercises designed to train the full body. Each exercise was performed with three sets of eight repetitions and approximately 75–80% 1RM in their previous study (Kanzleiter et al. 2014). In contrast, this project utilized only one exercise (knee extensions) with exercise parameters (sets, repetitions, and load) prescribed for the specific intervention type (LL-RE, BFR-RE, or HL-RE). This approach may have limited the observed

treatment effect in exchange for a greater level of control when compared to Kanzleiter et al. (2014). One could speculate that given similar training volume, a similar magnitude of decorin released into the systemic circulation would be observed. Supporting this, as Kanzleiter et al. (2014) performed moderate–high intensity resistance exercise in a non-blood flow restricted setting; their findings are most relatable to the positive control utilized during this project (HL-RE). Given that this project observed no statistical difference in decorin release between interventions, it is possible that resistance exercise of various intensities may confer a similar decorin release (assuming total exercise volume is equated). Further, Kanzleiter et al. (2014) observed a correlation ($r^2 = 0.44$) of decorin release and total weight utilized in the leg press exercise. However, given the difference in the magnitude of decorin release observed between these two experiments in conjunction with the equated-volume used between interventions in this project, it could be suggested that overall training volume or total muscle mass involvement may be predictors of the magnitude of decorin release rather than exercise intensity (leg press strength) alone (Kanzleiter et al. 2014).

Given their proposed role in modulating skeletal muscle hypertrophy (Kanzleiter et al. 2014; Miura et al. 2006), decorin may contribute to BFR-RE induced skeletal muscle hypertrophy through a decorin–myostatin interaction; however, as there was a time but no condition or condition by time interaction, this contribution would not be different than that of control conditions.

It is possible that the overall level of control exhibited in this project may have contributed to the lack of change in circulating concentrations of IL-6 and IL-15 following each intervention. IL-6 has robust increases in systemic circulation following long-duration running events (Peake et al. 2015); however, the paucity of experiments measuring IL-6 in response to BFR-RE limited the predictability of the appearance of this myokine in systemic circulation. Both Patterson et al. and Takarada et al. were able to observe a small increase in IL-6 found in systemic circulation

following a similar BFR-RE protocols (Patterson et al. 2013; Takarada et al. 2000); however, their protocols elected to perform each set of knee extensions to volitional fatigue as opposed to a sub-maximal protocol utilized in this project. Furthermore, IL-6 is known to exhibit pleiotropic characteristics with respect to exercise-induced adaptations (Pedersen et al. 2007). IL-6 has also been associated with the AMPK pathway (Pedersen 2012). As such, it could be hypothesized that the change in IL-6 observed by Takarada et al. (2000) is more indicative of IL-6 functioning as an energy sensor. Our study, which failed to produce a systemic IL-6 response, may support the notion that IL-6 predominantly acts as an energy sensor during exercise, as it is unlikely there would have been an appreciable deprivation of energy stores with the exercise protocol we used and thus no need for the release of IL-6 systemically.

Previous literature has reported variability in the systemic appearance of IL-15 in response to different resistance training volumes. Riechman et al. (2004) observed a statistically significant increase in plasma IL-15 following a full body (non-blood flow restricted) resistance training regimen. This protocol included the completion of thirteen exercises, each for three sets of 6–10 repetitions at approximately 80% 1RM (Riechman et al. 2004). In contrast, Nielsen et al. did not observe any change in plasma IL-15 following a resistance exercise protocol designed specifically to fatigue the quadriceps muscle. This protocol (also non-blood flow restricted) employed four sets of leg press and knee extension exercises at approximately 80% 1RM, with a goal of reaching complete exhaustion by the end of each set (Nielsen et al. 2007). Collectively, these findings seem to indicate that full-body exercise and higher total workloads may stimulate the appearance of IL-15 to a greater extent than that of the isolated resistance training provided by our interventions. Our findings appear to support the proposed pleiotropic effects of IL-15. Initial research into the functionality of IL-15 appeared to indicate a role in skeletal muscle hypertrophy (Quinn et al. 1995); however, recent research has also indicated a potential alternative role in muscle oxidative and fatigability properties (Pistilli and Quinn 2013; Ye 2015). It is possible, therefore, that our limited exercise volume did not trigger a significant IL-15 response as the total workload incurred did not stimulate the necessity for its release.

Limitations

Recent reviews have indicated that approximately 40–50% of an individual's estimated arterial occlusion pressure appears to be an optimal BFR-RE pressure stimulus (Scott et al. 2015). During familiarization, however, all participants reached the maximum external pressure application capabilities of the KAATSU Mini system (400 mmHg). It has been theorized that BFR-RE may act

through a hormesis effect, whereby, a potentially harmful stimulus when given at high doses (blood flow restriction) may actually be beneficial at lower doses (Loenneke et al. 2014). Following this theory, an inappropriately high external pressure may be detrimental while lower pressures may be sub-optimal. As all participants reached the maximum pressure capacity of the KAATSU Mini without experiencing vascular occlusion, it is impossible to determine what percentage of their estimated arterial occlusion pressure was actually applied during exercise, or, if this pressure fell within the optimal range.

Another limitation of this study is that blood sample analysis served as an indirect measure for the outcome of interest. The overall narrative of this project is to understand the capacity for low-intensity blood flow restricted resistance training to produce a similar skeletal muscle hypertrophy adaptation when compared to more classically prescribed (moderate-vigorous intensity) exercise parameters. The purpose of this study, therefore, was to analyze systemic concentrations of select myokines as they have been shown to act as biomarkers of skeletal muscle hypertrophy signalling (Nielsen and Pedersen 2007; Quinn 2008; Serrano et al. 2008). However, the pleiotropic nature of myokines confers a potential for vastly different effects given a local or systemic environment of action. This limits the interpretation of this project and suggests that future research should explore a similar study design with the primary analysis coming directly from muscle biopsy.

Conclusion

A novel finding of this work is that blood flow restricted resistance training does in fact produce an increase in the myokine decorin detected within systemic circulation immediately post-exercise. While it is possible that decorin plays some role in the hypertrophy response induced by BFR-RE, the lack of significant differences observed between the three interventions employed indicates that decorin variability may not be a differentiating factor between the hypertrophic responses. However, the variation in exercise protocols utilized within this study and that of Kanzleiter et al. (2014) provides a more nuanced understanding of the exercise-induced appearance of systemically measured decorin. While the magnitude of systemically measured decorin was once suggested to be correlated with exercise intensity (Kanzleiter et al. 2014), the results of this study seem to indicate that total exercise volume may be another predictor of the systemic appearance of decorin.

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Author contributions EB conceived and designed the research as well as conducted the experiments. EB and SC analyzed data. EB wrote the manuscript. TD, JP, and SC refined the research design, data collection, data analysis, interpretation, and manuscript writing. All authors read and approved the manuscript.

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