frontiers | Research Topics

Characteristics of blood flow restriction (BFR) protocols enhancing aerobic and anaerobic fitness, muscle strength and hypertrophy

Edited by
Gregory C. Bogdanis and Adam Zajac

Published in
Frontiers in Physiology

ISSN 1664-8714
ISBN 978-2-8325-3007-8
DOI 10.3389/978-2-8325-3007-8

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Characteristics of blood flow restriction (BFR) protocols enhancing aerobic and anaerobic fitness, muscle strength and hypertrophy

Topic editors
Gregory C. Bogdanis — National and Kapodistrian University of Athens, Greece
Adam Zajac — University School of Physical Education in Wroclaw, Poland

Citation
Bogdanis, G. C., Zajac, A., eds. (2023). *Characteristics of blood flow restriction (BFR) protocols enhancing aerobic and anaerobic fitness, muscle strength and hypertrophy*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-3007-8

Table of contents

frontiers in Physiology

ORIGINAL RESEARCH
published: 30 March 2021
doi: 10.3389/fphys.2021.663665

Check for updates

Effects of Resting vs. Continuous Blood-Flow Restriction-Training on Strength, Fatigue Resistance, Muscle Thickness, and Perceived Discomfort

Carsten Schwiete[1], Alexander Franz[2], Christian Roth[1] and Michael Behringer[1]*

[1]Department of Sports Medicine and Exercise Physiology, Institute of Sports Sciences, Goethe University Frankfurt, Frankfurt am Main, Germany, [2]Department of Adult Reconstruction, ATOS Orthoparc Clinic Cologne, Cologne, Germany

Introduction: The purpose of this study was to clarify whether blood-flow restriction during resting intervals [resting blood-flow restriction (rBFR)] is comparable to a continuous BFR (cBFR) training regarding its effects on maximum strength, hypertrophy, fatigue resistance, and perceived discomfort.

Materials and Methods: Nineteen recreationally trained participants performed four sets (30-15-15-15 repetitions) with 20% 1RM on a 45° leg press twice a week for 6 weeks (cBFR, $n = 10$; rBFR, $n = 9$). Maximum strength, fatigue resistance, muscle thickness, and girth were assessed at three timepoints (pre, mid, and post). Subjective pain and perceived exertion were determined immediately after training at two timepoints (mid and post).

Results: Maximum strength ($p < 0.001$), fatigue resistance ($p < 0.001$), muscle thickness ($p < 0.001$), and girth ($p = 0.008$) increased in both groups over time with no differences between groups ($p > 0.05$). During the intervention, the rBFR group exposed significantly lower perceived pain and exertion values compared to cBFR ($p < 0.05$).

Discussion: Resting blood-flow restriction training led to similar gains in strength, fatigue resistance, and muscle hypertrophy as cBFR training while provoking less discomfort and perceived exertion in participants. In summary, rBFR training could provide a meaningful alternative to cBFR as this study showed similar functional and structural changes as well as less discomfort.

Keywords: blood-flow restriction, hypertrophy, maximum strength, fatigue resistance, perceived discomfort

Edited by:
*Adam Zajac,
University School of Physical Education in Wroclaw, Poland*

Reviewed by:
*Michał Krzysztofik,
Jerzy Kukuczka Academy of Physical Education in Katowice, Poland
Ryan Miller,
University of Oklahoma, United States*

****Correspondence:***
*Carsten Schwiete
carsten.schwiete@stud.uni-frankfurt.de*

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *03 February 2021*
Accepted: *12 March 2021*
Published: *30 March 2021*

Citation:
Schwiete C, Franz A, Roth C and Behringer M (2021) Effects of Resting vs. Continuous Blood-Flow Restriction-Training on Strength, Fatigue Resistance, Muscle Thickness, and Perceived Discomfort. Front. Physiol. 12:663665. doi: 10.3389/fphys.2021.663665

INTRODUCTION

It has long been assumed that high mechanical stress is required to achieve improvements in muscle mass and strength. In this context, the American College of Sports Medicine (ACSM) recommends exercising with at least 65% of the one repetition maximum (1RM) to induce hypertrophy in the skeletal muscle (American College of Sports Medicine, 2009). However, there has been an increasing number of studies within the last decades demonstrating that low-intensity strength training with external blood-flow restriction (BFR) induces similar effects compared to resistance training with heavier loads (65 + % 1RM). For instance, significant improvements in muscle mass, strength, and fatigue resistance were reported (Loenneke and Pujol, 2009; Luebbers et al., 2019; Pignanelli et al., 2020). BFR-training is characterized by a short-term, external restriction of the blood flow of the exercising muscles during the training session (Loenneke, 2011). This restriction is usually induced by inflatable cuffs or elastic bands which are wrapped around the proximal parts of the upper or lower extremities and typically applied with an individual cuff pressure ranging between 50 and 200 mmHg (Loenneke et al., 2012). Recent studies indicate that wider cuffs and higher arterial occlusion pressure might be more beneficial for improvements in power output and bar velocity due to increased mechanical compression (Gepfert et al., 2020; Wilk et al., 2020b,c). During continuous BFR (cBFR)-training, the cuffs are usually inflated before the exercise and deflated once the exercise is carried out. Since the cuffs are kept inflated throughout the entire exercise, the applied pressure alters the blood flow through a reduction in arterial influx and a concomitant block of venous return. This creates a state of increased metabolic stress for the exercising muscles due to the inability to remove the accumulated metabolites through the venous system (Pearson and Hussain, 2015).

However, high rates of perceived exertion and discomfort have been reported for cBFR training (Wernbom et al., 2006; Neto et al., 2018). One possible way of reducing discomfort might be the implementation of intermittent BFR-training which (1) is commonly characterized by deflated cuffs during the resting intervals (Yasuda et al., 2013; Freitas et al., 2019) and (2) has produced significant adaptations regarding hypertrophy (Freitas, 2020) and peak bar velocity (Wilk et al., 2020d). Although this approach leads to a reduced total time under BFR, deflating the cuffs during resting intervals do not seem to alter perceptual responses (Freitas et al., 2019). Alternatively, another way of BFR-training could be applied by solely inflating the cuffs during resting intervals (rBFR). Briefly, contractions of 15–20% of the maximal voluntary contraction can cause intramuscular pressure that impairs arterial blood flow (De Ruiter et al., 2007). This natural occurring ischemia probably maintains metabolic stress and hypoxia when supplemented with external restriction during inter-set rest. Termed as "metabolic freeze," this has already been theorized by Okita et al. (2019). Using a cross-sectional approach, the authors reported that the resting BFR protocol lead to significant lower rates of perceived exertion (RPE). A recent work by Wilk et al. (2021) also showed enhanced bar velocity and power output in the bench press after ischemic conditioning during resting intervals compared to a control group without ischemic conditioning. Those results indicate possible benefits of resting BFR in terms of explosiveness and strength development in professional athletes.

Therefore, the main aim of this study was to find out whether (1) rBFR reveals lower rates of discomfort and perceived exertion than cBFR while (2) inducing comparable gains in hypertrophy, maximum strength, and fatigue resistance. Referring to what has been reported for strength development (Wilk et al., 2021), we hypothesize that rBFR induces similar hypertrophy, maximum strength, and fatigue resistance adaptations compared to cBFR.

MATERIALS AND METHODS

Participants

Since data are lacking to adequately calculate an effect size regarding an rBFR protocol, no *a priori* power analysis was conducted. Instead, we agreed to recruit 21 recreationally trained participants in order to account for dropouts while having enough power to examine possible between-group differences. As there were two dropouts due to lacking protocol compliance, only 19 participants (all male, 22.8 ± 1.8 years, 78.9 ± 3.71 kg, 179.6 ± 4.3 cm) were included in the data analysis (**Figure 1**). All participants were randomly assigned to two groups (continuous BFR = cBFR, n = 10 and resting BFR = rBFR, n = 9) using an online tool ("Random Team Generator").[1] While the cBFR group had their cuffs inflated throughout all load sets and rests, the rBFR group applied BFR only during the rest periods.

Participants were only included when they (1) were healthy and physically active and (2) had experience in resistance training, quantified as a resistance training experience of 2–3 times a week with an average of 10 sets for each muscle group. Exclusion criteria included neurological or cardiovascular disorders and acute or lasting injuries on the lower extremities. Both groups were instructed to maintain their usual training and living habits over the period of the study. The participants were extensively elucidated about the risks of BFR training, data protection, privacy, the study goal, as well as the study conduction procedure. Particularly, interventional strains and requirements were highlighted. Every individual voluntarily agreed and provided written consent to participate in the study. The study was approved by the local ethics committee (ethics committee department 05, Goethe University, Frankfurt am Main, Germany, no.: 2018-69) and was conducted in accordance to the ethical standards set by the declaration of Helsinki. Furthermore, it was retrospectively registered at the German register for clinical trials (DRKS00023510/11.11.2020).

Study Design and Training Protocol

The 6-week parallel research design investigated the effects of rBFR and cBFR on maximum strength, fatigue resistance, muscle thickness girth, pain sensation, and perceived exertion. The study was preceded by a familiarization phase to accustom the participants to the cuff pressure and the feeling of BFR during training. For familiarization, the participants completed the training protocol, but only with the weight of the sled (20 kg). On the same occasion, pretests on the 45° leg press were performed that consisted of a 1RM test and a fatigue test (AMRAP). Muscle thickness was determined by ultrasound and thigh circumference was measured with a tape. Pain sensation was assessed using visual analog scale and rating of perceived exertion was quantified using the Borg scale. The same tests were repeated after 3 (mid) and 6 weeks (post).

Both groups had two supervised BFR-training sessions per week, as suggested by (Patterson et al., 2019). Each session

[1]www.jamestease.co.uk/team-generator

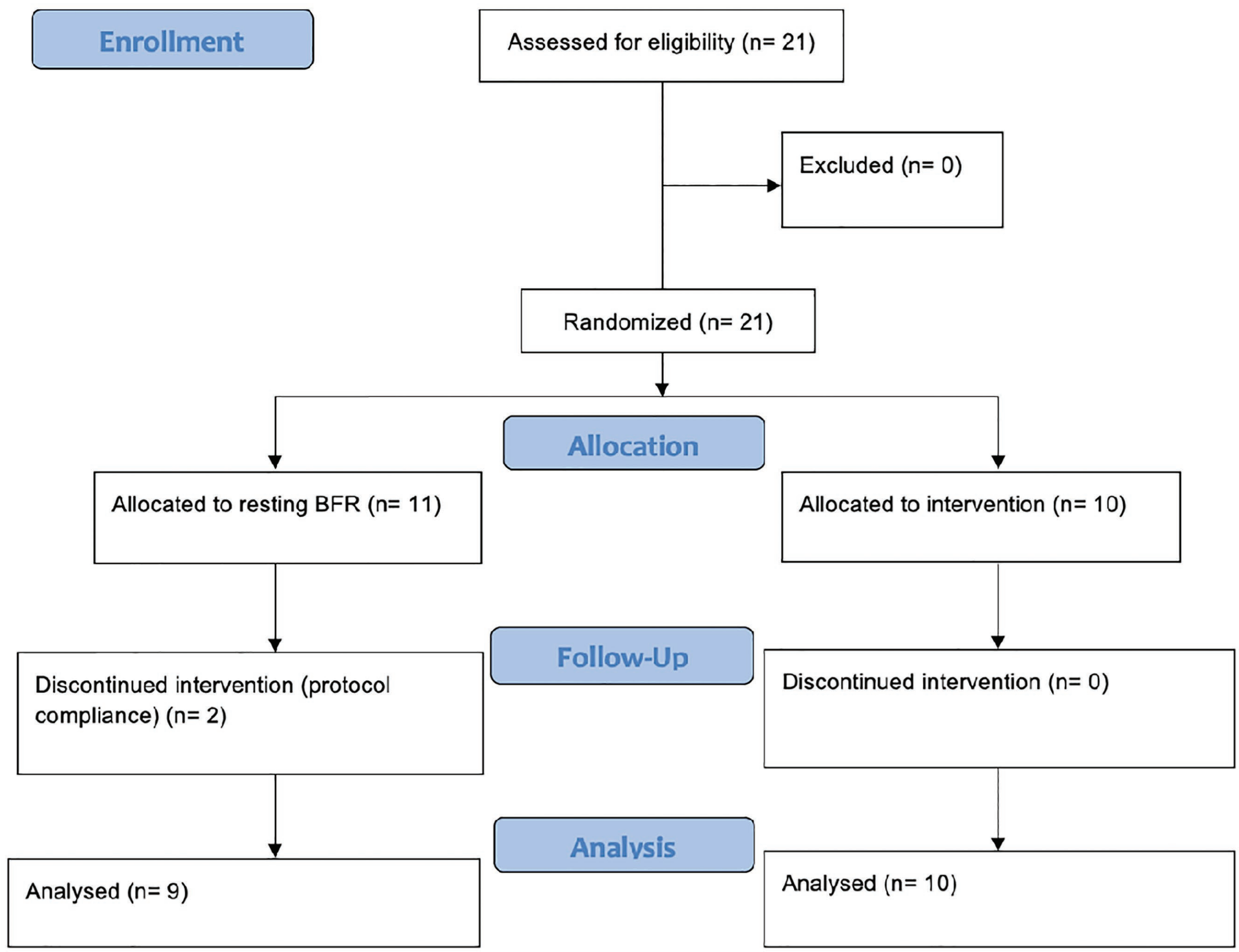

FIGURE 1 | Flow chart of study conduction (Moher et al., 2001).

lasted approximately 15 min, equating to an average workload of 30 min per week (Luebbers et al., 2019). We aimed for a between-training recovery of at least 1–2 days (**Figure 2**).

For both groups, each training session started with a warm-up set on the 45° leg press without BFR cuffs. Warm-up set weight was the same as during the BFR training (20% based on the 1RM as assessed in pre) and differed between 8 and 10 repetitions. The exercise protocol was based on a previous study by Madarame et al. (2013). Briefly, four sets were performed by both groups (30-15-15-15 repetitions) with 30 s of in-between-sets rest (**Table 1**). If the participants were able to complete two protocols with the predetermined weight the load was increased by 2.5 kg.

To account for contraction velocity, a metronome was used and set to 40 beats per minute as previously used in a similar protocol (Freitas et al., 2019). This resulted in contraction velocity of 1.5 s each concentric and eccentric phase. A hip-wide position was selected for all subjects and adjusted until 90° hip and knee flexion was achieved at the lowest position of the movement. Immediately after the completion of each set, all participants were instructed to move their legs into a more comfortable position so that both knees and the hip were relaxed.

Blood-Flow Restriction

Inflatable cuffs (Signature Series BFR bands, Scottsdale, AZ, United States) were used for BFR-training which were 8 cm (3 inches) wide and 76 cm (30 inches) long. The cuffs were always positioned as proximally as possible to the thigh. Occlusion pressure was individually determined by Doppler ultrasound (Acuson X150, Siemens, Munich, Germany) with the participants lying in a supine position (Lixandrão et al., 2019). For blood-flow restriction, we determined the blood flow of the *arteria tibialis posterior* 5 cm proximal of the medial malleolus (Behringer et al., 2017). The cuffs were then inflated until no arterial pulse was visible or audible on the Doppler ultrasound (Husmann et al., 2018).

For the exercise protocol, 80% of the individual arterial occlusion pressure was prescribed as recommend by Lixandrão et al. (2015) in order to increase maximum strength and muscle thickness. In the rBFR group, the cuffs were inflated prior to

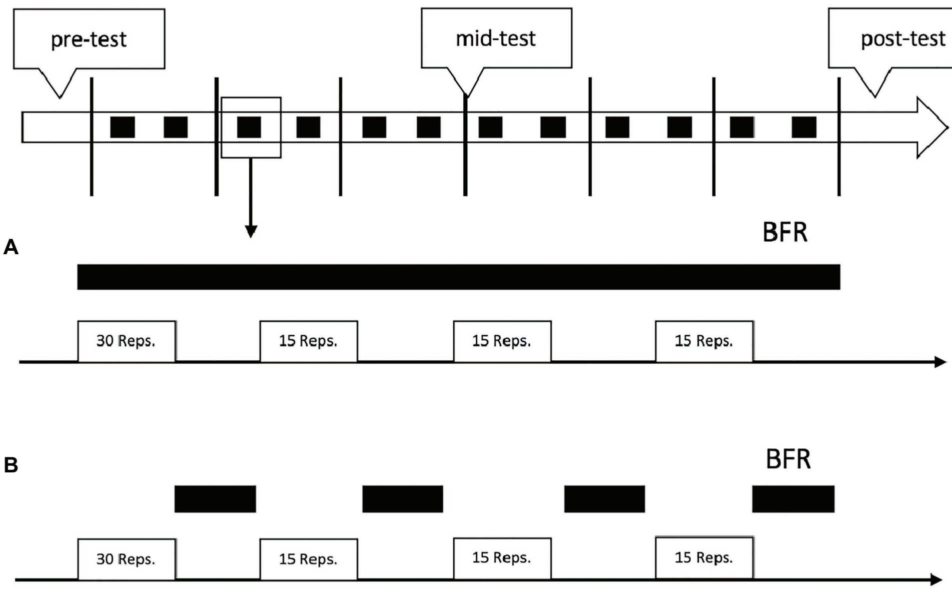

FIGURE 2 | Schematic overview of the study design and training protocol. The black squares in the top figure represent the blood-flow restriction (BFR)-trainings. The black bars in **(A,B)** indicate the time under BFR during each training. **(A)** represents the training regimen of the continuous BFR (cBFR) group and **(B)** the training regimen of the resting BFR (rBFR) group.

TABLE 1 | Overview of training variables.

Protocol	Sets	Repetitions	1RM (%)	Rest interval (s)	Occlusion pressure (mmHg)
rBFR	4	30-15-15-15	20	30	183.33 ± 10.00
cBFR	4	30-15-15-15	20	30	186.00 ± 15.78

rBFR, resting BFR; cBFR, continuous BFR; 1RM, one repetition maximum. Data in means ± SD.

the training protocol and immediately opened so that they were loose on the thigh but did not exert pressure. At the end of the set, both cuffs were closed as quickly as possible and reopened at the end of the interval. Since the cuffs lost some pressure after the first one or two sets, both hand pumps were constantly controlled, and the pressure readjusted if necessary. Contrarily, the cBFR group had continuous external BFR during working sets and resting intervals as described in various studies (Loenneke and Pujol, 2009; Yasuda et al., 2013; Freitas et al., 2019). An additional resting interval was added to both BFR protocols to increase comparability.

Measurements

To avoid possible measuring interferences, all measures were obtained at least 48 h after a resistance training session (Yu et al., 2015; Yitzchaki et al., 2020).

Maximal Strength

Since the loads of a 45° leg press can be very high, the test persons' safety must be considered. We, therefore, estimated the 1RM from the 5-repetition maximum using Lombardi's equation: $1RM = R^{0.1} \times W$, where R represents the repetitions and W the used weight. McNair et al. (2011) reported an excellent ICC of 0.97 for the Lombardi equation using the leg press. The study followed the recommendation of a recent review on strength testing (Grgic et al., 2020). Briefly, following a 5-min warm-up on the bicycle ergometer, the participants completed two submaximal warm-up sets on the leg press. Eight repetitions were performed with 50% of the estimated 1RM and three repetitions with 70% (Niewiadomski et al., 2008). There was a 3-min break between the sets to ensure sufficient regeneration. Thereafter, the resistance was increased until the participants were only able to perform five repetitions or less. The cadence of the RM tests was similar to contraction velocity of the training regimen, as emphasized by Wilk et al. (2020a). If the participants were not able to perform more than five repetitions, the test was stopped. Reliability measures showed excellent outcomes between pre, mid, and post (ICC = 0.903; CI: 0.808–0.958).

Fatigue Resistance

During the fatigue test, participants were asked to perform as many repetitions as possible with 50% of the previously estimated 1RM on the 45° leg press. The fatigue test was stopped when the participants were unable to perform any further repetitions over the full range of motion (ROM) or when volitional failure was reached. A metronome was used and set to 40 beats per minute to provide the same standards as used in the regular exercise protocol.

Muscle Thickness and Girth

Muscle thickness of the *M. rectus femoris* was measured using a B-mode transversal plane ultrasound (model Acuson X300, Siemens, Munich, Germany) using a 10 MHz linear-array probe (50 mm width). The participants were positioned as described above. For this study, muscle thickness of the *M. rectus femoris* was measured. The measuring point was halfway between the origin (*spina iliaca anterior inferior*) and the attachment (*tuberositas tibiae*) of the muscle. A water-resistant marking was placed at 50% of the segment length to increase repeatability (Rustani et al., 2019). The probe was then held over the marking with minimal pressure. A screenshot was taken from the ultrasound image and thickness was measured. Muscle thickness was defined as the distance between the lower margin of the upper fascia and the upper margin of the lower fascia of the *M. rectus femoris*. At each time point (pre-mid-post), three measurements were taken per participant and a mean value was determined from these three values. The ultrasound images were saved and used as a reference for mid- and post-tests to measure the muscle at the same location (Giles et al., 2017). In our lab, the ICC of muscle thickness using ultrasound has been found to be excellent (ICC = 0.963; CI: 0.913–0.985) in a sample size of $n = 21$, supporting its re-test reliability.

After measuring muscle thickness, girth was determined with the help of a tape. The participants were measured at the same point and in the same position as described for the ultrasound measurement (Doxey, 1987; Douciette, 1992).

Perceived Exertion and Pain Sensation

Rates of perceived exertion was immediately assessed after the training using a BORG scale which ranged from 6 (no effort at all) to 20 (maximum effort). RPE scales are well-accepted tools to evaluate exertion in resistance training populations (Helms et al., 2020). Pain sensation was additionally determined using visual analog scale (VAS). The scale was 10 cm long (3.94 inches) and ranged from "no pain" to "worst pain imaginable" (Heller et al., 2016). Directly after the training, the participants were asked to mark the line as accurately as possible relating to their experienced pain. RPE and pain sensation were both measured with the BFR cuffs deflated. All participants were instructed about the scales and their proper utilization prior to each assessment.

Data Presentation and Statistical Analysis

The data are presented as mean values ± SD. When adequate, effect sizes were reported. Boxplots and Shapiro-Wilk test were used to determine outliers and normal distribution of the data, respectively. A general linear two-way repeated measures ANOVA [time (3) × group (2)] with pairwise comparisons (Bonferroni correction) was performed separately for each dependent variable (SPSS version 24.0, Chicago, IL, United States). When a significant time × group interaction was revealed, simple main effects were examined separately using (a) a repeated-measures ANOVA (time) and (b) univariate ANCOVA covarying for t_1 (group). Contrarily, if no significant interaction between group and time could be found, main effects for groups and time were interpreted as suggested by statistic-laerds (statistics.laerd.com, 2021). ANCOVA was performed additionally for the mid-post variables (RPE, VAS) using mid-values as the covariate. Statistical significance was set at $p < 0.05$.

RESULTS

Twelve BFR training sessions in total were performed by each participant during the course of the study with no differences between the groups ($p > 0.05$). During the intervention, there were no dropouts or injuries attributable to BFR. In sum, the four sets and the resting intervals resulted in 6 min training per individual session. With respect to the training protocols, the rBFR group increased their training weight from 59.29 ± 9.32 to 65.28 ± 7.75 kg (Δ +5.99 kg, 10.10%) over the course of the study. Contrarily, cBFR increased weights from 66.22 ± 17.91 to 68.35 ± 15.09 kg (Δ +2.13, 3.22%). No significant difference in training weight could be revealed for pre ($p = 0.370$), post ($p = 0.845$), or change ($p = 0.845$). Total tonnage was calculated for the training weight using the formula weight × repetitions × sets. While rBFR increased their total tonnage from 4446.43 ± 699.17 to 4895.83 ± 581.28 kg (Δ +449.4 kg, 10.11%), cBFR increased total tonnage in a similar extent [4966.67 ± 1343.62 to 5126.2 ± 1131.93 kg (Δ +159.58 kg, 3.21%)]. Since training weight was the only variable which changed throughout the study, total tonnage did not differ at any timepoint or between groups over time ($p > 0.05$). Descriptive are presented in **Table 2**.

Muscle Strength

Both rBFR and cBFR increased muscle strength from 314.8 ± 42.3 to 341.7 ± 32.2 kg (Δ +26.9 kg, 8.5%) from 335.1 to 366.3 kg (Δ +31.2 kg, 9.3%), respectively (**Figure 3**). As the Box's test revealed statistical significance, we separately assessed change over time for each group (ANOVA with repeated measures) as well as differences between groups for each time point (univariate ANOVA). Simple main effect time revealed a significant difference in maximum strength for rBFR $F(1.141, 9.128) = 5.076$, $p = 0.047$ between pre and post and for cBFR F(1.139, 10.248 = 32.904 = $p < 0.001$) between pre and mid, pre and post, as well as mid and post ($p < 0.05$). Contrarily, no significant differences between the groups could be seen for pre ($p = 0.508$), mid ($p = 0.270$), and post ($p = 0.431$), respectively.

Fatigue Resistance

Both groups increased their fatigue resistance (rBFR: 28.2–38.3 ± 8.1 repetitions, Δ +10.1 reps., 35.8%; cBFR: 30.9–38.8 ± 7.1 repetitions; Δ +7.9 reps., 25.6%; **Figure 3**). Since the time × group interaction did not reveal significance ($p = 0.545$), main effects were interpreted. While both groups increased their fatigue resistance over time $F(2,34) = 26.974$, $p < 0.001$, we could not observe any between-group differences ($p = 0.442$). Pairwise comparisons revealed significant differences between pre- and mid ($p = 0.002$), mid and post ($p = 0.002$), and pre and post ($p < 0.001$).

TABLE 2 | rBFR, resting BFR; cBFR, continuous BFR; 1RM, one repetition maximum; FR, fatigue resistance; MT, muscle thickness; VAS, visual analog scale; M, mean; SD, standard deviation; CI, confidence interval; η^2, partial eta squared; d_z, Cohen's d.

		rBFR			cBFR		
		Pre	**Mid**	**Post**	**Pre**	**Mid**	**Post**
1RM (Kg)	M	314.78	316.00	341.44*,†	335.10	351.40*	366.30*,†
	SD	±42.25	±42.19	±32.26	±80.64	±83.84	±87.01
	CI (95%)	282.30–347.25	283.57–348.43	316.65–366.24	277.41–392.79	291.42–411.38	304.05–428.55
	η^2			0.39			0.79
FR (reps.)	M	28.22	32.44*	38.33*,†	30.90	35.40*	38.80*,†
	SD	±7.77	±5.27	±8.11	±4.31	±5.17	±7.11
	CI	22.25–34.20	28.39–36.50	32.10–44.57	27.82–33.98	31.70–39.10	33.71–43.89
	η^2			0.65			0.57
MT (mm)	M	22.93	23.20	23.62*,†	22.03	22.40*	22.91*,†
	SD	±2.87	±2.80	±2.94	±1.59	±1.51	±1.53
	CI	20.72–25.14	21.05–25.35	21.36–25.88	20.89–23.17	21.32–23.48	21.81–24.01
	η^2			0.80			0.76
Girth (mm)	M	54.62	54.89	55.02	55.10	55.45	55.89*
	SD	±2.51	±2.42	±2.41	±3.36	±3.10	±3.37
	CI	52.69–56.55	53.03–56.75	53.17–56.87	52.70–57.50	53.23–57.67	53.48–58.30
	η^2			0.15			0.35
BORG (RPE)	M		13.22	13.89		14.90#	14.00†
	SD		±1.30	±1.36		±1.10	±1.25
	CI		12.22–14.22	12.84–14.94		14.11–15.69	13.11–14.89
	d_z			0.47			−0.82
VAS (mm)	M		28.33	28.00		48.50#	44.20
	SD		±14.54	±10.59		±13.92	±10.30
	CI		17.15–39.51	19.86–36.14		38.54–58.46	36.83–51.57
	d_z			−0.04			−0.53

**Significant difference to pre-value.*

#Significant difference between groups.

†Significant difference between mid and post.

Muscle Thickness and Girth

Muscle thickness increased from 22.9 to 23.6 mm (Δ +0.7 mm, 3.05%) in the rBFR and from 22.0 to 22.9 mm (Δ +0.9 mm, 4.1%) in the cBFR group (**Figure 3**). The same trend could be observed in girth increasing from 54.6 to 55.0 cm (Δ +0.4 mm, 0.73%) in the rBFR and from 55.1 to 55.9 cm (Δ +0.8 cm, 1.45%) in cBFR group. There was no significant time × group interaction for muscle thickness $F(1.390, 23.637) = 0.849$, $p = 0.402$ or girth $F(2, 34) = 0.670$, $p = 0.518$. While muscle thickness ($p = 0.970$) and thigh circumference change ($p = 0.638$) did not differ between groups, both groups significantly increased muscle thickness $F(1.390, 23.637) = 57.736$, $p < 0.001$ and girth $F(2,34) = 5.626$, $p = 0.008$ over the study course. Pairwise comparisons revealed significant differences between pre- and mid, mid and post, and pre and post for muscle thickness (all $p < 0.001$) and pre and post for girth ($p = 0.043$).

VAS and BORG Scale

When analyzed for between-group differences, rBFR revealed a significant lower pain sensation (VAS) for mid $F(1,17) = 9.530$, $p = 0.007$ as well as perceived exertion for mid $F(1,17) = 9.269$, $p = 0.007$ when compared to cBFR (**Figure 4**). However, this between-group difference was no longer seen at post for either VAS ($p = 0.266$) or Borg scale ($p = 0.855$). Gain scores were additionally calculated to account for changes over time. However, no significant difference regarding delta change was found for either VAS (rBFR: Δ −0.33 ± 8.47; cBFR: Δ −4.33 ± 8.17, $p = 0.266$) or Borg scale (rBFR: Δ +0.66 ± 1.41, cBFR: Δ −0.90 ± 1.10, $p = 0.249$).

DISCUSSION

The main aims of this 6-week longitudinal study were to investigate whether rBFR (1) reveals lower rates of discomfort and perceived exertion compared to cBFR and (2) induces hypertrophy, strength gains, and fatigue resistance comparable to that of cBFR. To the authors' best knowledge, the present study is the first to investigate the effects of rBFR training in a longitudinal fashion. All previous studies were cross-sectional and, therefore, limited to acute effects (Teixeira et al., 2018; Okita et al., 2019). In contrast to standard BFR training, the present study applied external restriction during the resting intervals (rBFR) with the aim of maximal metabolite accumulation.

With respect to discomfort, a significant lower pain perception while exercising (VAS) was revealed in the rBFR group at mid ($p = 0.007$), which was also seen in perceived exertion at mid ($p = 0.007$). These results are consistent with those of a previous study by Fitschen et al. (2014). In their study, the intermittent group recorded lower ratings of pain compared to the continuous protocol.

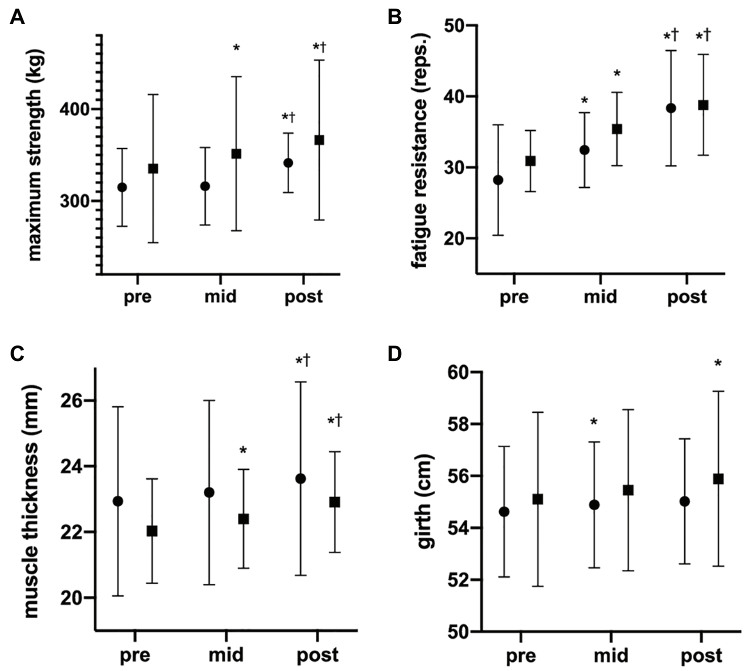

FIGURE 3 | Development of maximum strength, fatigue resistance, muscle thickness, and girth. The data are presented as mean values ± SD. The graphs show **(A)** 1RM, **(B)** fatigue resistance, **(C)** muscle thickness, and **(D)** girth changes during the 6 weeks of the study (pre = after 0 weeks, mid = after 3 weeks, and post = after 6 weeks). [*] = statistically significant difference to pre-value; • = rBFR, ■ = cBFR. †Significant difference between mid and post.

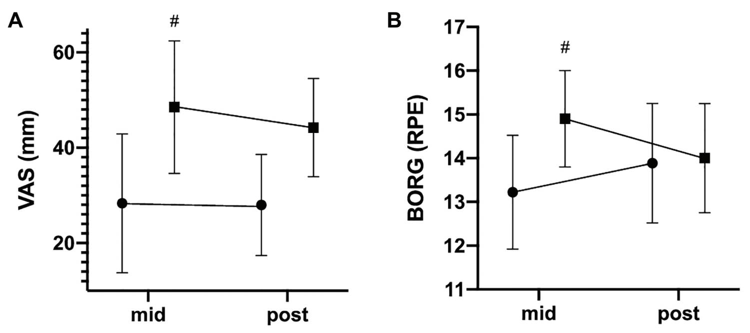

FIGURE 4 | Development of perceived exertion and pain sensation. The data are presented as mean values ± SD. The graphs show the participants' **(A)** pain sensation (VAS) and **(B)** perceived exertion on the Borg scale after 3 and 6 weeks. #statistically significant difference between groups. • = rBFR, ■ = cBFR.

Contrary, Freitas et al. (2019) did not find any differences between the intermittent and continuous BFR training groups in regard discomfort. Although using a training protocol similar to this study (Freitas et al., 2019), the intermittent BFR application differs to our work since we applied external restriction only during resting intervals thus limiting comparability. Since the rBFR group spend less time under BFR in total, we hypothesize that the lower levels of RPE and pain sensation result from reduced absolute metabolic stress, which is associated with higher levels of discomfort (Lagally et al., 2002). While the reasons explaining the differences between the intermittent protocols as well as the underlying mechanisms leading to lower discomfort in rBFR remain unclear, rBFR seems to be a viable alternative for athletes seeking to reduce high levels of discomfort during continuous BFR. Notably, between-group differences were no longer seen at post for both VAS ($p = 0.266$) and RPE ($p = 0.855$) indicating small to medium familiarization effects in cBFR (dz = −0.53). However, familiarization effects must be interpreted with great caution as delta change did not reveal significant group-differences probably attributed to high individual variance.

The present study revealed significant increases in maximum strength, fatigue resistance, muscle thickness, and girth with no differences between-groups. Maximum strength increased by Δ +26.9 kg (8.5%) and Δ +31.2 kg (9.3%) in the rBFR and cBFR group, respectively. Notably, effect sizes favor strength development in the cBFR condition ($\eta^2 = 0.79$) compared to rBFR ($\eta^2 = 0.39$) indicating that cBFR might be more effective in the long-term. However, rBFR still evoked a significant increase in maximum strength which is in line with previous research for continuous BFR-training (Yamanaka et al., 2012; Cook et al., 2014).

Fatigue tolerance also increased in both groups with the rBFR group improving by 10.1 repetitions (35.8%) and the cBFR group improving by +7.9 repetitions (25.6%). This is in line with previous findings (Fahs et al., 2015) reporting that cBFR can improve fatigue resistance in skeletal muscles by extending the resting levels of muscular glycogen and ATP. Briefly, BFR-training creates a hypoxic state in the trained muscle and leads to an accumulation of metabolites due to an increased ATP-hydrolysis outside the mitochondria (Robergs et al., 2004; Allen et al., 2008). Even though cBFR induces superior metabolic stress when compared to an intermittent BFR protocol relating to our findings (Suga et al., 2012), rBFR might be sufficient as well to alter local muscular environment.

In the context of structural changes, both groups were able to achieve significant improvements in muscle thickness and girth. Muscle thickness increased by Δ + 0.7 mm (3.05%) in the rBFR group and Δ + 0.9 mm (4.1%) in the cBFR group (both $p < 0.001$). Girth improved by Δ + 0.4 cm (0.73%) in the rBFR group and Δ + 0.8 cm (1.45%) in the cBFR group ($p = 0.008$). Since both groups significantly improved muscle thickness and girth, both continuous and resting BFR seem to elicit region-specific muscle hypertrophy in recreationally trained males. Various studies have reported significant muscle hypertrophy following BFR-training, mainly explained through high levels of metabolic stress (Yasuda et al., 2011; Conceição et al., 2019; Ramis et al., 2020). Current theory lists metabolite-induced fatigue and cell swelling and as the most likely mechanisms underpinning BFR-training benefits. Relating to the results reported in this study, inflating the cuffs only during resting intervals (rBFR) might already induce a sufficient accumulation of metabolic stress. This is in line with recent research reporting no physiological differences between intermittent and continuous BFR. In a previous study, Okita et al. (2019) compared several low-intensity BFR protocols (20 and 40% 1RM) including intermittent BFR (iBFR; BFR during exercise) and resting BFR (rBFR; BFR during resting intervals) protocols. Contrary to Freitas et al. (2020), they concluded that blood flow might be sufficiently restored when the cuffs are deflated during resting intervals finally leading to hampered muscle hypertrophy. In this context, rBFR might be a more effective strategy to maximize hypertrophy since inflating the cuffs during rest might create a metabolic freeze in the exercising muscles as proposed by Okita et al. (2019). In particular, metabolic stress might be maintained due to the inability of metabolite clearance during resting intervals.

CONCLUSION

In conclusion, our findings indicate that BFR during resting intervals only (rBFR) might serve as an effective alternative to cBFR-training regarding maximum strength, fatigue resistance, and muscle thickness in recreationally trained males. At the same time, participants reported significantly lower discomfort during rBFR compared to cBFR. This could implement rBFR as an effective BFR alternative in professional sports and rehabilitation. Nevertheless, it should be noted that the obtained results refer only to the training regimen used as in this study, which does not have to translate into the same results. Therefore, further research is warranted with those specific populations.

LIMITATIONS

The present study is not free of limitations. All Participants of this study were asked to continue their normal training routine in order to minimize bias in outcomes. Since we did not explicitly account for volume differences between the groups, the obtained results cannot exclusively be attributed to the BFR training. Another limitation of this study is the lack of a control group without BFR. This would have allowed to better evaluate the BFR induced effects of each training protocols. Also, no women were included due to the differences in hypertrophic response to resistance training compared to men.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The present study involving human participants was reviewed and approved by Ethics Committee Department 05, Goethe University, Frankfurt am Main, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to designing the study, analyzing and interpreting the data, and writing and proofreading the manuscript. All authors also approved the content of the manuscript's final version.

ACKNOWLEDGMENTS

We would like to thank all the participants who took part in the study.

REFERENCES

Allen, D. G., Lamb, G. D., and Westerblad, H. (2008). Skeletal muscle fatigue: cellular mechanisms. *Physiol. Rev.* 88, 287–332. doi: 10.1152/physrev.00015.2007

American College of Sports Medicine (2009). American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med. Sci. Sports Exerc.* 41, 687–708. doi: 10.1249/MSS.0b013e3181915670

Behringer, M., Behlau, D., Montag, J. C. K., McCourt, M. L., and Mester, J. (2017). Low-intensity Sprint training with blood flow restriction improves 100-m dash. *J. Strength Cond. Res.* 31, 2462–2472. doi: 10.1519/JSC.0000000000001746

Conceição, M. S., Junior, E. M. M., Telles, G. D., Libardi, C. A., Castro, A., Andrade, A. L. L., et al. (2019). Augmented anabolic responses after 8-wk cycling with blood flow restriction. *Med. Sci. Sports Exerc.* 51, 84–93. doi: 10.1249/MSS.0000000000001755

Cook, C. J., Kilduff, L. P., and Beaven, C. M. (2014). Improving strength and power in trained athletes with 3 weeks of occlusion training. *Int. J. Sports Physiol. Perform.* 9, 166–172. doi: 10.1123/ijspp.2013-0018

De Ruiter, C. J., Goudsmit, J. F. A., Van Tricht, J. A., and De Haan, A. (2007). The isometric torque at which knee-extensor muscle reoxygenation stops. *Med. Sci. Sports Exerc.* 39, 443–453. doi: 10.1249/mss.0b013e31802dd3cc

Douciette, S. A. (1992). The effect of exercise on patellar tracking in lateral patellar compression syndrome. *Am. J. Sports Med.* 20, 434–440. doi: 10.1177/036354659202000412

Doxey, G. E. (1987). Assessing quadriceps Femoris muscle bulk with girth measurements in subjects with patellofemoral pain. *J. Orthop. Sports Phys. Ther.* 9, 177–183. doi: 10.2519/jospt.1987.9.5.177

Fahs, C. A., Loenneke, J. P., Thiebaud, R. S., Rossow, L. M., Kim, D., Abe, T., et al. (2015). Muscular adaptations to fatiguing exercise with and without blood flow restriction. *Clin. Physiol. Funct. Imaging* 35, 167–176. doi: 10.1111/cpf.12141

Fitschen, P. J., Kistler, B. M., Jeong, J. H., Chung, H. R., Wu, P. T., Walsh, M. J., et al. (2014). Perceptual effects and efficacy of intermittent or continuous blood flow restriction resistance training. *Clin. Physiol. Funct. Imaging* 34, 356–363. doi: 10.1111/cpf.12100

Freitas, E. D., Miller, R. M., Heishman, A. D., Ferreira-Júnior, J. B., Araújo, J. P., and Bemben, M. G. (2020). Acute physiological responses to resistance exercise with continuous versus intermittent blood flow restriction: a randomized controlled trial. *Front. Physiol.* 11:132. doi: 10.3389/fphys.2020.00132

Freitas, E. D. S., Miller, R. M., Heishman, A. D., Aniceto, R. R., Silva, J. G. C., and Bemben, M. G. (2019). Perceptual responses to continuous versus intermittent blood flow restriction exercise: a randomized controlled trial. *Physiol. Behav.* 212:112717. doi: 10.1016/j.physbeh.2019.112717

Gepfert, M., Krzysztofik, M., Kostrzewa, M., Jarosz, J., Trybulski, R., Zajac, A., et al. (2020). The acute impact of external compression on back squat performance in competitive athletes. *Int. J. Environ. Res. Public Health* 17:4674. doi: 10.3390/ijerph17134674

Giles, L., Webster, K. E., McClelland, J., and Cook, J. L. (2017). Quadriceps strengthening with and without blood flow restriction in the treatment of patellofemoral pain: a double-blind randomised trial. *Br. J. Sports Med.* 51, 1688–1694. doi: 10.1136/bjsports-2016-096329

Grgic, J., Lazinica, B., Schoenfeld, B. J., and Pedisic, Z. (2020). Test–retest reliability of the one-repetition maximum (1RM) strength assessment: a systematic review. *Sports Med. Open* 6, 1–31. doi: 10.1186/s40798-020-00260-z

Heller, G. Z., Manuguerra, M., and Chow, R. (2016). How to analyze the visual analogue scale: myths, truths and clinical relevance. *Scand. J. Pain* 13, 67–75. doi: 10.1016/j.sjpain.2016.06.012

Helms, E. R., Kwan, K., Sousa, C. A., Cronin, J. B., Storey, A. G., and Zourdos, M. C. (2020). Methods for regulating and monitoring resistance training. *J. Hum. Kinet.* 74:20. doi: 10.2478/hukin-2020-0011

Husmann, F., Mittlmeier, T., Bruhn, S., Zschorlich, V., and Behrens, M. (2018). Impact of blood flow restriction exercise on muscle fatigue development and recovery. *Med. Sci. Sports Exerc.* 50, 436–446. doi: 10.1249/MSS.0000000000001475

Lagally, K. M., Robertson, R. J., Gallagher, K. I., Goss, F. L., Jakicic, J. M., Lephart, S. M., et al. (2002). Perceived exertion, electromyography, and blood lactate during acute bouts of resistance exercise. *Med. Sci. Sports Exerc.* 34, 552–559. doi: 10.1097/00005768-200203000-00025

Lixandrão, M. E., Roschel, H., Ugrinowitsch, C., Miquelini, M., Alvarez, I. F., and Libardi, C. A. (2019). Blood-flow restriction resistance exercise promotes lower pain and ratings of perceived exertion compared with either high- or low-intensity resistance exercise performed to muscular failure. *J. Sport Rehabil.* 28, 706–710. doi: 10.1123/jsr.2018-0030

Lixandrão, M. E., Ugrinowitsch, C., Laurentino, G., Libardi, C. A., Aihara, A. Y., Cardoso, F. N., et al. (2015). Effects of exercise intensity and occlusion pressure after 12 weeks of resistance training with blood-flow restriction. *Eur. J. Appl. Physiol.* 115, 2471–2480. doi: 10.1007/s00421-015-3253-2

Loenneke, J. P. (2011). Blood flow restriction: the metabolite/volume threshold theory. *Med. Hypotheses* 77, 748–752. doi: 10.1016/j.mehy.2011.07.029

Loenneke, J. P., Fahs, C. A., Rossow, L. M., Sherk, V. D., Thiebaud, R. S., Abe, T., et al. (2012). Effects of cuff width on arterial occlusion: implications for blood flow restricted exercise. *Eur. J. Appl. Physiol.* 112, 2903–2912. doi: 10.1007/s00421-011-2266-8

Loenneke, J. P., and Pujol, T. J. (2009). The use of occlusion training to produce muscle hypertrophy. *Strength and Conditioning Journal* 31, 77–84. doi: 10.1519/SSC.0b013e3181a5a352

Luebbers, P. E., Witte, E. V., Oshel, J. Q., and Butler, M. S. (2019). Effects of practical blood flow restriction training on adolescent lower-body strength. *J. Strength Cond. Res.* 33, 2674–2683. doi: 10.1519/JSC.0000000000002302

Madarame, H., Kurano, M., Fukumura, K., Fukuda, T., and Nakajima, T. (2013). Haemostatic and inflammatory responses to blood flow-restricted exercise in patients with ischaemic heart disease: a pilot study. *Clin. Physiol. Funct. Imaging* 33, 11–17. doi: 10.1111/j.1475-097X.2012.01158.x

McNair, P. J., Colvin, M., and Reid, D. (2011). Predicting maximal strength of quadriceps from submaximal performance in individuals with knee joint osteoarthritis. *Arthritis Care Res.* 63, 216–222. doi: 10.1002/acr.20368

Moher, D., Schulz, K. F., and Altman, D. G. (2001). The CONSORT statement: revised recommendations for improving the 429 quality of reports of parallel group randomized trials. *BMC Med. Res. Methodol.* 1:2. doi: 10.1186/1471-2288-1-2

Neto, G. R., Novaes, J. S., Salerno, V. P., Gonçalves, M. M., Batista, G. R., and Cirilo-Sousa, M. S. (2018). Does a resistance exercise session with continuous or intermittent blood flow restriction promote muscle damage and increase oxidative stress? *J. Sports Sci.* 36, 104–110. doi: 10.1080/02640414.2017.1283430

Niewiadomski, W., Laskowska, D., Gąsiorowska, A., Cybulski, G., Strasz, A., and Langfort, J. (2008). Determination and prediction of one repetition maximum (1RM): safety considerations. *J. Hum. Kinet.* 19, 109–120. doi: 10.2478/v10078-008-0008-8

Okita, K., Takada, S., Morita, N., Takahashi, M., Hirabayashi, K., Yokota, T., et al. (2019). Resistance training with interval blood flow restriction effectively enhances intramuscular metabolic stress with less ischemic duration and discomfort. *Appl. Physiol. Nutr. Metab.* 44, 759–764. doi: 10.1139/apnm-2018-0321

Patterson, S. D., Hughes, L., Warmington, S., Burr, J., Scott, B. R., Owens, J., et al. (2019). Blood flow restriction exercise: considerations of methodology, application, and safety. *Front. Physiol.* 10:533. doi: 10.3389/fphys.2019.00533

Pearson, S. J., and Hussain, S. R. (2015). A review on the mechanisms of blood-flow restriction resistance training-induced muscle hypertrophy. *Sports Med.* 45, 187–200. doi: 10.1007/s40279-014-0264-9

Pignanelli, C., Petrick, H. L., Keyvani, F., Heigenhauser, G. J. F., Quadrilatero, J., Holloway, G. P., et al. (2020). Low-load resistance training to task failure with and without blood flow restriction: muscular functional and structural adaptations. *Am. J. Phys. Regul. Integr. Comp. Phys.* 318, R284–R295. doi: 10.1152/ajpregu.00243.2019

Ramis, T. R., Muller, C. H. d. L., Boeno, F. P., Teixeira, B. C., Rech, A., Pompermayer, M. G., et al. (2020). Effects of traditional and vascular restricted strength training program with equalized volume on isometric and dynamic strength, muscle thickness, Electromyographic activity, and endothelial function adaptations in young adults. *J. Strength Cond. Res.* 34, 689–698. doi: 10.1519/JSC.0000000000002717

Robergs, R. A., Ghiasvand, F., and Parker, D. (2004). Biochemistry of exercise-induced metabolic acidosis. *Am. J. Phys. Regul. Integr. Comp. Phys.* 287, R502–R516. doi: 10.1152/ajpregu.00114.2004

Rustani, K., Kundisova, L., Capecchi, P. L., Nante, N., and Bicchi, M. (2019). Ultrasound measurement of rectus femoris muscle thickness as a quick screening test for sarcopenia assessment. *Arch. Gerontol. Geriatr.* 83, 151–154. doi: 10.1016/j.archger.2019.03.021

Suga, T., Okita, K., Takada, S., Omokawa, M., Kadoguchi, T., Yokota, T., et al. (2012). Effect of multiple set on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *Eur. J. Appl. Physiol.* 112, 3915–3920. doi: 10.1007/s00421-012-2377-x

Teixeira, E. L., Barroso, R., Silva-Batista, C., Laurentino, G. C., Loenneke, J. P., Roschel, H., et al. (2018). Blood flow restriction increases metabolic stress but decreases muscle activation during high-load resistance exercise. *Muscle Nerve* 57, 107–111. doi: 10.1002/mus.25616

Wernbom, M., Augustsson, J., and Thomee, R. (2006). Effects of vascular occlusion on muscular endurance in dynamic knee extension exercise at different submaximal loads. *J. Strength Cond. Res.* 20, 372–377. doi: 10.1519/R-16884.1

Wilk, M., Gepfert, M., Krzysztofik, M., Mostowik, A., Filip, A., Hajduk, G., et al. (2020a). Impact of duration of eccentric movement in the one-repetition maximum test result in the bench press among women. *J. Sports Sci. Med.* 19, 317–322.

Wilk, M., Gepfert, M., Krzysztofik, M., Stastny, P., Zajac, A., and Bogdanis, G. C. (2020b). Acute effects of continuous and intermittent blood flow restriction on movement velocity during bench press exercise against different loads. *Front. Physiol.* 11:569915. doi: 10.3389/fphys.2020.569915

Wilk, M., Krzysztofik, M., Filip, A., Lockie, R., and Zajac, A. (2020c). The acute effects of external compression with blood flow restriction on maximal strength and strength-endurance performance of the upper limbs. *Front. Physiol.* 11:567. doi: 10.3389/fphys.2020.00567

Wilk, M., Krzysztofik, M., Filip, A., Zajac, A., Bogdanis, G. C., and Lockie, R. G. (2020d). Short-term blood flow restriction increases power output and bar velocity during the bench press. *J. Strength Cond. Res.* doi: 10.1519/JSC.0000000000003649 [Epub ahead of print]

Wilk, M., Krzysztofik, M., Jarosz, J., Krol, P., Leznicka, K., Zajac, A., et al. (2021). Impact of ischemic intra-conditioning on power output and bar velocity of the upper limbs. *Front. Physiol.* 12:626915. doi: 10.3389/fphys.2021.626915

Yamanaka, T., Farley, R. S., and Caputo, J. L. (2012). Occlusion training increases muscular strength in division IA football players. *J. Strength Cond. Res.* 26, 2523–2529. doi: 10.1519/JSC.0b013e31823f2b0e

Yasuda, T., Loenneke, J., Ogasawara, R., and Abe, T. (2013). Influence of continuous or intermittent blood flow restriction on muscle activation during low-intensity multiple sets of resistance exercise. *Acta Physiol. Hung.* 100, 419–426. doi: 10.1556/APhysiol.100.2013.4.6

Yasuda, T., Ogasawara, R., Sakamaki, M., Ozaki, H., Sato, Y., and Abe, T. (2011). Combined effects of low-intensity blood flow restriction training and high-intensity resistance training on muscle strength and size. *Eur. J. Appl. Physiol.* 111, 2525–2533. doi: 10.1007/s00421-011-1873-8

Yitzchaki, N., Zhu, W. G., Kuehne, T. E., Vasenina, E., Dankel, S. J., and Buckner, S. L. (2020). An examination of changes in skeletal muscle thickness, echo intensity, strength and soreness following resistance exercise. *Clin. Physiol. Funct. Imaging* 40, 238–244. doi: 10.1111/cpf.12630

Yu, J.-Y., Jeong, J.-G., and Lee, B.-H. (2015). Evaluation of muscle damage using ultrasound imaging. *J. Phys. Ther. Sci.* 27, 531–534. doi: 10.1589/jpts.27.531

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Physiology

REVIEW
published: 28 June 2021
doi: 10.3389/fphys.2021.678407

Check for updates

Blood Flow Restriction Training: To Adjust or Not Adjust the Cuff Pressure Over an Intervention Period?

Mikhail Santos Cerqueira[1], Eduardo Caldas Costa[2], Ricardo Santos Oliveira[2], Rafael Pereira[3] and Wouber Hérickson Brito Vieira[1]*

[1] Neuromuscular Performance Analysis Laboratory, Department of Physical Therapy, Federal University of Rio Grande do Norte, Natal, Brazil, [2] Department of Physical Education, Federal University of Rio Grande do Norte, Natal, Brazil, [3] Integrative Physiology Research Center, Department of Biological Sciences, Universidade Estadual do Sudoeste da Bahia (UESB), Jequié, Brazil

OPEN ACCESS

Edited by:
Adam Zajac,
University School of Physical Education in Wrocław, Poland

Reviewed by:
Jonato Prestes,
Catholic University of Brasilia (UCB), Brazil
Gilberto Candido Laurentino,
University of São Paulo, Brazil

****Correspondence:***
Wouber Hérickson Brito Vieira
wouber.vieira@ufrn.br

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *09 March 2021*
Accepted: *02 June 2021*
Published: *28 June 2021*

Citation:
Cerqueira MS, Costa EC, Santos Oliveira R, Pereira R and Brito Vieira WH (2021) Blood Flow Restriction Training: To Adjust or Not Adjust the Cuff Pressure Over an Intervention Period? Front. Physiol. 12:678407. doi: 10.3389/fphys.2021.678407

Blood flow restriction (BFR) training combines exercise and partial reduction of muscular blood flow using a pressured cuff. BFR training has been used to increase strength and muscle mass in healthy and clinical populations. A major methodological concern of BFR training is blood flow restriction pressure (BFRP) delivered during an exercise bout. Although some studies increase BFRP throughout a training intervention, it is unclear whether BFRP adjustments are pivotal to maintain an adequate BFR during a training period. While neuromuscular adaptations induced by BFR are widely studied, cardiovascular changes throughout training intervention with BFR and their possible relationship with BFRP are less understood. This study aimed to discuss the need for BFRP adjustment based on cardiovascular outcomes and provide directions for future researches. We conducted a literature review and analyzed 29 studies investigating cardiovascular adaptations following BFR training. Participants in the studies were healthy, middle-aged adults, older adults and clinical patients. Cuff pressure, when adjusted, was increased during the training period. However, cardiovascular outcomes did not provide a plausible rationale for cuff pressure increase. In contrast, avoiding increments in cuff pressure may minimize discomfort, pain and risks associated with BFR interventions, particularly in clinical populations. Given that cardiovascular adaptations induced by BFR training are conflicting, it is challenging to indicate whether increases or decreases in BFRP are needed. Based on the available evidence, we suggest that future studies investigate if maintaining or decreasing cuff pressure makes BFR training safer and/or more comfortable with similar physiological adaptation.

Keywords: vascular occlusion exercise, kaatsu training, discomfort, perceived, pain, resistance training

INTRODUCTION

Exercise with blood flow restriction (BFR) has been widely implemented in recent years (Patterson et al., 2019) due to increases in strength and muscle mass following low-load resistance training. Individuals with muscle weakness, such as patients with knee osteoarthritis (Cerqueira and de Brito Vieira, 2019), or who aim hypertrophy, such as athletes (Scott et al., 2016), can benefit from

BFR training interventions. BFR is applied using a pneumatic cuff on the proximal aspect of the exercising limb. This cuff blocks venous return and partially occludes arterial blood flow, inducing increased metabolic stress (Suga et al., 2009).

Blood flow restriction pressure (BFRP) is a paramount aspect for exercise prescription with BFR. Historically, the first approach in BFRP application was to choose arbitrary absolute pressures (Takarada et al., 2000) or individualized cuff pressure at the lower limbs based on percentage of systolic blood pressure measured at the arms (Takano et al., 2005). Currently, it is known that BFRP needs to be individualized and adequate to limit muscle arterial blood flow partially with a recommended 40–80% of total restriction pressure (Patterson et al., 2019). Variables such as cuff width, limb circumference, ankle-brachial index, fat and muscle thickness, arterial stiffness, endothelial function, and blood pressure may influence BFRP (Loenneke et al., 2012, 2015; Hunt et al., 2016; Jessee et al., 2016; Bezerra de Morais et al., 2017). Doppler ultrasound (Bezerra de Morais et al., 2017), handheld Doppler (Laurentino et al., 2018), pulse oximetry (Zeng et al., 2019), and predictive equations (Hunt et al., 2016) have been proposed to adequately obtain and individually prescribe BFRP to maximize benefits and minimize discomfort/risks during BFR exercise (Singer et al., 2020; Spitz et al., 2020).

Nevertheless, no clear justification is provided in the literature for BFRP prescription during BFR exercises (Clarkson et al., 2020) and no specific recommendation of whether BFRP should be adjusted or not during a BFR training intervention. Previous studies reported daily or weekly adjustments increasing BFRP during 3–6 weeks of training in young males (Fahs et al., 2012; Crisafulli et al., 2018), while others did not adjust it in patients with musculoskeletal disorders (Bryk et al., 2016; Giles et al., 2017). Studies that observed increased BFRP (Fahs et al., 2012; Crisafulli et al., 2018) along intervention period probably considered relationships between limb circumference and BFRP, where greater gains in limb circumference following training required greater BFRP (Loenneke et al., 2015). However, increases in BFRP may not be imperative to induce neuromuscular adaptations (Lixandrão et al., 2015; Counts et al., 2016), whereas BFRP increments throughout training periods may not attenuate the perceived effort (Hughes et al., 2019).

Although neuromuscular adaptations are more studied, BFR training also promotes cardiovascular adaptations. For instance, arterial blood flow becomes turbulent during BFR exercise, altering central and peripheral hemodynamics (Takano et al., 2005; Hunt et al., 2016). After cuff deflation at the end of BFR exercise, ischemic reperfusion causes shear stress (Patterson and Ferguson, 2010; Hunt et al., 2013) and metabolic stimuli, which may affect vessel adaptations over time (Green et al., 2011). Also, BFR training can increase exercise pressor reflex, which is a reflex-mediated cardiovascular response, via engagement of the muscle metaboreflex (Sundblad et al., 2018; Cristina-Oliveira et al., 2020) and cardiac autonomic changes (Junior et al., 2019). Additionally, systolic blood pressure is directly proportional to BFRP (Loenneke et al., 2015; Bezerra de Morais et al., 2017), and studies showed SBP to reduce over weeks of BFR training (Cezar et al., 2016; Kambič et al., 2019).

Although important, the debate regarding magnitude of BFRP adjustments during training interventions is scarce (Clarkson et al., 2020). Considering that (1) the BFRP changes little over the course of training weeks (Mattocks et al., 2019), (2) the perceived effort tends to decrease throughout training with BFR (Martín-Hernández et al., 2017), and (3) the cardiovascular adaptations may reduce the required BFRP, increases in cuff pressure may unnecessarily cause discomfort, pain and risks (Loenneke et al., 2014; Spitz et al., 2020). In this sense, the present review aimed to discuss the need for BFRP adjustment based on cardiovascular outcomes and provide directions for future studies. Considering the well-established effects of BFR training on neuromuscular adaptations (Hughes et al., 2017; Centner et al., 2019), herein we focused on possible association between BFRP and cardiovascular adaptations induced by BFR training. Nevertheless, neuromuscular adaptations were addressed when necessary.

MATERIALS AND METHODS

An electronic search was conducted from inception to May 2021 on PubMed and Scopus databases to retrieve studies investigating the effects of BFR training on cardiovascular outcomes. Search strategy was restricted to English language literature, and the following terms were combined: "blood flow restriction," "vascular occlusion," "kaatsu training," "exercise," "training," "chronic," "vascular function," "arterial stiffness," "heart rate," "metabolic stress," and "blood pressure." Forward and backward citations were conducted to locate further relevant titles. The following inclusion criteria were adopted: (a) assessment of chronic effects of BFR (>3 weeks training); (b) inclusion of outcomes that may influence directly or indirectly BFRP, such as macro- and microvascular function, arterial compliance, arterial stiffness and diameter, blood pressure, heart rate, and heart rate variability; (c) inclusion of humans older than 18-year-old. Study quality was assessed individually using PEDro scale (Maher et al., 2003).

CARDIOVASCULAR ADAPTATIONS INDUCED BY BLOOD FLOW RESTRICTION TRAINING INTERVENTIONS: WHAT DO WE KNOW SO FAR?

Structural adaptations in the vascular tree can occur due to metabolic changes elicited by hypoxia, mechanical stretch, shear stress, and increased growth factors, such as vascular endothelial growth factor (VEGF) (Hudlicka and Brown, 2009). BFR training can stimulate vascular adaptations, including severe hypoxia and increased expression of VEGF (Gustafsson et al., 1999; Takada et al., 2012). In addition, the reactive hyperemia occurring after BFR can stimulate capillarization (Evans et al., 2010). BFR training has been reported to improve arterial compliance and stiffness, as well as increase arterial diameter (Ozaki et al., 2011; Hunt et al., 2013). During BFR, there is an accumulation of metabolites that culminates in elevated metabolic stress as well as metaboreflex-induced increases in heart rate, blood pressure, and cardiac sympathetic modulation (Junior et al., 2019; Cristina-Oliveira et al., 2020). In the next sections, we discuss the main cardiovascular adaptations related to BFR training and how such adaptations could impact BFRP prescription during BFR training intervention. **Table 1** summarizes the most common cardiovascular outcomes investigated during BFR training interventions and their potential impact on BFRP. A total of 29 studies met inclusion criteria and were included in this narrative review. Characteristics of the included studies and their main findings are shown in **Table 2**.

Macro- and Microvascular Function

Macro- and microvascular function were investigated during BFR training interventions using measures of flow-mediated dilation (FMD), peak of post-occlusive blood flow (reactive hyperemia), and capillarity index. FMD is a measure of NO-dependent endothelial function (i.e., artery dilation following increased blood flow) (Kelm, 2002), calculated as the difference in arterial diameter between pre- and post-blood flow occlusion. Reactive hyperemia and capillarity index are usually measured using plethysmography. The former is defined as the transient increase in blood flow following a period of ischemia (arterial occlusion) (Patterson and Ferguson, 2010) and may be related to capillarity index, an indirect marker of microvascular network expansion that can facilitate muscle oxygen delivery (Evans et al., 2010; Hunt et al., 2013).

The effect of BFR training on macro- and microvascular function is contradictory. Hunt et al. (2013) observed increased popliteal artery FMD of healthy young males 2–4 weeks following unilateral plantar flexion training with BFR (30% of one-repetition maximum [1RM]; 3 sets until failure; 3x/week; BFRP 110 mmHg). Similarly, increased brachial artery FMD was found in healthy young adults following 8 weeks of upper and lower limbs exercises (30% 1RM; 3–4 sets of 21–30 reps; 3x/week; BFRP between 120 and 270 mmHg or based on SBP) (Early et al., 2020; Ramis et al., 2020); and healthy older adults following 12 weeks of knee extension and leg press exercises with BFR (20–30% 1RM; 75 reps; 2x/week; BFRP between 120 and 270 mmHg) (Yasuda et al., 2014). In contrast, no significant changes were observed in brachial artery FMD following handgrip training with BFR (40% 1RM until failure; 3x/week for 3 weeks; BFRP 80 mm Hg) in healthy young individuals (Hunt et al., 2012) or arm training with BFR in older adults (elastic resistance; 75 reps; 2x/week; BFRP between 120 and 270 mmHg) (Yasuda et al., 2015a,b).

Interestingly, Credeur et al. (2010) showed a significant reduction in brachial artery FMD in healthy young adults following handgrip training with BFR [60% of maximal voluntary contraction (MVC); 15 grips per minute during 20 min; 3x/week

TABLE 1 | Cardiovascular outcomes and their potential impacts on blood flow restriction pressure.

Outcomes	Definition	Measurement	Possible physiological repercussion	Possible repercussions on BFRP
FMD	Measurement of endothelial function. Defined as the artery dilatation in response to increases in blood flow	Doppler ultrasonography	Lower FMD indicates a reduction in endothelial function; increased FMD reflects an increase in reactive hyperemia	Lower FMD may be related to reduced vasodilatory response and increased BP and BFRP
Arterial compliance	The ability of an artery to expand and recoil during cardiac contraction and relaxation	PWV; CAVI; Doppler ultrasound	Its reduction is associated with increased BP; its increase is associated with reduced BP	Its reduction may result in increased BFRP; its increase may result in reduced BFRP
Arterial Stiffness	The decrease in arterial distensibility	PWV; CAVI	Its reduction may result in a reduced SBP; its increase may increase BP	Its reduction may result in a reduction of BFRP; its increase may result in increased BFRP
Arterial diameter	The straight line passing from side to side through the center of an artery	Doppler ultrasonography	Its reduction may result in increased SBP; its increase may result in a BP reduction.	Its reduction may result in increased BFRP; its increase may result in a reduced BFRP
Capillarity Index (microvascular filtration capacity)	An indirect measurement of the amount (expansion) of the capillary network	Plethysmography	Its reduction may result in increased peripheral vascular resistance and SBP; its increase may result in reduced peripheral vascular resistance and BP	Its reduction can result in increased BFRP; its increase may result in reduced BFRP
Blood pressure	The pressure of the blood against the inner walls of the blood vessels	Sphygmomanometer; Oscillometric device	It may be influenced by cardiac output, total peripheral resistance, and arterial stiffness.	Its reduction may result in reduced BFRP; its increase may result in increased BFRP
Heart rate	The number of times that the heart beats per minute	Electrocardiogram; Heart rate monitor	Its reduction may result in reduced BP; its increase may result in increased BP	Its reduction may result in reduced BFRP; its increase may result in increased BFRP
Heart rate variability	The variability of successive heart rate intervals	Heart rate monitor	Activation of baroreceptors leads to greater parasympathetic activity and sympathetic withdrawal	Increased parasympathetic activity and sympathetic withdrawal lead to hemodynamic adjusts, and increases in BFRP may be necessary

FMD, flow-mediated dilation; PWV, pulse wave velocity; CAVI, cardio-ankle vascular index testing; BP, blood pressure; BRFP, blood flow restriction pressure.

TABLE 2 | Characteristics of the studies that investigated the effects of BFR training on cardiovascular outcomes.

Reference (year)	Sample (n)	Exercises protocol	Cardiovascular outcomes	BFR protocol	BFRP adjusted yes/no (reason)	Main findings
Healthy young adults						
Kim et al. (2009)	Young males (30)	Leg press, knee flexion, and knee extension (20% 1RM; 2 sets of 10 reps; 3x/week; 3 weeks)	AC, HR, SBP, and DBP	BFRP: 20% above systolic SBP; Cuff width: 5 cm	No (NR)	↔
Credeur et al. (2010)	Young males and females (20)	Handgrip (60% MVC; 15 grips/min; 20 min; 3x/week; 4 weeks)	FMD and AD	BFRP:80 mmHg; Cuff width: 4 cm	No (NR)	↓FMD and ↔ for other outcomes
Evans et al. (2010)	Young males (9)	Heel raises (30% MVC; 4 sets of 50 reps; 3x/week; 4 weeks)	MFC	BFRP:150 mmHg; Cuff width: 15 cm	No (NR)	↑MFC
Patterson and Ferguson (2010)	Young females (16)	Heel raises (25–50% 1RM; 3 sets until failure; 3x/week; 4 weeks)	RH	BFRP:110 mmHg; Cuff width: NR	No (NR)	↑RH
Clark et al. (2011)	Young males and females (16)	Knee extension (30% 1RM; 3 sets until failure; 3x/week; 4 weeks)	PWV	BFRP:30% above SBP; Cuff width: 6 cm	No (NR)	↔
Kacin and Strazar (2011)	Young males (10)	Knee extension (15% MVC; reps until failure; 4x/week; 4 weeks)	HR, SBP, and DBP	BFRP:230 mmHg; Cuff width: 13 cm	No (NR)	↑DBP and ↔ for other outcomes
Hunt et al. (2012)	Young males (9)	Handgrip (40% 1RM; 3 sets until failure; 3x/week; 4 weeks)	FMD and AD	BFRP:80 mmHg; Cuff width:13 cm	No (NR)	↑AD and ↔ for other outcomes
Fahs et al. (2012)	Young males (46)	Knee extension and knee flexion exercises (20% 1RM; 75 reps; 3x/week; 6 weeks)	AC, HR, SBP, DBP, and VCo	BFRP:160–200 mmHg; Cuff width: 5 cm	Yes (NR)	↑VCo ↓DBP and ↔ for other outcomes
Ozaki et al. (2013)	Young males (19)	Bench press (30% 1RM; 30 reps; 3x/week; 6 weeks)	AC, SBP, and DBP	BFRP:100–160 mmHg; Cuff width: 3 cm	Yes (to reduce arterial blood flow by 60% at rest and by 30% during exercise)	↔
Hunt et al. (2013)	Young males (11)	Heel raises (30% of 1RM; 3 sets until failure; 3x/week; 6 weeks)	FMD and AD	BFRP:110 mmHg; Cuff width: 13 cm	No (NR)	↑FMD ↑AD
Fahs et al. (2014)	Young males and females (16)	Knee extension (30% 1RM; 2–4 sets until failure;3x/week; 6 weeks)	PWV	BFRP: 80% of total restriction pressure; Cuff width: 5 cm	No (NR)	↑PWV
Crisafulli et al. (2018)	Young males (17)	Handgrip (30% MVC; 30 reps per minute for 3 min; 3x/week; 4 weeks)	HR and MAP	BFRP:75–150% of SBP; Cuff width: NR	Yes (NR)	↓MAP and ↔ for other outcomes
Mouser et al. (2019)	Young males and females (40)	Biceps curl and knee extension (15% 1RM; 4 sets of 90 reps; 2x/week; 8 weeks)	VCo	BFRP: 40 and 80% of total restriction pressure Cuff width: 5 cm	No (NR)	↑VCo
Christiansen et al. (2020)	Young males (10)	Interval cycling (61–81% of MAPO; 3 sets of three 2-min bouts; 3x/week; 6 weeks)	AD	BFRP: 180 mmHg; Cuff width: 13 cm	No (NR)	↑AD
Early et al. (2020)	Young males and females (31)	Biceps curl, elbow extension, knee extension, leg curl and heel raise (30% 1RM; 3sets of 30 reps; 2–3x/week; 8 weeks	HR, SBP, DBP, and FMD	BFRP: 250 or 350 mmHg Cuff width: 5.5 or 7.0 cm	No (NR)	↓SBP ↑FMD and ↔ for other outcomes

(Continued)

TABLE 2 | Continued

Reference (year)	Sample (n)	Exercises protocol	Cardiovascular outcomes	BFR protocol	BFRP adjusted yes/no (reason)	Main findings
Ramis et al. (2020)	Young males (28)	Elbow flexion and knee extension (30% 1RM; 4 sets of 21–23 reps; 3x/week; 8 weeks)	FMD	BFRP: 20 mmHg below SBP; Cuff width: 14–16 cm	No (NR)	↑FMD
Zhao et al. (2020)	Young males (24)	Elbow flexion (30% 1RM; 5 sets of 20 reps; 5xweek; 8 weeks)	HR, SBP, DBP, and MAP	BFRP: 65 or 130% of SBP; Cuff width: NR	No (NR)	↓HR and ↔ for other outcomes
Healthy middle-aged and older adults						
Ozaki et al. (2011)	Older males and females (23)	Treadmill walking (45% of heart rate reserve; 20 min; 4x/week; 10 weeks)	AC, HR, SBP, and DBP	BFRP:140–200 mmHg; Cuff width: 5 cm	Yes (to impose progressive overload in muscle and central circulation)	↑AC and ↔ for other outcomes
Patterson and Ferguson (2011)	Older males and females (10)	Heel raises (25% 1RM; 3 sets until failure;3x/week; 4 weeks)	RH	BFRP:110 mmHg; Cuff width: NR	No (NR)	↑RH
Yasuda et al. (2014)	Older males and females (19)	Knee extension and leg press (20–30% 1RM; 75 reps; 2x/week; 12 weeks)	FMD, HR, SBP,DBP, and AS	BFRP:120–270 mmHg; Cuff width: 5 cm	Yes (to achieve high levels of perceived effort).	↑FMD and ↔ for other outcomes
Yasuda et al. (2015a)	Older females (14)	Arm curl and triceps down (elastic resistance; 75 reps; 2x/week; 12 weeks)	HR, SBP, DBP, FMD, and AS	BFRP:120–270 mmHg; Cuff width: 3 cm	Yes (to achieve high levels of perceived effort).	↔
Yasuda et al. (2015b)	Older males and females (17)	Arm curl and triceps down (Elastic resistance; 75 reps; 2x/week; 12 weeks)	HR, SBP, DBP, FMD, and AS	BFRP:120–270 mmHg; Cuff width: 3 cm	Yes (to achieve high levels of perceived effort).	↔
Shimizu et al. (2016)	Older males and females (40)	Leg extension, leg press, rowing and chest press (20% 1RM; 3 × 20 reps; 3x/week; 4 weeks)	RH	BFRP: 100% of SBP Cuff width: 10 or 7 cm	No (NR)	↑RH
Kim et al. (2017)	Young and older males and females (27)	Handgrip (20% MVC; 3 sets until failure; 2x/week; 4 weeks)	VCo, HR, SBP, and DBP	BFRP:130% of SBP; Cuff width: 16 cm	No (NR)	↑VCo and ↔ for other outcomes
Junior et al. (2019)	Middle-aged males (21)	Treadmill walking (6 km·h^{-1}, 5% grade; 5 sets of 3 min; 3x/week; 6 weeks)	HR and HRV	BFRP:80–100 mmHg; Cuff width: 18 cm	Yes (to allow participants to adapt to the BFRP during the early phase of the training)	↓HR ↑HRV
Ferreira Junior et al. (2019)	Middle-aged males (21)	Treadmill walking (6 km·h^{-1}, 5% grade; 5 sets of 3 min; 3x/week; 6 weeks)	SBP, DBP, and HRV	BFRP:80–100 mmHg; Cuff width: 18 cm	Yes (to allow participants to adapt to the BFRP during the early phase of the training)	↑HRV ↓SBP and ↔ for other outcomes
Clinical populations						
Cezar et al. (2016)	Hypertensive females (23)	Wrist flexion (30% MVC; 3 sets until failure; 2x/week; 8 weeks)	HR, SBP, and DBP	BFRP:70% of SBP; Cuff width: NR	Yes; based on SBP (to adjust BFRP to SBP in each training session).	↓SBP ↓DBP and ↔ for other outcomes
Barbosa et al., 2018	Patients with chronic kidney disease	Handgrip (40% MVC; 3 sets of 20 reps; 2x/week; 8 weeks)	AD	BFRP:50% of SBP; Cuff width: NR	No (NR)	↑AD
Kambič et al. (2019)	Patients with coronary artery disease (24)	Knee extensions (30–40% 1RM; 3 sets of 8–12 reps; 2x/week; 8 weeks)	HR, SBP, and DBP	BFRP:15–20 mmHg above systolic BP; Cuff width: 23 cm	Yes (NR)	↓SBP and ↔ for other outcomes

AC, arterial compliance; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; BFRP, blood flow restriction pressure; MVC, maximal voluntary contraction; MAPO, maximal aerobic power output; FMD, flow-mediated dilation; AD, arterial diameter; MFC, microvascular filtration capacity; RH, reactive hyperemia; PWV, pulse wave velocity; VCo, vascular conductance; MAP, mean arterial pressure; AS, arterial stiffness; HRV, heart rate variability; NR, not reported; ↔ no significant differences; ↑ increased; ↓ decreased.

for 4 weeks; BFRP 80 mmHg]. This finding suggests reduced vasodilatory capacity, a marker of vascular function. These results may be partially explained by both the high load (60% of MVC) and prolonged BFR (20 min) used, which were greater than other protocols (20–30% 1RM, 5–10 min) (Hunt et al., 2013; Yasuda et al., 2014). It can be argued that the combination of high load and prolonged BFR may increase oxidative stress (Biazon et al., 2019) and lead to endothelium dysfunction through decreased nitric oxide bioavailability (Förstermann, 2006). Age differences between participants and both the duration and training intensity may also explain contradictory findings among studies.

Regarding reactive hyperemia, increased post-occlusive calf blood flow following low load plantar flexion training with BFR for 4–6 weeks (25–50% 1RM until failure; 3x/week; BFRP 110 mm Hg) was found in young and older adults (Patterson and Ferguson, 2010, 2011; Hunt et al., 2013). Shimizu et al. (2016) demonstrated increased reactive hyperemia in older adults following multi-exercise (leg extension, leg press, rowing, and chest press) BFR training for 4 weeks (20% 1RM; 3 sets of 20 reps; 3x/week; BFRP equivalent to systolic blood pressure). Similarly, Fahs et al. (2012) observed an increase in the calf blood flow of healthy young males following 6 weeks of knee extension and flexion BFR training (20% 1RM; 75 reps; 3x/week; BFRP 160–200 mmHg). Mouser et al. (2019) also found increased forearm and calf vascular conductance in healthy young adults following 8 weeks of biceps curl and knee extension exercises (15% 1RM; 4 sets of 90 reps; 2x week; BFRP 40 or 80% of total restriction pressure). In healthy young adults Kim et al. (2017) showed increased forearm vascular conductance (i.e., blood flow/mean arterial pressure) following 4 weeks of isometric handgrip training with BFR (20% MVC until failure; 3x/week; BFRP 130% of systolic blood pressure). The above-mentioned improvements on vascular function following BFR training may also reflect improvements in microvascular tree, such as increased muscle capillarity (Hodges et al., 2010; Patterson and Ferguson, 2010). Calf capillary filtration capacity, an indirect capillarity index, also increased 14–26% following 4–6 weeks of unilateral calf raise or plantar flexion training with BFR (30% MVC; 4 sets of 50 reps or to failure; 3x/week; BFRP 110–150 mmHg) in young adult males (Evans et al., 2010; Hunt et al., 2013).

Overall, the possible increase in vasodilatory capacity to reactive hyperemia after BFR training may impact BFRP applied during exercise. For example, increased vasodilatory capacity may indicate a reduction in peripheral vascular resistance (Satoh, 2011; Hunt et al., 2013); however, contradictory findings preclude the recommendation of a reduction in BFRP during the training period based on macro- and microvascular adaptations.

Arterial Compliance, Stiffness, and Diameter

In studies involving BFR training, arterial stiffness and/or compliance are assessed non-invasively using pulse wave velocity (PWV), cardio-ankle vascular index testing (CAVI), or Doppler ultrasonography (Hunt et al., 2013; Yasuda et al., 2014; Karabulut et al., 2018). PWV is defined as the velocity at which pressure wave propagates along the arterial tree (Pereira et al., 2015), and lower PWV values indicate reduced arterial stiffness. CAVI is obtained by recording the distance from the level of the aortic valve to the ankle and the time delay between closure of aortic valve and detected change in arterial pressure wave at the ankle level (Yambe et al., 2004). Higher CAVI values indicate greater arterial stiffness (Sun, 2013).

Studies addressing arterial compliance and stiffness adaptations following BFR training are also controversial. Clark et al. (2011) did not observe changes in lower limb PWV of healthy young males following 4 weeks of bilateral knee extension BFR training (30% 1RM; 3 sets until failure; 3x/week; BFRP 1.3x above systolic blood pressure). No significant changes were observed in brachial artery stiffness of healthy older adults following 12 weeks of either knee extension and leg press BFR training (20–30% 1RM; 2x/week; BFRP between 120 and 270 mmHg) (Yasuda et al., 2014) or arm curl and triceps down BFR training (elastic resistance; 2x/week; BFRP 120 and 270 mmHg) (Yasuda et al., 2015b). Furthermore, no significant changes were found in brachial artery compliance of healthy young males following 3–6 weeks of upper and lower limb BFR training (20–30% 1RM; 20–75 reps; 3x/week; BFRP between 100 and 200 mmHg) (Kim et al., 2009; Fahs et al., 2012; Ozaki et al., 2013).

Fahs et al. (2014) observed an increase in peripheral PWV of middle-aged individuals following 6 weeks of knee extension BFR training (30% 1RM; 2–4 sets until failure; 3x/week; BFRP 50–80% of total restriction pressure). Specific effects of BFR on arterial compliance and stiffness, when different types of exercise training (aerobic vs. resistance) are performed, are still unknown. However, adaptations in these outcomes following aerobic or resistance training with BFR seem to be comparable to training without BFR. Therefore, based on these conflicting results, it is unclear whether arterial stiffness and compliance may impact the need for adjustments in BFRP.

Few data are available regarding the effect of BFR training on arterial diameter. Enlargement of brachial and radial artery was reported following 4–8 weeks of handgrip BFR training in young adult males (40% 1RM; 3 sets until failure; 3x/week; BFRP 80 mmHg) (Hunt et al., 2012) and patients with chronic kidney disease (40% MVC; 3 sets of 8–12 reps; 2x/week; BFRP 50% of SBP) (Barbosa et al., 2018). Similarly, Hunt et al. (2013) found an increase in popliteal artery diameter following 6 weeks of plantar flexion BFR training (30% 1RM until failure, 3x/week; BFRP 110 mmHg) in healthy males. Also, increased femoral artery diameter was found in young males following 6 weeks of interval cycling training (61–81% of maximal aerobic power output; 3 sets of three 2-min bouts; 3x/week) (Christiansen et al., 2020). Conversely, Credeur et al. (2010) observed no significant changes in brachial artery diameter of healthy young adults following 4 weeks of handgrip BFR training (60% of MVC; 15 grips per minute during 20 min; 3x/week; BFRP 80 mmHg). In summary, resistance BFR training may increase arterial diameter of upper and lower limbs, except following long sets of training (20 min). More data are needed to better understand the impact of aerobic BFR training interventions on arterial diameter.

Heart Rate and Blood Pressure

While heart rate (HR) and blood pressure (BP) increase during BFR exercise (Takano et al., 2005), adaptations in resting HR and BP following BFR training intervention are contradictory. For instance, Ozaki et al. (2011, 2013) did not observe changes in HR and BP following either 10 weeks of BFR walking training (20 min at 45% of heart rate reserve; 4x/week) or 6 weeks of bench press BFR training (30% 1RM; 3x/week; BFRP between 100 and 200 mmHg). Similarly, no significant changes in HR and BP were found in healthy older adults following BFR resistance training involving lower and upper limbs (20–30% 1RM or elastic resistance; 75 reps; 2x/week; BFRP between 120 and 270 mmHg) (Yasuda et al., 2014, 2015b). In young adults, no significant changes were observed in HR and BP following 3 weeks of leg press, knee flexion and knee extension training with BFR (20% 1RM; 2 sets of 10 reps; 3x/weeks; BFRP 20% above systolic BP) (Kim et al., 2009).

In contrast, Junior et al. showed a reduction in HR of healthy males following 6 weeks of BFR walking training (6 km·h^{-1}, 5% grade; 5 sets of 3 min; 3x/week; BFRP between 80 and 100 mmHg) (Junior et al., 2019). Similarly, reduced mean BP was observed in healthy young individuals following 4 weeks of BFR handgrip training (30 contractions per minute at 30% MVC; 3x/week; BFRP between 75 and 150% of systolic blood pressure) (Crisafulli et al., 2018) and 8 weeks of BFR elbow flexion training (30% 1RM; 5 sets of 20 reps; 5x/week; BFRP 65 of 130% of SBP) (Zhao et al., 2020). Fahs et al. (2012) also demonstrated a reduced diastolic BP of healthy young males following 6 weeks of BFR training with knee extension and flexion (75 reps with 20% 1RM; 3x/week; BFRP between 160 and 200 mmHg). An unexpected increase in diastolic BP was observed following 4 weeks of knee extension BFR training (15% MVC; reps until failure; 4x/week; BFRP 230 mmHg) in healthy young individuals (Kacin and Strazar, 2011).

Based on preliminary findings, BFR training has a BP-lowering effect in clinical populations. For example, Cezar et al. (2016) showed a reduction in systolic BP, diastolic BP, mean BP and double product of hypertensive women following 8 weeks of wrist flexion BFR training (30% of MVC; 3 sets until failure; 2x/week; BFRP 70% of systolic BP). More recently, Kambič et al. (2019) observed a reduced systolic BP of patients with coronary artery disease following 8 weeks of knee extension BFR training (30–40% 1RM; 3 sets of 8–12 reps; 2x/week; BFRP ∼140 mmHg). Lastly, two studies verified an increase in HR variability (Ferreira Junior et al., 2019; Junior et al., 2019). Although literature is inconsistent, there is evidence to support that BFR training may reduce both HR and BP and increase HR variability in clinical populations.

IS CUFF PRESSURE ADJUSTED IN BLOOD FLOW RESTRICTION TRAINING INTERVENTIONS?

Most included studies were performed with young adults, middle-aged and older adults, with or without clinical conditions, and used lower limb exercises (i.e., leg press, knee extension and flexion, or heel raises) (Kim et al., 2009; Evans et al., 2010; Patterson and Ferguson, 2010, 2011; Clark et al., 2011; Kacin and Strazar, 2011; Fahs et al., 2012, 2014; Hunt et al., 2013; Yasuda et al., 2014; Kambič et al., 2019). Studies also used upper limb exercises (i.e., handgrip, elbow flexion, bench press, or triceps down) (Credeur et al., 2010; Hunt et al., 2012; Ozaki et al., 2013; Yasuda et al., 2015b; Cezar et al., 2016; Kim et al., 2017; Crisafulli et al., 2018) and treadmill walking (Ferreira Junior et al., 2019; Junior et al., 2019). Importantly, many of the included studies had methodological limitations, such as failure in allocation concealment, blinding of participants and assessors; and intention-to-treat analysis (**Table 3**).

TABLE 3 | Methodological quality of eligible studies (*n* = 29).

Study	PEDro scale items[a]											PEDro score (0–10)
	1[b]	2	3	4	5	6	7	8	9	10	11	
Kim et al. (2009)	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Credeur et al. (2010)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Evans et al. (2010)	Y	N	N	Y	N	N	N	Y	Y	Y	Y	5
Patterson and Ferguson (2011)	N	N	N	Y	N	N	N	Y	Y	Y	Y	5
Clark et al. (2011)	N	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Kacin and Strazar (2011)	N	N	N	Y	N	N	N	Y	Y	Y	Y	5
Ozaki et al. (2011)	N	N	N	Y	N	N	Y	Y	Y	Y	Y	6
Patterson and Ferguson (2011)	N	N	N	Y	N	N	N	Y	Y	Y	Y	5
Hunt et al. (2012)	N	N	N	Y	N	N	N	Y	Y	Y	Y	5
Fahs et al. (2012)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Ozaki et al. (2013)	N	Y	N	Y	N	N	Y	Y	Y	Y	Y	6
Hunt et al. (2013)	N	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Fahs et al. (2014)	N	Y	N	Y	N	N	N	Y	N	Y	Y	5
Yasuda et al. (2014)	Y	Y	N	Y	N	N	N	N	Y	Y	Y	6
Yasuda et al. (2015a)	N	N	N	Y	N	N	N	Y	Y	Y	Y	5
Yasuda et al. (2015b)	N	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Cezar et al. (2016)	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Shimizu et al. (2016)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Kim et al. (2017)	Y	Y	N	Y	N	N	N	N	N	Y	Y	4
Barbosa et al., 2018	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	6
Crisafulli et al. (2018)	N	Y	N	Y	N	N	N	N	N	Y	Y	4
Ferreira Junior et al. (2019)	N	Y	N	Y	N	N	N	Y	N	Y	Y	5
Junior et al. (2019)	N	Y	N	Y	N	N	N	Y	N	Y	Y	5
Kambič et al. (2019)	Y	Y	Y	N	N	N	N	Y	Y	Y	Y	6
Mouser et al. (2019)	N	Y	N	Y	N	N	N	Y	N	Y	Y	5
Christiansen et al. (2020)	N	Y	N	Y	N	N	Y	N	N	Y	Y	5
Early et al. (2020)	N	Y	N	Y	N	N	N	Y	N	Y	Y	5
Ramis et al. (2020)	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6
Zhao et al. (2020)	N	Y	N	Y	N	N	N	Y	Y	Y	Y	6

Y, Yes; N, no.

[a] 1: Eligibility criteria and source of participants; 2: random allocation; 3: concealed allocation; 4: baseline comparability; 5: blinded participants; 6: blinded therapists; 7: blinded assessors; 8: adequate follow-up; 9: intention-to-treat analysis; 10: between-group comparison; 11: point estimates and variability.

[b] Item 1 does not contribute to total score.

Overall, 35% ($n = 10$) of the included studies adjusted BFRP during BFR training intervention; of these, three did not provide clear justification (Fahs et al., 2012; Crisafulli et al., 2018; Kambič et al., 2019). Rationale and methods for BFRP adjustments during BFR training interventions are diverse. Those who justified, argued that adjustments were performed to achieve high levels of perceived effort (Yasuda et al., 2014, 2015b), allow participants to adapt to the occlusion stimulus during the early phase of training (Ferreira Junior et al., 2019; Junior et al., 2019), impose progressive overload in skeletal muscles and central circulation (Ozaki et al., 2011), adjust BFRP to systolic BP in each session (Cezar et al., 2016), or reduce arterial blood flow by 60% at rest and 30% during exercise (Ozaki et al., 2013).

In three studies, BFRP adjustment was based on systolic BP changes (75–150% of the systolic BP) (Cezar et al., 2016; Crisafulli et al., 2018; Kambič et al., 2019), whereas six studies adjusted it arbitrarily by applying absolute restriction pressures ranging from 80 to 270 mmHg (Ozaki et al., 2011, 2013; Fahs et al., 2012; Yasuda et al., 2015b; Ferreira Junior et al., 2019; Junior et al., 2019). Applying arbitrary or SBP-based cuff pressures has not encouraged (Patterson et al., 2019). In fact, an absolute pressure of 160 mmHg in the upper limbs would result in partial arterial occlusion in some participants and in total arterial occlusion in others (Loenneke et al., 2013). As an alternative, researchers can use BFRP relative to PAS. However, the resulting pressure of this strategy may vary as a percentage of BFRP due to different cuff width/type (Loenneke et al., 2012).

Variability related to cuff width was also present in BFR protocols. For example, cuff width ranged from 3 to 16 cm for upper limb exercises (Ozaki et al., 2013; Kim et al., 2017) and from 5 to 23 cm for lower limbs (Yasuda et al., 2014; Kambič et al., 2019). Four of the included studies did not report cuff width. Although wide BFR cuffs restrict arterial blood flow at a lower pressure than narrow BFR cuffs (Loenneke et al., 2012), wider cuffs are associated with higher rate of perceived effort than narrow ones when the same arbitrary arterial occlusion pressure is prescribed for all participants (Rossow et al., 2012). Considering that high rates of perceived exertion can impair adherence to exercise (Chao et al., 2000), the influence of cuff width on rate of perceived exertion and discomfort should be investigated in future studies regarding BFRP adjustments (Spitz et al., 2020).

IS THERE A NEED TO ADJUST BLOOD FLOW RESTRICTION PRESSURE DURING A BLOOD FLOW RESTRICTION TRAINING INTERVENTION?

A common limitation of BFR training interventions is the variety of methods to prescribe BFRP. A broad range of cuff pressures has been used (Patterson et al., 2019; Clarkson et al., 2020), with few studies providing rationale for BFRP adjustment during BFR training interventions. Also, time under BFR is a variable that can influence cardiovascular adaptations and is inconsistent across studies. In fact, vascular function reduced when the time under BFR was 20 min (Credeur et al., 2010), while shorter times under BFR (∼11 min) improved vascular function (Yasuda et al., 2014). Training protocol also varied among studies and involved a wide range of training weeks, resistance exercise (dynamic or isometric) or aerobic exercise for the upper limbs, lower limbs, or both. This is relevant because cardiovascular adaptations to exercise can be influenced by modality (aerobic vs. resistance), frequency, intensity, time or duration, and volume (Green et al., 2011; Vanhees et al., 2012).

Of the 15 studies that assessed BP and/or HR following BFR training interventions, 12 used low-load resistance exercises with BFR, whereas three studies used treadmill walking protocols. Overall, no significant changes in HR were found in young participants, while diastolic BP was significantly reduced (−7 mmHg) in one study (Fahs et al., 2012) and increased (7 mmHg) in another study (Kacin and Strazar, 2011). In middle-aged and older adults, one study found a significant decrease in systolic BP (−10 mmHg) (Ferreira Junior et al., 2019), and another observed a decrease in HR (−10 bpm) (Junior et al., 2019). In clinical populations, two studies observed decreased systolic BP (−6 to −16 mm Hg) (Cezar et al., 2016; Kambič et al., 2019), and one study found a decreased diastolic BP (−11 mmHg) (Cezar et al., 2016). Thus, based on preliminary findings, it seems that BFR training may elicit BP-lowering effect and arterial diameter enlargement (Hunt et al., 2012, 2013; Barbosa et al., 2018; Christiansen et al., 2020).

Considering the isolated influence of cardiovascular factors (especially systolic BP) on BFRP (Loenneke et al., 2015; Bezerra de Morais et al., 2017), it seems plausible that a reduction in BFRP during BFR training period may be applied to minimize the discomfort caused by compression of the active musculature without compromising efficacy of the training method. However, in a more holistic perspective, the possible BFRP-lowering induced by cardiovascular adaptations may just compensate possible BFRP-increasing induced by neuromuscular adaptations (i.e., increased limb circumference secondary to muscle hypertrophy). Therefore, from a broader perspective, maintaining a percentage of BFRP levels seems the most plausible approach. In fact, the percentage of BFRP does not change appreciably over the course of a training intervention in healthy young (Mattocks et al., 2019), however this issue has not been investigated in clinical populations.

It is important to note that there is a minimum and maximum BFRP threshold (40–80% of total restriction pressure) recommended to induce neuromuscular adaptations (Patterson et al., 2019). In this sense, especially when working at the lower threshold (40% of total restriction pressure), periodic monitoring of BFRP may be important to reduce "low doses" of BFR. In addition, 40–80% of total restriction pressure is suggested to stimulate neuromuscular adaptations; however, minimum and maximum BFRP threshold to induce cardiovascular adaptations is not yet established. Based on a limited number of studies, a recent meta-analysis found no differences between high or low BFRP on vascular function compared to exercise without BFR (Liu et al., 2021). Nevertheless, the impact of different BFR pressures on adaptations in other cardiovascular variables, such as BP, heart rate and arterial diameter is unclear.

Of the 10 studies examining cardiovascular outcomes, only seven justified BFRP adjustments. Importantly, some studies (Yasuda et al., 2014, 2015b) reached extremely high pressures(e.g., 270 mmHg). If the applied BFRP increases as training progress, pain perception also increases (Weatherholt et al., 2013). Interestingly, to induce neuromuscular adaptations higher relative BFRP may not be necessary when exercising under BFR with loads of 30–40% 1RM (Lixandrão et al., 2015; Counts et al., 2016), whereas higher pressures (80% of total restraint pressure) may be required when exercising with lower loads (20% 1RM) (Lixandrão et al., 2015). This debate is relevant because perceived effort and pain may decrease without impairing neuromuscular gains over training weeks when fixed BFR is applied (Martín-Hernández et al., 2017; Teixeira et al., 2020), but perceived effort is not attenuated if pressure increases (Hughes et al., 2019). Thus, unnecessary increases in BFRP may contribute to discomfort, impair adherence (Spitz et al., 2020), and increase the risk of adverse events (Bond et al., 2019), such as venous thromboembolism, rhabdomyolysis, and bruising (Patterson et al., 2019; Whiteley, 2019).

CONCLUSION AND FUTURE PERSPECTIVES

In summary, cardiovascular adaptations induced by BFR training are conflicting. Based on the current literature, it is difficult to indicate whether increase or decrease BFR is needed, particularly in short-term BFR training interventions (i.e., < 6 weeks). Studies investigating whether BFRP adjustments throughout training are more effective, safe and/or tolerable than maintaining constant pressures are needed. Moreover, individualized and validated measures of BFRP, such as ultrasound Doppler (Bezerra de Morais et al., 2017), handheld Doppler (Laurentino et al., 2018), or pulse oximetry (Zeng et al., 2019) are encouraged. We also suggest that future studies investigate whether there is a minimum and maximum BFRP threshold to induce cardiovascular adaptations. Finally, considering possible BP-lowering effect of BFR training, longitudinal studies directly measuring BFRP are needed to establish whether cuff pressure is altered in clinical populations.

AUTHOR CONTRIBUTIONS

MSC conceived the study. MSC, EC, RS, RP, and WB participated to the design and coordination and wrote the manuscript. All authors have read and approved the final version of the manuscript, and agreed with the order of presentation of the authors.

ACKNOWLEDGMENTS

MSC would like to thank Coordination for the Improvement of Higher Education Personnel—Brazil (CAPES), finance code 001, for the scholarship concession.

REFERENCES

Barbosa, J. B. N., Maia, T. O., Alves, P. S., Bezerra, S. D., Moura, E. C. S. C., Medeiros, A. I. C., et al. (2018). Does blood flow restriction training increase the diameter of forearm vessels in chronic kidney disease patients? a randomized clinical trial. *J. Vascular Access* 19, 626–633. doi: 10.1177/1129729818768179

Bezerra, de Morais, A. T., Cerqueira, M. S., Moreira Sales, R., Rocha, T., Galvão, et al. (2017). Upper limbs total occlusion pressure assessment: doppler ultrasound reproducibility and determination of predictive variables. *Clin. Physiol. Funct. Imaging* 37, 437–441. doi: 10.1111/cpf.12330

Biazon, T. M. P. C., Ugrinowitsch, C., Soligon, S. D., Oliveira, R. M., Bergamasco, J. G., Borghi-Silva, A., et al. (2019). The association between muscle deoxygenation and muscle hypertrophy to blood flow restricted training performed at high and low loads. *Front. Physiol.* 10:446. doi: 10.3389/fphys.2019.00446

Bond, C. W., Hackney, K. J., Brown, S. L., and Noonan, B. C. (2019). Blood flow restriction resistance exercise as a rehabilitation modality following orthopaedic surgery: a review of venous thromboembolism risk. *J. Orthopaedic Sports Phys. Therapy* 49, 17–27. doi: 10.2519/jospt.2019.8375

Bryk, F. F., dos Reis, A. C., Fingerhut, D., Araujo, T., Schutzer, M., Cury, R., et al. (2016). Exercises with partial vascular occlusion in patients with knee osteoarthritis: a randomized clinical trial. *Knee. Surg. Sports Traumatol. Arthrosc.* 24, 1580–1586. doi: 10.1007/s00167-016-4064-4067

Centner, C., Wiegel, P., Gollhofer, A., and König, D. (2019). Effects of blood flow restriction training on muscular strength and hypertrophy in older individuals: a systematic review and meta-analysis. *Sports Med.* 49, 95–108. doi: 10.1007/s40279-018-0994-991

Cerqueira, M. S., and de Brito Vieira, W. H. (2019). Effects of blood flow restriction exercise with very low load and low volume in patients with knee osteoarthritis: protocol for a randomized trial. *Trials* 20:135. doi: 10.1186/s13063-019-3238-3232

Cezar, M. A., De Sá, C. A., da Corralo, V. S., Copatti, S. L., dos Santos, G. A. G., and da Grigoletto, M. E. S. (2016). Effects of exercise training with blood flow restriction on blood pressure in medicated hypertensive patients. *Motriz: Revista de Educação Física* 22, 9–17. doi: 10.1590/S1980-6574201600020002

Chao, D., Foy, C. G., and Farmer, D. (2000). Exercise adherence among older adults: challenges and strategies. *Controlled Clin. Trials*. 21 (5 Suppl.), S212–S217. doi: 10.1016/s0197-2456(00)00081-87

Christiansen, D., Eibye, K., Hostrup, M., and Bangsbo, J. (2020). Training with blood flow restriction increases femoral artery diameter and thigh oxygen delivery during knee-extensor exercise in recreationally trained men. *J. Physiol.* 598, 2337–2353. doi: 10.1113/JP279554

Clark, B. C., Manini, T. M., Hoffman, R. L., Williams, P. S., Guiler, M. K., Knutson, M. J., et al. (2011). Relative safety of 4 weeks of blood flow-restricted resistance exercise in young, healthy adults. *Scand. J. Med. Sci. Sports* 21, 653–662. doi: 10.1111/j.1600-0838.2010.01100.x

Clarkson, M. J., May, A. K., and Warmington, S. A. (2020). Is there rationale for the cuff pressures prescribed for blood flow restriction exercise? a systematic review. *Scand. J. Med. Sci. Sports* 30, 1318–1336. doi: 10.1111/sms.13676

Counts, B. R., Dankel, S. J., Barnett, B. E., Kim, D., Mouser, J. G., Allen, K. M., et al. (2016). Influence of relative blood flow restriction pressure on muscle activation and muscle adaptation. *Muscle Nerve* 53, 438–445. doi: 10.1002/mus.24756

Credeur, D. P., Hollis, B. C., and Welsch, M. A. (2010). Effects of handgrip training with venous restriction on brachial artery vasodilation. *Med. Sci. Sports Exerc.* 42, 1296–1302. doi: 10.1249/MSS.0b013e3181ca7b06

Crisafulli, A., de Farias, R. R., Farinatti, P., Lopes, K. G., Milia, R., Sainas, G., et al. (2018). Blood flow restriction training reduces blood pressure during exercise without affecting metaboreflex activity. *Front. Physiol.* 9:1736. doi: 10.3389/fphys.2018.01736

Cristina-Oliveira, M., Meireles, K., Spranger, M. D., O'Leary, D. S., Roschel, H., and Peçanha, T. (2020). Clinical safety of blood flow-restricted training? a comprehensive review of altered muscle metaboreflex in cardiovascular disease during ischemic exercise. *Am. J. Physiology-Heart Circulatory Physiol.* 318, H90–H109. doi: 10.1152/ajpheart.00468.2019

Early, K. S., Rockhill, M., Bryan, A., Tyo, B., Buuck, D., and McGinty, J. (2020). Effect of blood flow restriction training on muscular performance, pain and vascular function. *Int. J. Sports Phys. Therapy* 15, 892–900. doi: 10.26603/ijspt20200892

Evans, C., Vance, S., and Brown, M. (2010). Short-term resistance training with blood flow restriction enhances microvascular filtration capacity of human calf muscles. *J. Sports Sci.* 28, 999–1007. doi: 10.1080/02640414.2010.485647

Fahs, C. A., Rossow, L. M., Loenneke, J. P., Thiebaud, R. S., Kim, D., Bemben, D. A., et al. (2012). Effect of different types of lower body resistance training on arterial compliance and calf blood flow. *Clin. Physiol. Funct. Imaging* 32, 45–51. doi: 10.1111/j.1475-097X.2011.01053.x

Fahs, C. A., Rossow, L. M., Thiebaud, R. S., Loenneke, J. P., Kim, D., Abe, T., et al. (2014). Vascular adaptations to low-load resistance training with and without blood flow restriction. *Eur. J. Appl. Physiol.* 114, 715–724. doi: 10.1007/s00421-013-2808-2803

Ferreira Junior, A., Schamne, J. C., Altimari, L. R., Okano, A. H., and Okuno, N. M. (2019). Effect of walk training combined with blood flow restriction on resting heart rate variability and resting blood pressure in middle-aged men. *Motriz: Revista de Educação Física* 25:e101945. doi: 10.1590/s1980-6574201900020005

Förstermann, U. (2006). Endothelial NO synthase as a source of NO and superoxide. *Eur. J. Clin. Pharmacol.* 62, 5–12. doi: 10.1007/s00228-005-0006-x

Giles, L., Webster, K. E., McClelland, J., and Cook, J. L. (2017). Quadriceps strengthening with and without blood flow restriction in the treatment of patellofemoral pain: a double-blind randomised trial. *Br. J. Sports Med.* 51, 1688–1694. doi: 10.1136/bjsports-2016-096329

Green, D. J., Spence, A., Halliwill, J. R., Cable, N. T., and Thijssen, D. H. J. (2011). Exercise and vascular adaptation in asymptomatic humans. *Exp. Physiol.* 96, 57–70. doi: 10.1113/expphysiol.2009.048694

Gustafsson, T., Puntschart, A., Kaijser, L., Jansson, E., and Sundberg, C. J. (1999). Exercise-induced expression of angiogenesis-related transcription and growth factors in human skeletal muscle. *Am. J. Physiology-Heart Circulatory Physiol.* 276, H679–H685. doi: 10.1152/ajpheart.1999.276.2.H679

Hodges, G. J., Sharp, L., Clements, R. E., Goldspink, D. F., George, K. P., and Cable, N. T. (2010). Influence of age, sex, and aerobic capacity on forearm and skin blood flow and vascular conductance. *Eur. J. Appl. Physiol.* 109, 1009–1015. doi: 10.1007/s00421-010-1441-1447

Hudlicka, O., and Brown, M. D. (2009). Adaptation of skeletal muscle microvasculature to increased or decreased blood flow: role of shear stress, nitric oxide and vascular endothelial growth factor. *J. Vasc. Res.* 46, 504–512. doi: 10.1159/000226127

Hughes, L., Paton, B., Rosenblatt, B., Gissane, C., and Patterson, S. D. (2017). Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. *Br. J. Sports Med.* 51, 1003–1011. doi: 10.1136/bjsports-2016-097071

Hughes, L., Patterson, S. D., Haddad, F., Rosenblatt, B., Gissane, C., McCarthy, D., et al. (2019). Examination of the comfort and pain experienced with blood flow restriction training during post-surgery rehabilitation of anterior cruciate ligament reconstruction patients: a UK National Health Service trial. *Phys. Therapy Sport*. 39, 90–98. doi: 10.1016/j.ptsp.2019.06.014

Hunt, J. E. A., Galea, D., Tufft, G., Bunce, D., and Ferguson, R. A. (2013). Time course of regional vascular adaptations to low load resistance training with blood flow restriction. *J. Appl. Physiol.* 115, 403–411. doi: 10.1152/japplphysiol.00040.2013

Hunt, J. E. A., Stodart, C., and Ferguson, R. A. (2016). The influence of participant characteristics on the relationship between cuff pressure and level of blood flow restriction. *Eur. J. Appl. Physiol.* 116, 1421–1432. doi: 10.1007/s00421-016-3399-3396

Hunt, J. E. A., Walton, L. A., and Ferguson, R. A. (2012). Brachial artery modifications to blood flow-restricted handgrip training and detraining. *J. Appl. Physiol.* 112, 956–961. doi: 10.1152/japplphysiol.00905.2011

Jessee, M. B., Buckner, S. L., Dankel, S. J., Counts, B. R., Abe, T., and Loenneke, J. P. (2016). The influence of cuff width, sex, and race on arterial occlusion: implications for blood flow restriction research. *Sports Med.* 46, 913–921. doi: 10.1007/s40279-016-0473-475

Junior, A. F., Schamne, J. C., Perandini, L. A. B., Chimin, P., and Okuno, N. M. (2019). Effects of walking training with restricted blood flow on HR and HRV Kinetics and HRV recovery. *Int. J. Sports Med.* 40, 585–591. doi: 10.1055/a-0942-7479

Kacin, A., and Strazar, K. (2011). Frequent low-load ischemic resistance exercise to failure enhances muscle oxygen delivery and endurance capacity. *Scand. J. Med. Sci. Sports* 21, e231–e241. doi: 10.1111/j.1600-0838.2010.01260.x

Kambič, T., Novaković, M., Tomažin, K., Strojnik, V., and Jug, B. (2019). Blood flow restriction resistance exercise improves muscle strength and hemodynamics, but not vascular function in coronary artery disease patients: a pilot randomized controlled trial. *Front. Physiol.* 10:656. doi: 10.3389/fphys.2019.00656

Karabulut, U., Karabulut, M., and James, E. G. (2018). Small arteries stay stiff for a longer period following vibration exercises in combination with blood flow restriction. *Clin. Physiol. Funct. Imaging* 38, 1000–1007. doi: 10.1111/cpf.12516

Kelm, M. (2002). Flow-mediated dilatation in human circulation: diagnostic and therapeutic aspects. *Am. J. Physiology-Heart Circulatory Physiol.* 282, H1–H5. doi: 10.1152/ajpheart.2002.282.1.H1

Kim, J., Lang, J. A., Pilania, N., and Franke, W. D. (2017). Effects of blood flow restricted exercise training on muscular strength and blood flow in older adults. *Exp. Gerontol.* 99, 127–132. doi: 10.1016/j.exger.2017.09.016

Kim, S. J., Sherk, V. D., Bemben, M. G., and Bemben, D. A. (2009). Effects of short-term, low-intensity resistance training with vascular restriction on arterial compliance in untrained young men. *Int. J. KAATSU Training Res.* 5, 1–8. doi: 10.3806/ijktr.5.1

Laurentino, G. C., Loenneke, J. P., Mouser, J. G., Buckner, S. L., Counts, B. R., Dankel, S. J., et al. (2018). Validity of the handheld doppler to determine lower-limb blood flow restriction pressure for exercise protocols. *J. Strength Cond. Res.* 34, 2693–2696. doi: 10.1519/JSC.0000000000002665

Liu, Y., Jiang, N., Pang, F., and Chen, T. (2021). Resistance training with blood flow restriction on vascular function: a meta-analysis. *Int. J. Sports Med.* doi: 10.1055/a-1386-4846 Online ahead of print.

Lixandrão, M. E., Ugrinowitsch, C., Laurentino, G., Libardi, C. A., Aihara, A. Y., Cardoso, F. N., et al. (2015). Effects of exercise intensity and occlusion pressure after 12 weeks of resistance training with blood-flow restriction. *Eur. J. Appl. Physiol.* 115, 2471–2480. doi: 10.1007/s00421-015-3253-3252

Loenneke, J. P., Allen, K. M., Mouser, J. G., Thiebaud, R. S., Kim, D., Abe, T., et al. (2015). Blood flow restriction in the upper and lower limbs is predicted by limb circumference and systolic blood pressure. *Eur. J. Appl. Physiol.* 115, 397–405. doi: 10.1007/s00421-014-3030-3037

Loenneke, J. P., Fahs, C. A., Rossow, L. M., Sherk, V. D., Thiebaud, R. S., Abe, T., et al. (2012). Effects of cuff width on arterial occlusion: implications for blood flow restricted exercise. *Eur. J. Appl. Physiol.* 112, 2903–2912. doi: 10.1007/s00421-011-2266-2268

Loenneke, J. P., Fahs, C. A., Rossow, L. M., Thiebaud, R. S., Mattocks, K. T., Abe, T., et al. (2013). Blood flow restriction pressure recommendations: a tale of two cuffs. *Front. Physiol.* 4:249. doi: 10.3389/fphys.2013.00249

Loenneke, J. P., Thiebaud, R. S., Abe, T., and Bemben, M. G. (2014). Blood flow restriction pressure recommendations: the hormesis hypothesis. *Med. Hypotheses* 82, 623–626. doi: 10.1016/j.mehy.2014.02.023

Maher, C. G., Sherrington, C., Herbert, R. D., Moseley, A. M., and Elkins, M. (2003). Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys. Ther.* 83, 713–721.

Martín-Hernández, J., Ruiz-Aguado, J., Herrero, A. J., Loenneke, J. P., Aagaard, P., Cristi-Montero, C., et al. (2017). Adaptation of perceptual responses to low-load blood flow restriction training. *J. Strength Condition. Res.* 31, 765–772. doi: 10.1519/JSC.0000000000001478

Mattocks, K. T., Mouser, J. G., Jessee, M. B., Buckner, S. L., Dankel, S. J., Bell, Z. W., et al. (2019). Perceptual changes to progressive resistance training with and without blood flow restriction. *J. Sports Sci.* 37, 1857–1864. doi: 10.1080/02640414.2019.1599315

Mouser, J. G., Mattocks, K. T., Buckner, S. L., Dankel, S. J., Jessee, M. B., Bell, Z. W., et al. (2019). High-pressure blood flow restriction with very low load resistance training results in peripheral vascular adaptations similar to heavy resistance training. *Physiol. Meas.* 40:035003. doi: 10.1088/1361-6579/ab0d2a

Ozaki, H., Miyachi, M., Nakajima, T., and Abe, T. (2011). Effects of 10 weeks walk training with leg blood flow reduction on carotid arterial compliance and muscle size in the elderly adults. *Angiology* 62, 81–86. doi: 10.1177/0003319710375942

Ozaki, H., Yasuda, T., Ogasawara, R., Sakamaki-Sunaga, M., Naito, H., and Abe, T. (2013). Effects of high-intensity and blood flow-restricted low-intensity resistance training on carotid arterial compliance: role of blood pressure during training sessions. *Eur. J. Appl. Physiol.* 113, 167–174. doi: 10.1007/s00421-012-2422-2429

Patterson, S. D., and Ferguson, R. A. (2010). Increase in calf post-occlusive blood flow and strength following short-term resistance exercise training with blood flow restriction in young women. *Eur. J. Appl. Physiol.* 108, 1025–1033. doi: 10.1007/s00421-009-1309-x

Patterson, S. D., and Ferguson, R. A. (2011). Enhancing strength and postocclusive calf blood flow in older people with training with blood-flow restriction. *J. Aging Phys. Act.* 19, 201–213. doi: 10.1123/japa.19.3.201

Patterson, S. D., Hughes, L., Warmington, S., Burr, J., Scott, B. R., Owens, J., et al. (2019). Blood flow restriction exercise: considerations of methodology. application, and safety. *Front. Physiol.* 10:533. doi: 10.3389/fphys.2019.00533

Pereira, T., Correia, C., and Cardoso, J. (2015). Novel methods for pulse wave velocity measurement. *J. Med. Biol. Eng.* 35, 555–565. doi: 10.1007/s40846-015-0086-88

Ramis, T. R., Muller, C. H., de, L., Boeno, F. P., Teixeira, B. C., Rech, A., et al. (2020). Effects of traditional and vascular restricted strength training program with equalized volume on isometric and dynamic strength, muscle thickness, electromyographic activity, and endothelial function adaptations in young adults. *J. Strength Cond. Res.* 34, 689–698. doi: 10.1519/JSC.0000000000002717

Rossow, L. M., Fahs, C. A., Loenneke, J. P., Thiebaud, R. S., Sherk, V. D., Abe, T., et al. (2012). Cardiovascular and perceptual responses to blood-flow-restricted resistance exercise with differing restrictive cuffs. *Clin. Physiol. Funct. Imaging* 32, 331–337. doi: 10.1111/j.1475-097X.2012.01131.x

Satoh, I. (2011). Kaatsu training: application to metabolic syndrome. *Int. J. KAATSU Train. Res.* 7, 7–12. doi: 10.3806/ijktr.7.7

Scott, B. R., Loenneke, J. P., Slattery, K. M., and Dascombe, B. J. (2016). Blood flow restricted exercise for athletes: a review of available evidence. *J. Sci. Med. Sport* 19, 360–367. doi: 10.1016/j.jsams.2015.04.014

Shimizu, R., Hotta, K., Yamamoto, S., Matsumoto, T., Kamiya, K., Kato, M., et al. (2016). Low-intensity resistance training with blood flow restriction improves vascular endothelial function and peripheral blood circulation in healthy elderly people. *Eur. J. Appl. Physiol.* 116, 749–757. doi: 10.1007/s00421-016-3328-3328

Singer, T. J., Stavres, J., Elmer, S. J., Kilgas, M. A., Pollock, B. S., Kearney, S. G., et al. (2020). Knee extension with blood flow restriction: impact of cuff pressure on hemodynamics. *Eur. J. Appl. Physiol.* 120, 79–90. doi: 10.1007/s00421-019-04250-4252

Spitz, R. W., Wong, V., Bell, Z. W., Viana, R. B., Chatakondi, R. N., Abe, T., et al. (2020). Blood flow restricted exercise and discomfort. *J. Strength Cond. Res.* doi: 10.1519/JSC.0000000000003525 Online ahead of print.

Suga, T., Okita, K., Morita, N., Yokota, T., Hirabayashi, K., Horiuchi, M., et al. (2009). Intramuscular metabolism during low-intensity resistance exercise with blood flow restriction. *J. Appl. Physiol.* 106, 1119–1124. doi: 10.1152/japplphysiol.90368.2008

Sun, C.-K. (2013). Cardio-ankle vascular index (CAVI) as an indicator of arterial stiffness. *Integrated Blood Pressure Control* 6, 27–38. doi: 10.2147/IBPC.S34423

Sundblad, P., Kölegård, R., Rullman, E., and Gustafsson, T. (2018). Effects of training with flow restriction on the exercise pressor reflex. *Eur. J. Appl. Physiol.* 118, 1903–1909. doi: 10.1007/s00421-018-3911-3912

Takada, S., Okita, K., Suga, T., Omokawa, M., Kadoguchi, T., Sato, T., et al. (2012). Low-intensity exercise can increase muscle mass and strength proportionally to enhanced metabolic stress under ischemic conditions. *J. Appl. Physiol.* 113, 199–205. doi: 10.1152/japplphysiol.00149.2012

Takano, H., Morita, T., Iida, H., Asada, K., Kato, M., Uno, K., et al. (2005). Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. *Eur. J. Appl. Physiol.* 95, 65–73. doi: 10.1007/s00421-005-1389-1381

Takarada, Y., Takazawa, H., Sato, Y., Takebayashi, S., Tanaka, Y., and Ishii, N. (2000). Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. *J. Appl. Physiol.* 88, 2097–2106. doi: 10.1152/jappl.2000.88.6.2097

Teixeira, E. L., Painelli, V., de, S., Schoenfeld, B. J., Silva-Batista, C., Longo, A. R., et al. (2020). Perceptual and neuromuscular responses adapt similarly between high-load resistance training and low-load resistance training with blood flow restriction. *J. Strength Condition. Res.* doi: 10.1519/JSC.0000000000003879 Online ahead of print.

Vanhees, L., Geladas, N., Hansen, D., Kouidi, E., Niebauer, J., Reiner, Ž, et al. (2012). Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR (Part II). *Eur. J. Preventive Cardiol.* 19, 1005–1033. doi: 10.1177/1741826711430926

Weatherholt, A., Beekley, M., Greer, S., Urtel, M., and Mikesky, A. (2013). Modified Kaatsu training: adaptations and subject perceptions. *Med. Sci. Sports Exerc.* 45, 952–961. doi: 10.1249/MSS.0b013e31827ddb1f

Whiteley, R. (2019). Blood flow restriction training in rehabilitation: a useful adjunct or Lucy's latest trick? *J. Orthopaedic Sports Phys. Therapy* 49, 294–298. doi: 10.2519/jospt.2019.0608

Yambe, T., Yoshizawa, M., Saijo, Y., Yamaguchi, T., Shibata, M., Konno, S., et al. (2004). Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI). *Biomed. Pharmacotherapy* 58, S95–S98. doi: 10.1016/S0753-3322(04)80015-80015

Yasuda, T., Fukumura, K., Fukuda, T., Uchida, Y., Iida, H., Meguro, M., et al. (2014). Muscle size and arterial stiffness after blood flow-restricted low-intensity resistance training in older adults. *Scand. J. Med. Sci. Sports* 24, 799–806. doi: 10.1111/sms.12087

Yasuda, T., Fukumura, K., Iida, H., and Nakajima, T. (2015a). Effects of detraining after blood flow-restricted low-load elastic band training on muscle size and arterial stiffness in older women. *SpringerPlus* 4:348. doi: 10.1186/s40064-015-1132-1132

Yasuda, T., Fukumura, K., Uchida, Y., Koshi, H., Iida, H., Masamune, K., et al. (2015b). Effects of low-load, elastic band resistance training combined with blood flow restriction on muscle size and arterial stiffness in older adults. *J. Gerontol. Series A: Biol. Sci. Med. Sci.* 70, 950–958. doi: 10.1093/gerona/glu084

Zeng, Z., Centner, C., Gollhofer, A., and König, D. (2019). Blood-Flow-Restriction training: validity of pulse oximetry to assess arterial occlusion pressure. *Int. J. Sports Physiol. Perform.* 14, 1408–1414. doi: 10.1123/ijspp.2019-2043

Zhao, Y., Lin, A., and Jiao, L. (2020). Eight weeks of resistance training with blood flow restriction improve cardiac function and vascular endothelial function in healthy young Asian males. *Int. Health* 1–9. doi: 10.1093/inthealth/ihaa089

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acute Effect of Repeated Sprint Exercise With Blood Flow Restriction During Rest Periods on Muscle Oxygenation

Chihiro Kojima[1], Keiichi Yamaguchi[2], Hiroto Ito[2], Nobukazu Kasai[1], Olivier Girard[3] and Kazushige Goto[2]*

[1] Japan Institute of Sports Sciences, Tokyo, Japan, [2] Graduate School of Sport and Health Science, Ritsumeikan University, Shiga, Japan, [3] School of Human Sciences (Exercise and Sport Science), The University of Western Australia, Crawly, WA, Australia

OPEN ACCESS

Edited by:
Gregory C. Bogdanis,
National and Kapodistrian University of Athens, Greece

Reviewed by:
Richard Ferguson,
Loughborough University, United Kingdom
J. Grant Mouser,
Troy University, United States

***Correspondence:**
Kazushige Goto
kagoto@fc.ritsumei.ac.jp

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: 08 February 2021
Accepted: 21 June 2021
Published: 29 July 2021

Citation:
Kojima C, Yamaguchi K, Ito H, Kasai N, Girard O and Goto K (2021) Acute Effect of Repeated Sprint Exercise With Blood Flow Restriction During Rest Periods on Muscle Oxygenation. Front. Physiol. 12:665383. doi: 10.3389/fphys.2021.665383

Purpose: This study aimed to examine the effect of applying BFR during rest periods of repeated cycling sprints on muscle oxygenation.

Methods: Seven active males performed 5 × 10-s maximal pedaling efforts with 40-s passive rest, with or without BFR application during rest period. BFR was applied for 30 s between sprints (between 5 and 35 s into rest) through a pneumatic pressure cuff inflated at 140 mmHg. *Vastus lateralis* muscle oxygenation was monitored using near-infrared spectroscopy. In addition, blood lactate concentration and heart rate were also evaluated.

Results: The BFR trial showed significantly lower oxyhemoglobin (oxy-Hb) and tissue saturation (StO_2) levels than the CON trial ($P < 0.05$). However, power output and blood lactate concentration did not significantly differ between the two trials ($P > 0.05$).

Conclusion: Applying BFR during rest periods of repeated cycling sprints decreased muscle oxygenation of active musculature, without interfering with power output during sprints.

Keywords: local hypoxia, occlusion, perfusion, recovery, repeated sprint ability

INTRODUCTION

Repeated sprint exercise (RSE), consisting of several bouts of maximal sprints (<10 s) separated with relatively short rest periods (<60 s), has been shown to increase maximal oxygen uptake ($\dot{V}O_{2max}$), repeated sprint ability (Bishop et al., 2011) and improve muscle buffer capacity (Bishop et al., 2004). It is therefore not surprising that this training modality is popular in various sport activities such as soccer, lacrosse, and rugby. One of the most important training stimuli for maximizing the effects of RSE is metabolite (e.g., lactate and hydrogen ion) accumulations within working muscles (Bishop et al., 2004). A single bout of RSE can markedly increase muscle lactate content and decrease muscle glycogen content (Gaitanos et al., 1993). Because both metabolite production and clearance are both closely associated with local blood flow in surrounding muscle tissues, restricted blood flow (e.g., attenuated blood supply to muscles or blood outflow from muscles) would enhance metabolite accumulation.

Sprint interval exercise (SIE), consisting of repetition of several "all-out" efforts of longer duration (>20–30 s) separated with several minutes of rest periods, combined with post-sprint blood flow restriction (BFR) has been already reported (Taylor et al., 2016; Mitchell et al., 2019). For instance, BFR during rest period between sprints of SIE augmented hypoxia-inducible factor-1α (HIF-1α) (Taylor et al., 2016). The previous study indicated the possibility to activate HIF-1α-mediated signaling involved in angiogenesis induced by greater tissue hypoxia when combining SIE with BFR (Taylor et al., 2016). On the other hand, the effect of RSE with or without continuous (sprints + rest periods) BFR of upper limb or lower limb (thigh) muscles throughout the session (sprints + rest periods) on muscle oxygenation has been recently investigated (Willis et al., 2018, 2019b,c; Peyrard et al., 2019). Although the addition of BFR during repeated sprinting lowers the tissue saturation index (as a proxy for local hypoxia severity; Willis et al., 2019a), power output during the actual sprints efforts was attenuated (Peyrard et al., 2019). The attenuated power output during sprint exercise with BFR may be associated with the ability of the neuromuscular system to produce maximal force (Peyrard et al., 2019) and/or a relationship between force and velocity during repeated sprinting (Fenn and Marsh, 1935; Davies et al., 1984). Furthermore, phosphocreatine (PCr) degradation/resynthesis and aerobic metabolism might be partially involved (Gaitanos et al., 1993). Since the oxygen delivery to promote resynthesis of muscle PCr during rest periods would be insufficient due to BFR, detailed information of muscle oxygenation during RSE with BFR is likely to be informative. On the other hand, there was no studies which focused on the influences of BFR during rest periods of RSE on sprint performance and muscle oxygenation. It is possible (but unknown) that the application of BFR during the rest periods between sprints only may augment deoxygenation levels (larger training stimulus), yet without interrupting with power production (maintained training quality) in reference to a control trial during the actual efforts of a repeated sprint cycling exercise.

Therefore, the purpose of the present study was to test the hypothesis that the addition of BFR during rest periods of a repeated cycling sprint exercise would accentuate deoxygenation levels, while fatigue resistance during the actual sprint bouts will not be compromised.

MATERIALS AND METHODS

Participants

Seven active males volunteers [age (mean ± standard deviation, SD): 21.7 ± 0.8 years, height: 172.2 ± 5.4 cm, body weight: 65.9 ± 4.7 cm, body mass index: 22.2 ± 1.6 kg/m^2] belonging to the same lacrosse team, took part in this study. Participants were informed of the purpose, experimental procedure, and potential risk of this study, and written informed consent was obtained. This study was approved by the Ethics Committees of Ritsumeikan University, Japan.

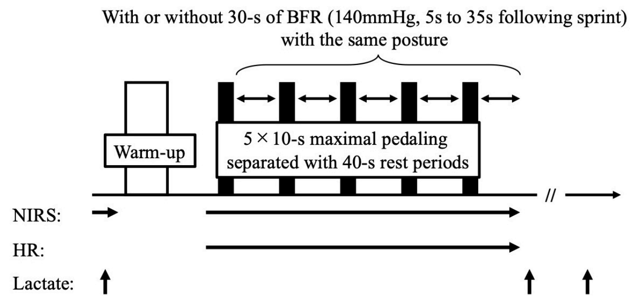

FIGURE 1 | Experimental protocol.

Experimental Overview

The present study was designed using a randomized cross-over design. All participants completed RSE either with BFR (BFR trial) or without BFR (CON trial) during rest periods between sprints on different days. Each trial was separated with at least 2 days. Muscle oxygenation, power output and heart rate were recorded during the exercise. Blood lactate concentrations were evaluated before and after exercise.

Experimental Protocol

Participants were instructed to replicate the last training and meal prior to the experiment and arrived at laboratory following their general daily training (14:00–15:00). Following sufficient rest (around 20 min), baseline muscle oxygenation and blood lactate concentration were evaluated. After the baseline measurements, participants performed warm-up (2 × 3 s maximal pedaling exercise with the load of equivalent to 5.0 and 7.5% of body weight, respectively) followed by RSE (5 × 10 s maximal pedaling exercise, separated by a 40 s rest between sprints) using an electromagnetically braked cycling ergometer (Power Max VIII; Konami Corporation, Tokyo, Japan) with or without BFR during rest periods (**Figure 1**). The load during the pedaling was set as equivalent to 7.5% of body weight. During the entire RSE, BFR cuffs (Rapid version cuff, Hokanson Inc., Bellevue, WA, United States) were placed bilaterally to the most proximal part of each leg in both trials. In the BFR trial, the cuffs were inflated to 140 mmHg for 30 s between sprints (between 5 and 35 s into rest) in each leg. When pressure was applied, participants maintained an upright posture by dropping the right leg while sitting on the bike. The pressure and duration for BFR were determined from previous studies (Taylor et al., 2016; Mitchell et al., 2019) and several our preliminary studies to confirm whether the exercise is possible to complete without profound power reduction and pain. During CON trial, the cuffs remained deflated (without pressure) while participants were requested to maintain an identical posture to in the BFR trial. Immediately and at 5 min after completing the fifth BFR (35 s later following completion of the exercise), blood lactate concentrations were measured.

Measurements

Muscle Oxygenation Evaluated by Near-Infrared Spectroscopy (NIRS)

Uninterrupted (sprints and rest periods) measurements of the muscle oxygenation of the right *vastus lateralis* were obtained using a portable NIRS system (Hb14-2; ASTEM Co., Ltd., Kanagawa, Japan). The probe was attached to the skin surface emits two different wavelengths from near-infrared light (wave length: 770 and 830 nm), with average optrode–detector distances of 20 and 30 mm, respectively, and the penetration light (depth below the skin surface; 100 and 150 mm) is detected in the light-receiving element. The probe was placed on the right thigh, at the middle point between the great trochanter and knee joint (*vastus lateralis* muscle) and covered with a black cloth to protect it from light. The oxy-Hb, deoxy-Hb, and total-hemoglobin (total-Hb) levels were recorded at a sampling frequency of 10 Hz and were averaged during each sprint and rest period. The values were expressed relative to pre-exercise values while the participant was in the sitting position for 1 min.

Blood Lactate Concentration

Blood samples were collected from a fingertip to evaluate blood lactate concentrations before, immediately (35 s later due to fifth BFR) after exercise and at 5 min following fifth BFR. Blood lactate concentrations were measured immediately after collecting blood samples using lactate analyzer (Lactate Pro, ARKRAY Co., Kyoto, Japan).

Heart Rate

Heart rate was recorded continuously every second throughout the exercise using heart rate monitor (RCX5, Polar Electro Oy, Finland). Also, heart rate was averaged during every sprint (10 s) and rest period (40 s) and used for further analysis.

Statistical Analyses

Data are expressed as means ± SD. Normal distribution was confirmed using Kolmogorov-Smirnov test for all variables. A two-way repeated-measure ANOVA was used to determine the main effects of trial, time, and trial × time interaction. If significant effects were found, a Tukey-Kramer *post-hoc* test was used for pairwise comparison. Power output was compared between trials using a paired *t*-test. Statistical significance was determined at $P < 0.05$. Effect sizes (ES) were calculated by partial eta squared (η^2) for two-way ANOVA with repeated measures.

RESULTS

Figure 2 showed time-course changes in oxy-Hb and deoxy-Hb levels. Statistical analysis revealed a significant trial × time interaction and main effects of time and trial for oxy-Hb during both sprints (interaction: $P < 0.001$, $\eta^2 = 0.797$, time: $P < 0.001$, $\eta^2 = 0.516$, trial: $P = 0.001$, $\eta^2 = 0.864$) and rest periods (interaction: $P < 0.001$, $\eta^2 = 0.746$, time: $P = 0.711$, $\eta^2 = 0.055$, trial: $P < 0.001$, $\eta^2 = 0.908$). Oxy-Hb levels were significantly lowered in the BFR trial than CON trial during sprint and rest periods ($P < 0.05$). A significant main effect for time was found in deoxy-Hb during sprints ($P = 0.009$, $\eta^2 = 0.620$) and rest periods ($P = 0.026$, $\eta^2 = 0.546$). In contrast, there was a tendency of interaction ($P = 0.050$) for deoxy-Hb during sprints, but the ES was modest ($\eta^2 = 0.450$).

Time-course changes in total-Hb and StO_2 levels were indicated in **Figure 3**. A significant main effect of time was detected in total-Hb during sprints ($P = 0.003$, $\eta^2 = 0.704$) and rest periods ($P = 0.024$, $\eta^2 = 0.539$). Two-way ANOVA reveled that a significant interaction, main effect for time and/or trial in StO_2 during sprints (interaction: $P < 0.001$, $\eta^2 = 0.700$, time: $P < 0.001$, $\eta^2 = 0.694$) and rest periods (interaction: $P < 0.001$, $\eta^2 = 0.629$, time: $P = 0.001$, $\eta^2 = 0.723$, trial: P = 0.003, $\eta^2 = 0.795$). StO_2 levels were significantly decreased throughout the exercise with BFR with significant lower values in BFR trial than in CON trial after the third set of sprints and rest periods between all sprints ($P < 0.05$).

Figure 4 indicated time-course changes in mean power output, heart rate throughout the exercise and blood lactate concentrations immediately and at 5 min after exercise. Statistical analysis revealed a significant main effect for time in mean power output ($P < 0.001$, $\eta^2 = 0.765$). Mean power output was significantly reduced from the third to fifth set of sprints in both trials. However, there was no significant difference between trials ($P > 0.05$). In addition, the total power output (sum of power output over first to fifth sets of sprints) did not differ between BFR and CON trials (46.8 ± 2.9 W/kg vs. 49.5 ± 2.4 W/kg for five sprints, $P = 0.16$). When the peak power output was calculated, a significant interaction ($P = 0.001$, $\eta^2 = 0.574$) and main effect of time ($P = 0.001$, $\eta^2 = 0.861$) and trial ($P = 0.014$, $\eta^2 = 0.735$) were observed. Peak power output was significantly decreased with progress of sprints in both trials ($P < 0.05$), and significantly lower values were observed in BFR trial than those in CON trial at fourth and fifth set of sprints ($P < 0.05$). A significant interaction ($P = 0.040$, $\eta^2 = 0.566$) and main effect for time ($P < 0.001$, $\eta^2 = 0.910$) were observed in time-course changes in heart rate. Heart rate was significantly increased with progress of sprints in both trials, and significantly higher value was observed in BFR trial than that in CON trial during fifth set of sprint ($P < 0.05$). For blood lactate concentrations, there was a significant main effect of time ($P < 0.001$, $\eta^2 = 0.921$). Blood lactate concentrations were significantly increased with exercise and significantly higher values were also observed even at 5 min after exercise in both trials.

DISCUSSION

The purpose of the present study was to investigate the acute effects of repeated sprints with or without BFR during rest periods between sprints on muscle oxygenation. Our main finding was that both oxy-Hb and StO_2 levels (but not deoxy-Hb and total-Hb levels) were significantly lower when BFR was applied during rest periods, despite mean power output throughout the exercise was similar between trials. Therefore, the application of BFR during rest periods of a RSE could be an efficient strategy for producing sustained local hypoxia in working muscles, without compromising power production.

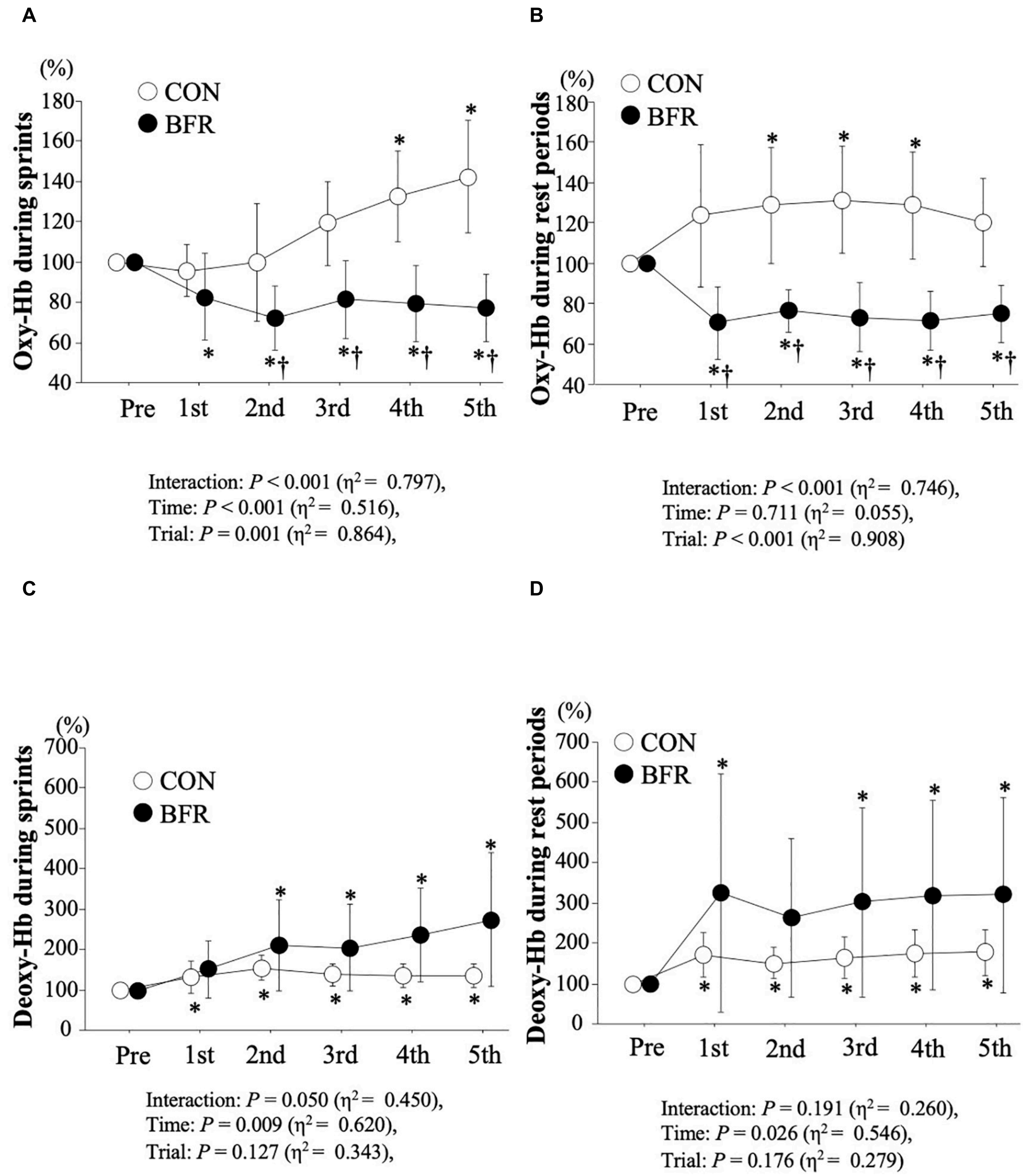

FIGURE 2 | Oxy-Hb levels (*top panel*; **(A,B)**, respectively) and deoxy-Hb levels (*bottom panel*; **(C,D)**, respectively) during sprints and rest periods. Values are means ± SD. *$P < 0.05$ vs. Pre, $^{\dagger}P < 0.05$ vs. CON.

In the present study, both oxy-Hb and StO_2 levels were lower when BFR was applied during rest periods. Generally, decreased oxy-Hb with increased deoxy-Hb are observed during the actual sprint across repetition, before rapidly returning near baseline during rest periods between efforts (Racinais et al., 2007; Smith and Billaut, 2010). Therefore, it appears that BFR during rest periods interferes with reoxygenation in working muscles. However, total-Hb, a marker of blood volume (Van Beekvelt et al., 2001), remained unchanged between trial at any time point. A recent study demonstrated that total-Hb levels during repeated double-poling sprint exercise were significantly higher under systemic hypoxia trials than under normoxia, probably due to augmented vasodilation via nitric oxide production (Yamaguchi et al., 2019). Furthermore, there was no significant difference in time-course changes in deoxy-Hb levels between trials. Christiansen et al. (2018) indicated that BFR during sprint interval running exercise significantly increased deoxy-Hb levels. In the present study, BFR was applied only during 30-s rest periods between sprints, and with same pressure among participants, suggesting that relative pressure was possible to be

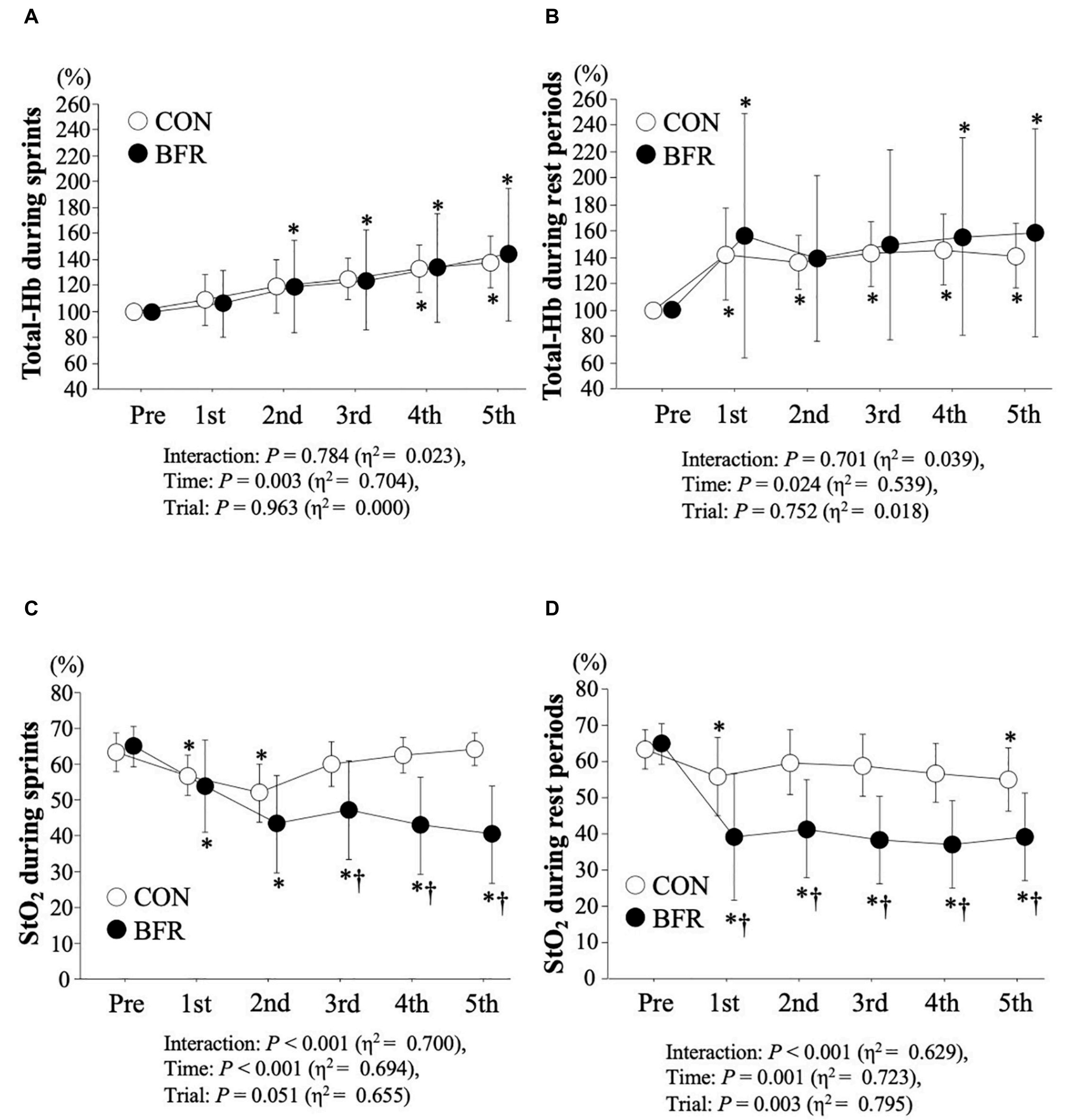

FIGURE 3 | Total-Hb levels (*top panel*; **(A,B)**, respectively) and StO_2 levels (*bottom panel*; **(C,D)**, respectively) during sprints and rest periods. Values are means ± SD. *$P < 0.05$ vs. Pre, †$P < 0.05$ vs. CON.

different for among participants. It is plausible that the duration of BFR and/or how to apply the pressure (140 mmHg), which would affect the severity of local hypoxia, was insufficient to alter total-Hb and deoxy-Hb levels.

Most previous studies (Fujita et al., 2007; Abe et al., 2010; Kim et al., 2014) have focused on the impact of BFR application during the actual exercise period (e.g., resistance or endurance exercise). Additionally, these BFR studies commonly utilized low-intensity exercise with BFR, since the application of cuff pressure during high-intensity exercise would not successfully restrict blood circulation within working muscles due to augmented muscle pump action. However, two previous studies succeeded to determine the combined effects of SIE (30 s maximal efforts with several minute of rest periods) with BFR (∼130 mmHg) during rest periods (Taylor et al., 2016; Mitchell et al., 2019). Actually, Taylor et al. (2016) investigated gene expression in working muscles following a single bout of SIE (repeated 30-s maximal sprints) with post-exercise BFR application during the first 2 min into the 4.5 min of rest periods between efforts. These authors observed that HIF-1α mRNA expression was significantly augmented following a single bout of SIT when post-exercise BFR was applied, suggesting that tissue was exposed to hypoxia and greater metabolic stress was produced with 2 min of BFR between sprints (Taylor et al., 2016). Unlike these previous studies, the present study is the first to directly report local hypoxia (decreased oxy-Hb and StO_2 levels within working

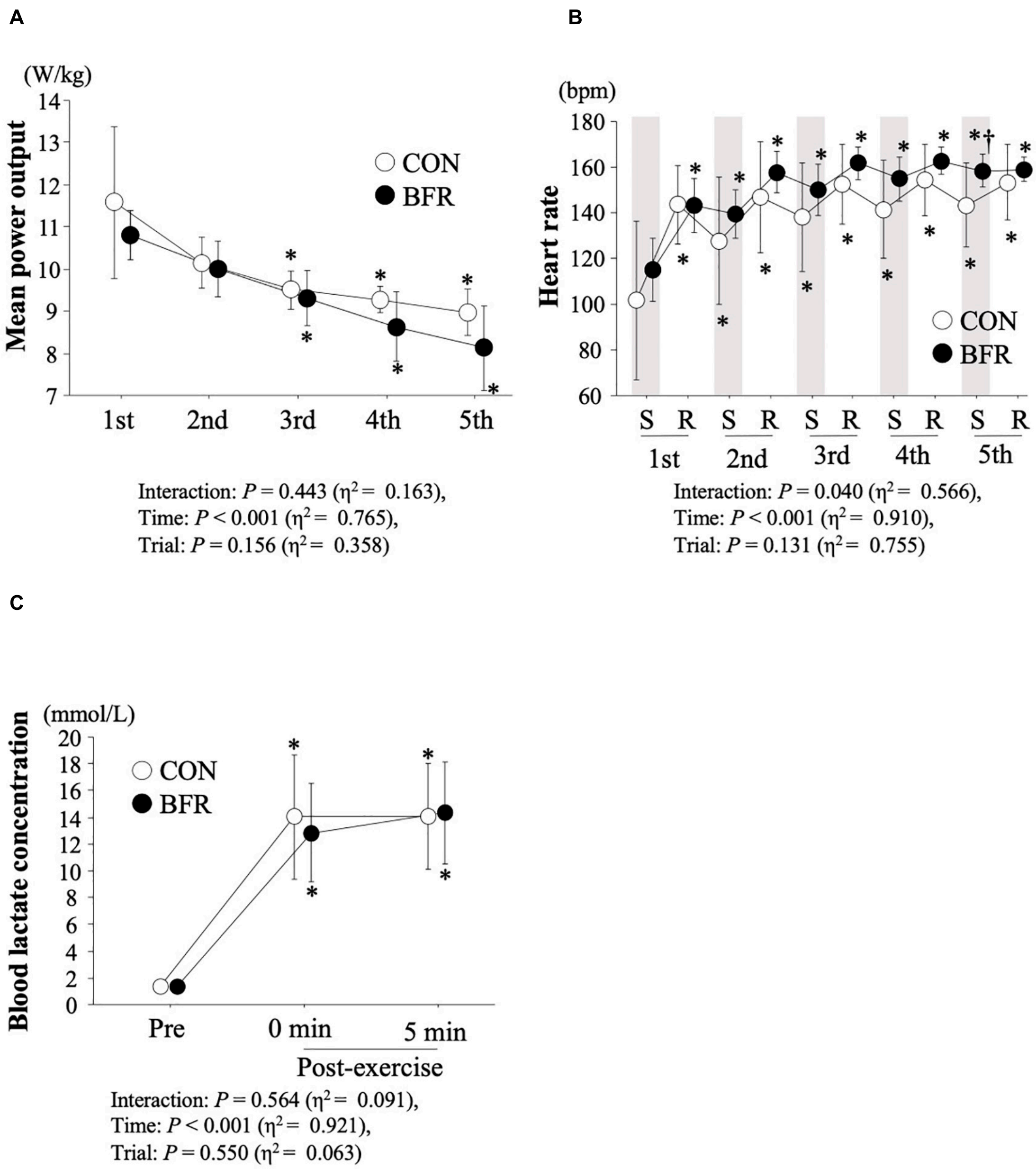

FIGURE 4 | Mean power putout **(A)**, heart rate **(B)** during sprints and rest periods, and lactate concentrations before and after exercise **(C)**. Values are means ± SD. *$P < 0.05$ vs. Pre, †$P < 0.05$ vs. CON. S, sprint; R, rest period. Gray bar indicates average heart rate during sprint exercise in each set.

muscles) induced by brief (30 s) periods of BFR after each sprint during an acute RSE session using NIRS. On the other hand, Peyrard et al. (2019) and Willis et al. (2019b,c) determined the effect of BFR throughout entire leg or arm RSE sessions on muscle oxygenation. In these studies, BFR was maintained during both sprints and rest periods, which was different from the present study. These authors indicated that the addition of BFR to RSE consequently augmented blood perfusion (Willis et al., 2019a), but that power output during arm sprint with BFR was significantly attenuated (Peyrard et al., 2019). In contrast, the application of BFR between sprints in the present study had no negative impact on power output. Our data indicate, for the first time, it is likely that blood flow restricted during rests of repeated cycling sprints would allow the working muscles to exert local hypoxia without attenuating power output across sprints repetition.

However, we did not find significant difference between trials in blood lactate concentrations, suggesting that metabolic perturbations might not be augmented in BFR trial. Future studies are necessary to evaluate intramuscular lactate concentration and metabolic acidosis (e.g., blood hydrogen ion, bicarbonate ion, and base excess) to clarify the impact of the present training strategy on metabolic regulations. In addition, peak power output was attenuated during the latter phase of exercise with BFR although there was no significant difference between trials in mean power output and total power output throughout the sprints. Several previous studies demonstrated that repeated sprint performance was associated with PCr resynthesis involving in blood flow and aerobic metabolism (Gaitanos et al., 1993; Bogdanis et al., 1996; Dawson et al., 1997) as well as glycolysis system. The present study demonstrated that Oxy-Hb and StO_2 levels were lowered in BFR trial, suggesting that PCr content might not be fully resynthesized due to BFR during rest period between sprints at the latter phase of sprints. Therefore, determinations of PCr kinetics during interest rest periods of RSE with BFR, in addition to muscle oxygenation, would be required in future studies. Furthermore, the comparison of acute physiological response and training adaptations between "local hypoxia (i.e., BFR)" and "systemic hypoxia (i.e., normobaric hypoxia)" would be a valuable challenge. A recent review demonstrated that a single session of strenuous exercise with BFR produced augmented physiological stimulus for vascular resistance and altered vasodilatory responses compared with systemic hypoxia during the same exercise (Willis et al., 2019a).

In conclusion, an acute RSE session combined with BFR during rest periods between sprints decreased oxy-Hb and StO_2 levels within working muscles, but did not affect power output, deoxy-Hb, or total-Hb. This represents a meaningful intervention for augmented internal stress (training stimulus) without negatively impacting training workload (training quality).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of Ritsumeikan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CK and KG designed the present study. CK, KY, HI, NK, and KG collected and analyzed the data. CK, OG, and KG undertook the data interpretation and manuscript preparation. All authors approved the final version of the manuscript.

ACKNOWLEDGMENTS

We wish to thank all of the participants in the present study. Also, we acknowledge the laboratory members for the technical supports.

REFERENCES

Abe, T., Fujita, S., Nakajima, T., Sakamaki, M., Ozaki, H., Ogasawara, R., et al. (2010). Effects of low-intensity cycle training with restricted leg blood flow on thigh muscle volume and VO2MAX in young men. *J. Sports Sci. Med.* 9, 452–458.

Bishop, D., Edge, J., and Goodman, C. (2004). Muscle buffer capacity and aerobic fitness are associated with repeated-sprint ability in women. *Eur. J. Appl. Physiol.* 92, 540–547. doi: 10.1007/s00421-004-1150-1

Bishop, D., Girard, O., and Mendez-Villanueva, A. (2011). Repeated-sprint ability – Part II. *Sports Med.* 41, 741–756. doi: 10.2165/11590560-000000000-00000

Bogdanis, G. C., Nevill, M. E., Boobis, L. H., and Lakomy, H. K. (1996). Contribution of phosphocreatine and aerobic metabolism to energy supply during repeated sprint exercise. *J. Appl. Physiol.* 80, 876–884. doi: 10.1152/jappl.1996.80.3.876

Christiansen, D., Murphy, R. M., Bangsbo, J., Stathis, C. G., and Bishop, D. J. (2018). Increased FXYD1 and PGC-1α mRNA after blood flow-restricted running is related to fibre type-specific AMPK signalling and oxidative stress in human muscle. *Acta Physiol. (Oxf)* 223:e13045. doi: 10.1111/apha.13045

Davies, C. T., Wemyss-Holden, J., and Young, K. (1984). Measurement of short term power output: comparison between cycling and jumping. *Ergonomics* 27, 285–296. doi: 10.1080/00140138408963490

Dawson, B., Goodman, C., Lawrence, S., Preen, D., Polglaze, T., Fitzsimons, M., et al. (1997). Muscle phosphocreatine repletion following single and repeated short sprint efforts. *Scand. J. Med. Sci. Sports* 7, 206–213. doi: 10.1111/j.1600-0838.1997.tb00141.x

Fenn, W. O., and Marsh, B. S. (1935). Muscular force at different speeds of shortening. *J. Physiol.* 85, 277–297. doi: 10.1113/jphysiol.1935.sp003318

Fujita, S., Abe, T., Drummond, M. J., Cadenas, J. G., Dreyer, H. C., Sato, Y., et al. (2007). Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *J. Appl. Physiol.* 103, 903–910. doi: 10.1152/japplphysiol.00195.2007

Gaitanos, G. C., Williams, C., Boobis, L. H., and Brooks, S. (1993). Human muscle metabolism during intermittent maximal exercise. *J. Appl. Physiol.* 75, 712–719. doi: 10.1152/jappl.1993.75.2.712

Kim, E., Gregg, L. D., Kim, L., Sherk, V. D., Bemben, M. G., and Bemben, D. A. (2014). Hormone responses to an acute bout of low intensity blood flow restricted resistance exercise in college-aged females. *J. Sports Sci. Med.* 13, 91–96.

Mitchell, E. A., Martin, N. R. W., Turner, M. C., Taylor, C. W., and Ferguson, R. A. (2019). The combined effect of sprint interval training and blood flow restriction on critical power, capillary growth and mitochondrial proteins in trained cyclists. *J. Appl. Physiol.* 126, 51–59. doi: 10.1152/japplphysiol.01082.2017

Peyrard, A., Willis, S. J., Place, N., Millet, G. P., Borrani, F., and Rupp, T. (2019). Neuromuscular evaluation of arm-cycling repeated sprints under hypoxia and/or blood flow restriction. *Eur. J. Appl. Physiol.* 119, 1–13. doi: 10.1007/s00421-019-04143-4

Racinais, S., Bishop, D., Denis, R., Lattier, G., Mendez-Villaneuva, A., and Perrey, S. (2007). Muscle deoxygenation and neural drive to the muscle during repeated sprint cycling. *Med. Sci. Sports Exerc.* 39, 268–274. doi: 10.1249/01.mss.0000251775.46460.cb

Smith, K. J., and Billaut, F. (2010). Influence of cerebral and muscle oxygenation on repeated-sprint ability. *Eur. J. Appl. Physiol.* 109, 989–999. doi: 10.1007/s00421-010-1444-4

Taylor, C. W., Ingham, S. A., and Ferguson, R. A. (2016). Acute and chronic effect of sprint interval training combined with postexercise blood-flow restriction in trained individuals. *Exp. Physiol.* 101, 143–154. doi: 10.1113/EP085293

Van Beekvelt, M. C. P., Shoemaker, J. K., Tschakovsky, M. E., Hopman, M. T. E., and Hughson, R. L. (2001). Blood flow and muscle oxygen uptake at the onset and end of moderate and heavy dynamic forearm exercise. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 280, R1741–R1747. doi: 10.1152/ajpregu.2001.280.6.R1741

Willis, S. J., Alvarez, L., Borrani, F., and Millet, G. P. (2018). Oxygenation time course and neuromuscular fatigue during repeated cycling sprints with bilateral blood flow restriction. *Physiol. Rep.* 6:e13872. doi: 10.14814/phy2.13872

Willis, S. J., Borrani, F., and Millet, G. P. (2019a). High-Intensity exercise with blood flow restriction or in hypoxia as valuable spaceflight countermeasures? *Front. Physiol.* 10:1266. doi: 10.3389/fphys.2019.01266

Willis, S. J., Borrani, F., and Millet, G. P. (2019b). Leg- vs arm-cycling repeated sprints with blood flow restriction and systemic hypoxia. *Eur. J. Appl. Physiol.* 119, 1819–1828. doi: 10.1007/s00421-019-04171-0

Willis, S. J., Peyrard, A., Rupp, T., Borrani, F., and Millet, G. P. (2019c). Vascular and oxygenation responses of local ischemia and systemic hypoxia during arm cycling repeated sprints. *J. Sci. Med. Sport* 22, 1151–1156. doi: 10.1016/j.jsams.2019.05.001

Yamaguchi, K., Kasai, N., Sumi, D., Yatsutani, H., Girard, O., and Goto, K. (2019). Muscle oxygenation during repeated double-poling sprint exercise in normobaric hypoxia and normoxia. *Front. Physiol.* 10:743. doi: 10.3389/fphys.2019.00743

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Physiology

ORIGINAL RESEARCH
published: 10 August 2021
doi: 10.3389/fphys.2021.715096

The Effects of Ischemia During Rest Intervals on Bar Velocity in the Bench Press Exercise With Different External Loads

Jakub Jarosz[1], Robert Trybulski[2,3], Michał Krzysztofik[1], Athanasios Tsoukos[4], Aleksandra Filip-Stachnik[1], Adam Zajac[1], Gregory C. Bogdanis[4] and Michal Wilk[1]*

[1] Institute of Sport Sciences, Jerzy Kukuczka Academy of Physical Education in Katowice, Katowice, Poland, [2] Department of Medical Sciences, The Wojciech Korfanty School of Economics, Katowice, Poland, [3] Provita Zory Medical Center, Zory, Poland, [4] School of Physical Education and Sport Science, National and Kapodistrian University of Athens, Athens, Greece

OPEN ACCESS

Edited by:
Antonio Paoli,
University of Padua, Italy

Reviewed by:
Hamid Arazi,
University of Guilan, Iran
Eduardo Carballeira,
University of A Coruña, Spain

****Correspondence:***
Michal Wilk
m.wilk@awf.katowice.pl

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *26 May 2021*
Accepted: *22 July 2021*
Published: *10 August 2021*

Citation:
Jarosz J, Trybulski R, Krzysztofik M, Tsoukos A, Filip-Stachnik A, Zajac A, Bogdanis GC and Wilk M (2021) The Effects of Ischemia During Rest Intervals on Bar Velocity in the Bench Press Exercise With Different External Loads. Front. Physiol. 12:715096. doi: 10.3389/fphys.2021.715096

The main aim of the present study was to evaluate the acute effects of ischemia used during rest periods on bar velocity changes during the bench press exercise at progressive loads, from 20 to 90% of 1RM. Ten healthy resistance trained men volunteered for the study (age = 26.3 ± 4.7 years; body mass = 89.8 ± 6.3 kg; bench press 1RM = 142.5 ± 16.9 kg; training experience = 7.8 ± 2.7 years). During the experimental sessions the subjects performed the bench press exercise under two different conditions, in a randomized and counterbalanced order: (a) ischemia condition, with ischemia applied before the first set and during every rest periods between sets, and (b) control condition where no ischemia was applied. During each experimental session eight sets of the bench press exercise were performed, against loads starting from 20 to 90% 1RM, increased progressively by 10% in each subsequent set. A 3-min rest interval between sets was used. For ischemia condition the cuffs was applied 3 min before the first set and during every rest period between sets. Ischemia was released during exercise. The cuff pressure was set to ~80% of full arterial occlusion pressure. The two-way repeated measures ANOVA showed a statistically significant interaction effect for peak bar velocity ($p = 0.04$) and for mean bar velocity ($p = 0.01$). There was also a statistically significant main effect of condition for peak bar velocity ($p < 0.01$) but not for mean bar velocity ($p = 0.25$). The *post hoc* analysis for interaction showed significantly higher peak bar velocity for the ischemia condition compared to control at a load of 20% 1RM ($p = 0.007$) and at a load of 50% 1RM ($p = 0.006$). The results of the present study indicate that ischemia used before each set even for a brief duration of <3 min, has positive effects on peak bar velocity at light loads, but it is insufficient to induce such effect on higher loads.

Keywords: blood flow restriction, occlusion, resistance exercise, sport performance, training, high-velocity resistance training, explosive strength

INTRODUCTION

Ischemia used in athletic training and rehabilitation is the temporary restriction of blood flow to the arms or legs through external compression (Eltzschig and Eckle, 2011; Schwiete et al., 2021). This compression is usually induced by inflatable cuffs or elastic bands which are wrapped around the proximal parts of the upper or lower limbs (Loenneke et al., 2012). Ischemia induced by a cuff is simple and non-invasive, and therefore easy for practical use (Marocolo et al., 2018). There are many methods of using ischemia as part of physical activity, such as continuous ischemia (used during exercise and rest periods) (Wilk et al., 2020b), intermittent ischemia (used only during exercise) (Wilk et al., 2020d,e), pre-conditioning ischemia (used before exercise) (Telles et al., 2020) and intra-conditioning (used only during the rest periods) (Wilk et al., 2021b). The use of ischemia during exercise, apart from inducing physiological responses, may be accompanied by high ratings of perceived exertion and discomfort or even pain among practitioners (Wernbom et al., 2006; Neto et al., 2018; Schwiete et al., 2021). A way to reduce this discomfort may be to reduce the time during which ischemia is applied, by using it only in the rest intervals between sets of resistance exercise (Yasuda et al., 2015; Freitas et al., 2019, 2020; Wilk et al., 2021b).

Previous studies demonstrated the beneficial effects of ischemic pre-conditioning on performance during different types of exercise (swimming, running, cycling, resistance exercise) (Marocolo et al., 2015, 2016; Ferreira et al., 2016; Paradis-Deschênes et al., 2016; Sabino-Carvalho et al., 2017). Ischemia improves exercise performance and stimulates several physiological responses (Liu et al., 1991; Lawson and Downey, 1993; Pang et al., 1995; Schroeder et al., 1996; Kimura et al., 2007; Li et al., 2012; Paradis-Deschênes et al., 2016; Tanaka et al., 2018), albeit the mechanisms underlying its effects have not been explored exhaustively. Kocman et al. (2015) suggested that the muscles previously subjected to ischemia, become more resistant to ischemia during exercise and its potential deleterious effects. Furthermore, ischemia used before exercise improves metabolic efficiency by attenuating ATP depletion, as well as glycogen depletion and lactate production (Pang et al., 1995; Schroeder et al., 1996; Addison et al., 2003; Lintz et al., 2013). Further, the ischemia pre-conditioning can improve blood flow in skeletal muscles, by inducing vasodilation (Enko et al., 2011), improving functional sympatholysis (Liu et al., 1991), and preserving microvascular endothelium function during stress (Kharbanda et al., 2002; Wang et al., 2004; Bailey et al., 2012; Horiuchi et al., 2015). A recent work by Wilk et al. (2021b) also showed a beneficial effect of ischemic intra-conditioning on explosive performance. In that study there was an increase in bar velocity and power output during the bench press exercise (five sets, three repetitions, 60% of one repetition maximum-RM; 5 min rest interval) when ischemia 80% of arterial occlusion pressure-AOP was used before the first set and during all rest periods between sets. Similarly, beneficial effects on explosive bench press performance were observed when ischemia was applied during the exercise (Wilk et al., 2020b,c). However, the positive effects of different types of ischemia during exercise (intermittent and continuous at 70% AOP) seem to be depended on external load used (Wilk et al., 2020b). Specifically, the positive effects on peak bar velocity during the bench press exercise were evident in lighter loads (20–50% 1RM) but disappeared when heavier loads (60–90% 1RM) were used (Wilk et al., 2020b). On the contrary, Wilk et al. (2020e) showed that intermittent, high pressure ischemia (90% AOP) significantly increased power output and bar velocity during the bench press exercise at a load of 70% 1RM, but only when a wider cuff was used, while there was no effect when a narrow cuff was used. Therefore, the benefits of ischemia on exercise performance appear to depend on the external load used, as well as the width and pressure of the cuff. However, the relationship between the external load used and the effects of ischemia applied during the rest intervals only, has not yet been examined. Therefore, it seems justified to determine whether there is a relationship between the changes in bar velocity and the external load used, when ischemia is applied only during the rest intervals between sets.

The bench press exercise was selected, as it is the most popular upper-body resistance exercise, commonly used in practice and science research (Wilk et al., 2019c; Maszczyk et al., 2020; Filip-Stachnik et al., 2021b; Krzysztofik et al., 2021), while ischemia during the rest intervals only may be more tolerated than continuous ischemia during resistance training. Thus, the main aim of the present study was to evaluate the acute effects of ischemia used during rest periods on bar velocity changes during the bench press exercise at progressive loads, from 20 to 90% of 1RM. Since previous studies showed a beneficial effect of resting ischemia on physical performance (Telles et al., 2020), it was hypothesized that ischemia used only during the rest intervals would increase bar velocity during the bench press exercise at all loads used.

MATERIALS AND METHODS

All stages of the study were performed in the Strength and Power Laboratory at the Academy of Physical Education in Katowice, Poland. A randomized crossover design was used, where each participant performed two training protocols in a random and counterbalanced order, 1 week apart: with ischemia used before exercise and during the rest intervals between sets (ischemia condition), and a control condition, without ischemia. During each training session, the participants performed eight sets of the bench press exercise with two repetitions in each set, with progressive loads from 20 to 90% 1RM (10% steps), and 3 min rest periods between each set. During the ischemia condition occlusion with 80% AOP was applied using a 10 cm wide cuff, before the first set of the bench press exercise and during all rest periods between sets. The ischemia was applied in close proximity to the axillary's fossa of both arms. During the control condition no ischemia was applied.

Subjects

Power analysis indicated a sample size of eight participants would be needed to detect significant differences if the effect size (ES) was 0.25. Power analysis was performed using the following parameters: type of analysis was set to repeated-measures ANOVA (within factors), the required power (1-β error) was set to 0.80, alpha was set to 0.05, and the correlation coefficient among repeated measures was set to 0.5 (G-Power software, v.3.1.9.2).

Ten healthy resistance trained men volunteered for the study [age = 26.3 ± 4.7 years; body mass = 89.8 ± 6.3 kg; bench press 1RM = 142.5 ± 16.9 kg; training experience = 7.8 ± 2.7 years; relative strength (1RM/body mass) = 1.59 ± 0.13]. The inclusion criteria were a bench press 1RM performance of at least 150% body mass (Wilk et al., 2019b) and no musculoskeletal injuries for at least 6 months prior to the study. Participants were instructed to maintain their normal dietary habits over the course of the study and not to use any supplements or stimulants for the duration of the experiment. The participants were informed about the potential risks of the study before providing their written informed consent for participation and were allowed to withdraw from the study at any time. The study protocol was approved by the Bioethics Committee for Scientific Research, at the Academy of Physical Education in Katowice, Poland (02/2019), and all procedures were in accordance with the ethical standards of the Declaration of Helsinki, 1983.

Procedures

Familiarization Session

Two weeks before the main experiment, the participants performed a familiarization session. Familiarization, and experimental sessions were performed at the same time of the day, between 9:00 a.m. and 11:00 a.m., to avoid the influence of circadian rhythm on performance. During the familiarization session, the participants performed a warm-up that was consistent with subjects normal training habits, followed by a specific warm-up during which they performed the free-weight barbell bench press exercise at 20 kg and then at 40%, 60% of their estimated 1RM with 8, 6, and 3 repetitions, respectively. During each warm-up set the participants performed 5–8 repetitions. During the familiarization sessions each participant performed six sets of the bench press exercise with ischemia used during the rest intervals. The load was increased by 10% from 40 to 80% of the estimated 1RM. In each set, two repetitions with maximal movement tempo were performed.

One Repetition Maximum Test (1RM)

One week before the main experiment a 1RM free-weight barbell bench press test was performed as described elsewhere (Filip-Stachnik et al., 2021a; Wilk et al., 2021a). The 1RM test is considered the gold standard for assessing muscle strength under non-laboratory conditions (Levinger et al., 2009). Briefly, the session started with the general upper body warm-up, similar to that performed during familiarization. Afterwards, the participants performed specific bench press warm-up at a load of 20, 40, and 60% of their estimated 1RM with 8, 6, and 3 repetitions, respectively. The first testing load was set to an estimated 80% 1RM and was increased by 2.5–10 kg for each subsequent trial. This process was repeated until failure. Grip width on the bar was set at 150% of the individual bi-acromial distance, and the same grip width was used in the main experimental sessions (Wilk et al., 2019a).

Experimental Sessions

The experimental procedure was similar to that described in the study of Wilk et al. (2020b) with the exception of the ischemia method. The subjects performed the free-weight barbell bench press exercise under two different conditions, in a randomized and counterbalanced order: (a) ischemia condition, with ischemia applied before the first set and during every rest interval between sets, and (b) control condition where no ischemia was applied. During each experimental session eight sets of the bench press exercise were performed, against loads starting from 20 to 90% 1RM, increased progressively by 10% in each subsequent set. In each set, two repetitions were performed. Research has shown that the fastest movement velocity (peak and mean) is achieved in the first two repetitions (García-Ramos et al., 2021). Furthermore it was chosen two repetitions to avoid the cumulative fatigue in the last loads. Each repetition was performed with a 2 s duration for the eccentric phase and maximal velocity in the concentric phase of movement (Wilk et al., 2020a,c). A 3-min rest interval between sets was used. Bar velocity was monitored using a linear position transducer system (Tendo Power Analyzer, Tendo Sport Machines, Trencin, Slovakia). This device has shown high reliability and validity, intra-class correlation co-efficient (ICC) of 0.984 for peak bar velocity and 0.989 for mean bar velocity, and a coefficient of variation (CV) ranging from 9 to 9.6% (Garnacho-Castaño et al., 2015). Peak bar velocity was obtained from the best repetition performed in each set. Mean bar velocity was obtained as the mean of two repetitions performed in each set.

Ischemia

Ischemia was induced by cuffs worn at the most proximal region of both arms. For this experiment we used SmartCuffs (Smart Tools Plus LLC, Strongsville, OH, United States) which are 10-cm wide. The ischemia was applied 3 min before the first set and during every rest period between sets. The ischemia was applied for approximately 2.5 min during each rest interval, as it took about 20 s to inflate and 10 s to deflate the cuffs. Occlusion was released during exercise. The cuff pressure was set to ∼80% of full arterial occlusion pressure (115 ± 10 mmHg). The individual pressure value was determined by a handheld Edan SD3 Doppler with an OLED screen and a 2-mHz probe (Edan Instruments Inc., Shenzhen, China) placed over the radial artery to assess the blood pressure required for interruption of auscultatory pulse (Wilk et al., 2020b,e, 2021b).

Statistical Analysis

All statistical analyses were performed using Statistica 9.1. Results are presented as means with standard deviations. The Shapiro–Wilk, Levene, and Mauchly's tests were used to verify normality, homogeneity, and sphericity of the sample data variances, respectively. Differences between the ischemia and control conditions were examined using two-way repeated measures ANOVA [2 conditions (ischemia vs. control) × 8 sets (load 20–90% 1RM)]. ES for main effects and interactions were determined by partial eta squared (η^2). Partial eta squared values were classified as small (0.01–0.059), moderate (0.06–0.137), and large (>0.137) (Hopkins et al., 2009). *Post hoc* comparisons using the Tukey's test were conducted to locate the differences between mean values, when a main effect or an interaction was found. For pairwise comparisons, ESs were determined by Cohen's *d* which was characterized as large ($d > 0.8$), moderate (*d* between 0.8 and 0.5), small (*d* between 0.49 and 0.20), and trivial ($d < 0.2$) (Cohen, 1988). Percent changes with 90% confidence intervals (90CI) were also calculated. Statistical significance was set at $p < 0.05$.

RESULTS

Peak and mean bar velocity in all sets of the two conditions are presented in **Table 1**. The two-way repeated measures ANOVA showed a statistically significant interaction effect for peak bar velocity ($p = 0.04$; $\eta^2 = 0.20$) and for mean bar velocity ($p = 0.01$; $\eta^2 = 0.20$). There was also a statistically significant main effect of condition for peak bar velocity ($p < 0.01$; $\eta^2 = 0.40$) but not for mean bar velocity ($p = 0.25$; $\eta^2 = 0.15$).

The *post hoc* analysis for interaction showed significantly higher peak bar velocity for the ischemia condition compared to control at a load of 20% 1RM (2.30 ± 0.24 vs. 2.17 ± 0.24 m/s, $p = 0.007$) and at a load of 50% 1RM (1.34 ± 0.21 vs. 1.21 ± 0.25 m/s, $p = 0.006$, **Table 1**).

DISCUSSION

The main finding of the present study was that ischemia used before each set significantly increased peak bar velocity during the bench press exercise only against the 20 and 50% 1RM loads. Furthermore, no positive effects of ischemia were observed on mean bar velocity. Therefore, it appears that the effect of ischemia on peak bench press performance was limited to lighter load, while increasing the load during the subsequent sets canceled out any effects of between-sets ischemia on performance.

Previous studies have confirmed that muscular ischemia during exercise (Gepfert et al., 2020) or before exercise increases physical performance in various types of physical activity (Telles et al., 2020). However, only one previous study assessed the effect of ischemia applied before exercise and during rest intervals between sets of resistance exercise on explosive performance. In that study, ischemia significantly increased peak power output and peak bar velocity during the bench press exercise, while it had no effect on mean values (Wilk et al., 2021b). However, in the present study, the bench press exercise was performed against increasing loads (8 sets at 20–90% 1RM), while in the study of Wilk et al. (2021b) the load was constant for all sets (5 sets at 60% 1RM). This indicates that the increase in load during subsequent sets cancels any positive effects of between-sets ischemic on performance. Thus, ischemia applied before the first sets, appears to be beneficial for peak bench press performance at 20 and 50% 1RM (**Table 1**). Similar findings regarding the positive effect of ischemic preconditioning have been observed during strength-endurance resistance exercise (Marocolo et al., 2015). In that study, the number of repetitions during leg extension exercise to exhaustion was increased following ischemia compared to control (Marocolo et al., 2015). Furthermore, ischemia used during rest periods may enhance ATP production by glycolytic and phosphogenic pathways (Janier et al., 1994; Mendez-Villanueva et al., 2012), as well as peak contractile force (Andreas et al., 2011). Since the level of power output generated by the muscle depends on these substrates and metabolic mechanisms (Kraemer et al., 1987; Robergs et al., 1991), this may be the physiological basis for explaining the obtained results. Furthermore, the reactive hyperemia (during the reperfusion phase after occlusion) may be associated with potentiated force production and with a beneficial effect on explosive performance (Libonati et al., 1998; Marocolo et al., 2015).

TABLE 1 | Bar velocity during eight sets of the bench press exercise under two conditions.

Condition	20% 1RM	30% 1RM	40% 1RM	50% 1RM	60% 1RM	70% 1RM	80% 1RM	90% 1RM
				Peak bar velocity (m/s)				
Control	2.17 ± 0.24 (2.04–2.31)	1.81 ± 0.16 (1.72–1.90)	1.52 ± 0.32 (1.33–1.71)	1.21 ± 0.25 (1.06–1.35)	1.04 ± 0.15 (0.96–1.13)	0.90 ± 0.11 (0.83–0.96)	0.72 ± 0.11 (0.66–0.78)	0.56 ± 0.13 (0.48–0.63)
Ischemia	2.30 ± 0.24 (2.16–2.44)	1.90 ± 0.24 (1.76–2.04)	1.58 ± 0.29 (1.41–1.75)	1.34 ± 0.21 (1.21–1.46)	1.10 ± 0.17 (1.00–1.20)	0.93 ± 0.15 (0.84–1.02)	0.72 ± 0.16 (0.63–0.81)	0.59 ± 0.15 (0.5–0.68)
Control vs. Ischemia (*p*-value)	0.007*	0.264	0.836	0.006*	0.852	0.998	1.000	0.997
Cohen's *d*	0.56	0.45	0.20	0.58	0.38	0.28	0.01	0.27
				Mean bar velocity (m/s)				
Control	1.44 ± 0.16 (1.39–1.60)	1.24 ± 0.11 (1.15–1.35)	1.03 ± 0.20 (0.95–1.17)	0.86 ± 0.13 (0.81–1.01)	0.74 ± 0.13 (0.66–0.82)	0.62 ± 0.11 (0.57–0.70)	0.50 ± 0.10 (0.43–0.55)	0.37 ± 0.10 (0.28–0.43)
Ischemia	1.50 ± 0.18 (1.34–1.53)	1.25 ± 0.18 (1.18–1.31)	1.06 ± 0.19 (0.91–1.15)	0.91 ± 0.17 (0.78–0.94)	0.74 ± 0.14 (0.66–0.82)	0.64 ± 0.11 (0.55–0.68)	0.49 ± 0.11 (0.44–0.56)	0.36 ± 0.13 (0.31–0.43)
Control vs. Ischemia (*p*-value)	0.088	1.000	0.996	0.372	1.000	0.999	0.999	0.999
Cohen's *d*	0.40	0.06	0.13	0.36	0.02	0.21	0.13	0.15

Values are mean ± SD, while 90% confidence intervals (CI) are presented in parentheses.
**p < 0.01 from the corresponding value in the control condition.*

Although that present study showed a main effect of condition in peak bar velocity, which favored the ischemia condition, this was due mainly to the difference in the light load, as shown by the *post hoc* test following the significant load × condition interaction. Comparisons between corresponding sets of ischemia and control in peak bar velocity showed statistically significant differences with small to moderate ES at least up to a load of 50% 1RM (ES = 0.20–0.58, **Table 1**). Therefore, there are some other possible factors that may explain the tendency of ischemia during recovery to increase peak bar velocity. One such factor may be the duration of ischemia. In the study Wilk et al. (2021b) the ischemia was applied for approximately 5 min during each rest period, while in the present study the rest interval was approximately half (i.e., 2.5 min). Previous studies have examined the effect of ischemia pre-conditioning lasting from 6 to 20 min (Lalonde and Curnier, 2015). The most common ischemia protocol involves three or four cycles of 5 min of ischemia and reperfusion (Murry et al., 1986; de Groot et al., 2010; Jean-St-Michel et al., 2011). Therefore, the duration of ischemia used in this study could be insufficient to induce improvement of explosive performance at higher loads, and this was also observed in the study by Wilk et al. (2021b). Nevertheless, it should be emphasized that the optimal methodology for implementing ischemia is unknown (Sharma et al., 2014; Incognito et al., 2016). The characteristics of the ischemia protocols, such as the pressure applied, training experience, type and intensity of exercise used, number of ischemia–reperfusion cycles, and time between the removal of ischemia until the start of exercise, are certainly factors that influence the effectiveness of ischemia application (Incognito et al., 2016; Wilk et al., 2018). However, currently there are no clear guidelines for the optimal methodology of ischemia application according to individual characteristics and training variables.

Furthermore, the ischemic conditioning may delay the development of fatigue and prolong the time to task failure, as demonstrated by Barbosa et al. (2015) during grip exercises, however, the reported improvement was not accompanied by physiological changes (e.g., increased blood flow or oxygen utilization). Similar Marocolo et al. (2015) showed that ischemia preconditioning (four cycles of 5 min of occlusion at 220 mmHg) increased the number of repetitions during leg extension exercise. However, the same improvement as for ischemia condition was noted for the placebo condition (20 mmHg). Therefore, there may be additional, unknown factors that influence the effect of ischemia on exercise performance. One limitation of the present study was the lack of a placebo condition. The placebo and/or nocebo effects are both methodological confounding factors in studies involving potential ergogenic aids (Ferreira et al., 2016; Marocolo et al., 2017; Wilk et al., 2019c). Another limitation of the present study is the lack of assessment of physiological changes that could constitute the basis for explaining the obtained results. Since this study is the second one that evaluates the acute effects of ischemia used during the rest periods between sets, further research on such ischemia application practices are required. Furthermore, in presented study the successive sets were performed using loads in an ascending order. Although an order effect of load is possible, the effect of ischemia on performance was observed in the initial sets, i.e., first (20% 1RM) and fourth set (50% 1RM), while no difference was seen in the last sets. Nevertheless, despite the low number of repetitions per set (only two) and the relatively long rest interval between sets (3 min), it is possible that fatigue may have affected performance in the last sets, thus confounding a possible positive effect of ischemia. Therefore, further research is needed, examining the effects of load on ischemia-induced performance enhancement using randomized loads.

CONCLUSION

Ischemia application during and between exercise bouts is an innovative intervention allowing to temporarily increase exercise capacity and efficiency (Incognito et al., 2016; Marocolo et al., 2017). The results of the present study indicate that ischemia used before each set even for a brief duration of <3 min, has positive effects on peak bar velocity at light loads (20–50%), but it is insufficient to induce such effect on higher loads. However, in subsequent sets, the effect of increasing load is stronger than that of ischemia during the recovery interval, thus preventing any further increase in explosive performance. Although more research is needed to determine the effects of ischemia application during the recovery intervals between sets of exercise, it seems that the duration of ischemia application during recovery (i.e., <3 min) was not sufficient to induce positive changes in performance.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Bioethics Committee for Scientific Research, at the Academy of Physical Education in Katowice, Poland (02/2019). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JJ, RT, and MW: study conception and design. JJ and AF-S: acquisition of data. MW, AT, and GB: analysis and interpretation of data. MW, MK, RT, and AF-S: drafting of manuscript. MW, AZ, AT, and GB: critical revision. All authors contributed to the article and approved the submitted version.

FUNDING

The study was supported and funded by the statutory research of the Jerzy Kukuczka Academy of Physical Education in Katowice, Poland.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2021.715096/full#supplementary-material

REFERENCES

Addison, P. D., Neligan, P. C., Ashrafpour, H., Khan, A., Zhong, A., Moses, M., et al. (2003). Noninvasive remote ischemic preconditioning for global protection of skeletal muscle against infarction. *Am. J. Physiol. Heart Circ. Physiol.* 285, H1435–H1443. doi: 10.1152/ajpheart.00106.2003

Andreas, M., Schmid, A. I., Keilani, M., Doberer, D., Bartko, J., Crevenna, R., et al. (2011). Effect of ischemic preconditioning in skeletal muscle measured by functional magnetic resonance imaging and spectroscopy: a randomized crossover trial. *J. Cardiovasc. Magn. Reson.* 13:32. doi: 10.1186/1532-429X-13-32

Bailey, T. G., Birk, G. K., Cable, N. T., Atkinson, G., Green, D. J., Jones, H., et al. (2012). Remote ischemic preconditioning prevents reduction in brachial artery flow-mediated dilation after strenuous exercise. *Am. J. Physiol. Heart Circ. Physiol.* 303, H533–H538. doi: 10.1152/ajpheart.00272.2012

Barbosa, T. C., Machado, A. C., Braz, I. D., Fernandes, I. A., Vianna, L. C., Nobrega, A. C., et al. (2015). Remote ischemic preconditioning delays fatigue development during handgrip exercise. *Scand. J. Med. Sci. Sports* 25, 356–364. doi: 10.1111/sms.12229

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences, 2nd Edn.* Hillsdale, NJ: L. Erlbaum Associates.

de Groot, P. C., Thijssen, D. H., Sanchez, M., Ellenkamp, R., and Hopman, M. T. (2010). Ischemic preconditioning improves maximal performance in humans. *Eur. J. Appl. Physiol.* 108, 141–146. doi: 10.1007/s00421-009-1195-2

Eltzschig, H. K., and Eckle, T. (2011). Ischemia and reperfusion–from mechanism to translation. *Nat. Med.* 17, 1391–1401. doi: 10.1038/nm.2507

Enko, K., Nakamura, K., Yunoki, K., Miyoshi, T., Akagi, S., Yoshida, M., et al. (2011). Intermittent arm ischemia induces vasodilatation of the contralateral upper limb. *J. Physiol. Sci.* 61, 507–513. doi: 10.1007/s12576-011-0172-9

Ferreira, T. N., Sabino-Carvalho, J. L., Lopes, T. R., Ribeiro, I. C., Succi, J. E., Da Silva, A. C., et al. (2016). Ischemic preconditioning and repeated sprint swimming: a placebo and nocebo study. *Med. Sci. Sports Exerc.* 48, 1967–1975. doi: 10.1249/MSS.0000000000000977

Filip-Stachnik, A., Krzysztofik, M., Kaszuba, M., Leznicka, K., Kostrzewa, M., Del Coso, J., et al. (2021a). Effects of acute caffeine intake on power output and movement velocity during a multiple-set bench press exercise among mild caffeine users. *J. Hum. Kinet.* 78, 219–228. doi: 10.2478/hukin-2021-0044

Filip-Stachnik, A., Wilk, M., Krzysztofik, M., Lulińska, E., Tufano, J. J., Zajac, A., et al. (2021b). The effects of different doses of caffeine on maximal strength and strength-endurance in women habituated to caffeine. *J. Int. Soc. Sports Nutr.* 18:25. doi: 10.1186/s12970-021-00421-9

Freitas, E. D. S., Miller, R. M., Heishman, A. D., Aniceto, R. R., Silva, J. G. C., and Bemben, M. G. (2019). Perceptual responses to continuous versus intermittent blood flow restriction exercise: a randomized controlled trial. *Physiol. Behav.* 212:112717. doi: 10.1016/j.physbeh.2019.112717

Freitas, E. D. S., Miller, R. M., Heishman, A. D., Ferreira-Júnior, J. B., Araújo, J. P., and Bemben, M. G. (2020). Acute physiological responses to resistance exercise with continuous versus intermittent blood flow restriction: a randomized controlled trial. *Front. Physiol.* 11:132. doi: 10.3389/fphys.2020.00132

García-Ramos, A., Weakley, J., Janicijevic, D., and Jukic, I. (2021). Number of repetitions performed before and after reaching velocity loss thresholds: First repetition versus fastest repetition-mean velocity versus peak velocity. *Int. J. Sports Physiol. Perform.* 16, 950–957. doi: 10.1123/ijspp.2020-0629

Garnacho-Castaño, M. V., Lo'pez-Lastra, S., and Mate'-Muñoz, J. L. (2015). Reliability and validity assessment of a linear position transducer. *J. Sports Sci. Med.* 14, 128–136.

Gepfert, M., Golas, A., Zajac, T., and Krzysztofik, M. (2020). The use of different modes of post-activation potentiation (PAP) for enhancing speed of the slide-step in basketball players. *Int. J. Environ. Res.* 17:5057. doi: 10.3390/ijerph17145057

Hopkins, W. G., Marshall, S. W., Batterham, A. M., and Hanin, J. (2009). Progressive statistics for studies in sports medicine and exercise science. *Med. Sci. Sports Exerc.* 41, 3–12. doi: 10.1249/mss.0b013e31818cb278

Horiuchi, M., Endo, J., and Thijssen, D. H. (2015). Impact of ischemic preconditioning on functional sympatholysis during handgrip exercise in humans. *Physiol. Rep.* 3:e12304. doi: 10.14814/phy2.12304

Incognito, A. V., Burr, J. F., and Millar, P. J. (2016). The effects of ischemic preconditioning on human exercise performance. *Sports Med.* 46, 531–544. doi: 10.1007/s40279-015-0433-5

Janier, M. F., Vanoverschelde, J. L., and Bergmann, S. R. (1994). Ischemic preconditioning stimulates anaerobic glycolysis in the isolated rabbit heart. *Am. J. Physiol.* 267, H1353–H1360. doi: 10.1152/ajpheart.1994.267.4.H1353

Jean-St-Michel, E., Manlhiot, C., Li, J., Tropak, M., Michelsen, M. M., Schmidt, M. R., et al. (2011). Remote preconditioning improves maximal performance in highly trained athletes. *Med. Sci. Sports Exerc.* 43, 1280–1286. doi: 10.1249/MSS.0b013e318206845d

Kharbanda, R. K., Mortensen, U. M., White, P. A., Kristiansen, S. B., Schmidt, M. R., Hoschtitzky, J. A., et al. (2002). Transient limb ischemia induces remote ischemic preconditioning in vivo. *Circulation* 106, 2881–2883. doi: 10.1161/01.cir.0000043806.51912.9b

Kimura, M., Ueda, K., Goto, C., Jitsuiki, D., Nishioka, K., Umemura, T., et al. (2007). Repetition of ischemic preconditioning augments endothelium-dependent vasodilation in humans: role of endothelium-derived nitric oxide and endothelial progenitor cells. *Arterioscler. Thromb. Vasc. Biol.* 27, 1403–1410. doi: 10.1161/ATVBAHA.107.143578

Kocman, E. A., Ozatik, O., Sahin, A., Guney, T., Kose, A. A., Dag, I., et al. (2015). Effects of ischemic preconditioning protocols on skeletal muscle ischemia-reperfusion injury. *J. Surg. Res.* 193, 942–952. doi: 10.1016/j.jss.2014.09.032

Kraemer, W. J., Noble, B. J., Clark, M. J., and Culver, B. W. (1987). Physiologic responses to heavy-resistance exercise with very short rest periods. *Int. J. Sports Med.* 8, 247–252. doi: 10.1055/s-2008-1025663

Krzysztofik, M., Jarosz, J., Matykiewicz, P., Wilk, M., Bialas, M., Zajac, A., et al. (2021). A comparison of muscle activity of the dominant and non-dominant side of the body during low versus high loaded bench press exercise performed to muscular failure. *J. Electromyogr. Kinesiol.* 56:102513. doi: 10.1016/j.jelekin.2020.102513

Lalonde, F., and Curnier, D. Y. (2015). Can anaerobic performance be improved by remote ischemic preconditioning? *J. Strength Cond. Res.* 29, 80–85. doi: 10.1519/JSC.0000000000000609

Lawson, C., and Downey, J. (1993). Preconditioning: state of the art myocardial protection. *Cardiovasc. Res.* 27, 542–550. doi: 10.1093/cvr/27.4.542

Levinger, I., Goodman, C., Hare, D. L., Jerums, G., Toia, D., and Selig, S. (2009). The reliability of the 1RM strength test for untrained middle- aged individuals. *J. Sci. Med. Sport* 12, 310–316. doi: 10.1016/j.jsams.2007.10.007

Li, X. D., Cheng, Y. T., Yang, Y. J., Meng, X. M., Zhao, J. L., Zhang, H. T., et al. (2012). PKA-mediated eNOS phosphorylation in the protection of ischemic preconditioning against no-reflow. *Microvasc. Res.* 84, 44–54. doi: 10.1016/j.mvr.2012.04.002

Libonati, J. R., Cox, M., Incanno, N., Melville, S. K., Musante, F. C., Glassberg, H. L., et al. (1998). Brief periods of occlusion and reperfusion increase skeletal muscle force output in humans. *Cardiologia* 43, 1355–1360.

Lintz, J. A., Dalio, M. B., Joviliano, E. E., and Piccinato, C. E. (2013). Ischemic pre and postconditioning in skeletal muscle injury produced by ischemia and reperfusion in rats. *Acta Circ. Bras.* 28, 441–446. doi: 10.1590/s0102-86502013000600007

Liu, G. S., Thornton, J., Van Winkle, D. M., Stanley, A. W., Olsson, R. A., and Downey, J. M. (1991). Protection against infarction afforded by preconditioning is mediated by A1 adenosine receptors in rabbit heart. *Circulation* 84, 350–356. doi: 10.1161/01.cir.84.1.350

Loenneke, J. P., Fahs, C. A., Rossow, L. M., Sherk, V. D., Thiebaud, R. S., Abe, T., et al. (2012). Effects of cuff width on arterial occlusion: implications for blood flow restricted exercise. *Eur. J. Appl. Physiol.* 112, 2903–2912. doi: 10.1007/s00421-011-2266-8

Marocolo, I. C., Da Mota, G. R., Londe, A. M., Patterson, S. D., Barbosa Neto, O., and Marocolo, M. (2017). Acute ischemic preconditioning does not influence high-intensity intermittent exercise performance. *PeerJ* 5:e4118. doi: 10.7717/peerj.4118

Marocolo, M., Billaut, F., and da Mota, G. R. (2018). Ischemic preconditioning and exercise performance: an ergogenic aid for whom? *Front. Physiol.* 9:1874. doi: 10.3389/fphys.2018.01874

Marocolo, M., Da Mota, G. R., Pelegrini, V., and Appell Coriolano, H. J. (2015). Are the beneficial effects of ischemic preconditioning on performance partly a placebo effect? *Int. J. Sports Med.* 36, 822–825. doi: 10.1055/s-0035-1549857

Marocolo, M., Marocolo, I. C., da Mota, G. R., Simão, R., Maior, A. S., and Coriolano, H. J. (2016). Beneficial effects of ischemic preconditioning in resistance exercise fade over time. *Int. J. Sports Med.* 37, 819–824. doi: 10.1055/s-0042-109066

Maszczyk, A., Wilk, M., Krzysztofik, M., Gepfert, M., Zając, A., Petr, M., et al. (2020). The effects of resistance training experience on movement characteristics in the bench press exercise. *Biol. Sport.* 37, 79–83. doi: 10.5114/biolsport.2019.83008

Mendez-Villanueva, A., Edge, J., Suriano, R., Hamer, P., and Bishop, D. (2012). The recovery of repeated-sprint exercise is associated with PCr resynthesis, while muscle pH and EMG amplitude remain depressed. *PLoS One* 7:e51977. doi: 10.1371/journal.pone.0051977

Murry, C. E., Jennings, R. B., and Reimer, K. A. (1986). Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 74, 1124–1136. doi: 10.1161/01.cir.74.5.1124

Neto, G. R., Novaes, J. S., Salerno, V. P., Gonçalves, M. M., Batista, G. R., and Cirilo-Sousa, M. S. (2018). Does a resistance exercise session with continuous or intermittent blood flow restriction promote muscle damage and increase oxidative stress? *J. Sports Sci.* 36, 104–110. doi: 10.1080/02640414.2017.1283430

Pang, C. Y., Yang, R. Z., Zhong, A., Xu, N., Boyd, B., and Forrest, C. R. (1995). Acute ischaemic preconditioning protects against skeletal muscle infarction in the pig. *Cardiovasc. Res.* 29, 782–788. doi: 10.1016/0008-6363(96)88613-5

Paradis-Deschênes, P., Joanisse, D. R., and Billaut, F. (2016). Ischemic preconditioning increases muscle perfusion, oxygen uptake, and forcein strength-trained athletes. *Appl. Physiol. Nutr. Metab.* 41, 938–944. doi: 10.1139/apnm-2015-0561

Robergs, R. A., Pearson, D. R., Costill, D. L., Fink, W. J., Pascoe, D. D., Benedict, M. A., et al. (1991). Muscle glycogenolysis during differing intensities of weight-resistance exercise. *J. Appl. Physiol.* 70, 1700–1706. doi: 10.1152/jappl.1991.70.4.1700

Sabino-Carvalho, J. L., Lopes, T. R., Obeid-Freitas, T., Ferreira, T. N., Succi, J. E., Silva, A. C., et al. (2017). Effect of ischemic preconditioning on endurance performance does not surpass placebo med. *Sci. Sports Exerc.* 49, 124–132. doi: 10.1249/MSS.0000000000001088

Schroeder, C. A., Lee, H. T., Shah, P. M., Babu, S. C., Thompson, C. I., and Belloni, F. L. (1996). Preconditioning with ischemia or adenosine protects skeletal muscle from ischemic tissue reperfusion injury. *J. Surg. Res.* 63, 29–34. doi: 10.1006/jsre.1996.0217

Schwiete, C., Franz, A., Roth, C., and Behringer, M. (2021). Effects of resting vs. continuous blood-flow restriction-training on strength, fatigue resistance, muscle thickness, and perceived discomfort. *Front. Physiol.* 12:663665. doi: 10.3389/fphys.2021.663665

Sharma, V., Cunniffe, B., Verma, A. P., Cardinale, M., and Yellon, D. (2014). Characterization of acute ischemia-related physiological responses associated with remote ischemic preconditioning: a randomized controlled, crossover human study. *Physiol. Rep.* 2:e12200. doi: 10.14814/phy2.12200

Tanaka, D., Suga, T., Tanaka, T., Kido, K., Honjo, T., Fujita, S., et al. (2018). Ischemic preconditioning enhances muscle endurance during sustained isometric exercise. *Int. J. Sports Med.* 37, 614–618. doi: 10.1055/s-0035-1565141

Telles, L. G. S., Carelli, L. C., Bráz, I. D., Junqueira, C., Monteiro, E. R., Reis, V. M., et al. (2020). Effects of ischemic preconditioning as a warm-up on leg press and bench press performance. *J. Hum. Kinet.* 75, 267–277. doi: 10.2478/hukin-2020-0055

Wang, W. Z., Stepheson, L. L., Fang, X. H., Khiabani, K. T., and Zamboni, W. A. (2004). Ischemic preconditioning-induced microvascular protection at a distance. *J. Reconstr. Microsurg.* 20, 175–181. doi: 10.1055/s-2004-820775

Wernbom, M., Augustsson, J., and Thomee, R. (2006). Effects of vascular occlusion on muscular endurance in dynamic knee extension exercise at different submaximal loads. *J. Strength Cond. Res.* 20, 372–377. doi: 10.1519/R-16884.1

Wilk, M., Gepfert, M., Krzysztofik, M., Golas, A., Mostowik, A., Maszczyk, A., et al. (2019a). The influence of grip width on training volume during the bench press with different movement tempos. *J. Hum. Kinet.* 68, 49–57. doi: 10.2478/hukin-2019-0055

Wilk, M., Gepfert, M., Krzysztofik, M., Mostowik, A., Filip, A., Hajduk, G., et al. (2020a). Impact of duration of eccentric movement in the one-repetition maximum test result in the bench press among women. *J. Sports Sci. Med.* 19, 317–322.

Wilk, M., Gepfert, M., Krzysztofik, M., Stastny, P., Zajac, A., and Bogdanis, G. C. (2020b). Acute effects of continuous and intermittent blood flow restriction on movement velocity during bench press exercise against different loads. *Front. Physiol.* 11:569915. doi: 10.3389/fphys.2020.569915

Wilk, M., Golas, A., Krzysztofik, M., Nawrocka, M., and Zajac, A. (2019b). The effects of eccentric cadence on power and velocity of the bar during the concentric phase of the bench press movement. *J. Sports Sci. Med.* 18, 191–197.

Wilk, M., Golas, A., Zmijewski, P., Krzysztofik, M., Filip, A., Coso, J. D., et al. (2020c). The effects of the movement tempo on the one-repetition maximum bench press results. *J. Hum. Kinet.* 72, 151–159. doi: 10.2478/hukin-2020-0001

Wilk, M., Jarosz, J., Krzysztofik, M., Filip-Stachnik, A., Bialas, M., Rzeszutko-Belzowska, A., et al. (2021a). Contrast tempo of movement and its effect on power output and bar velocity during resistance exercise. *Front. Physiol.* 11:629199. doi: 10.3389/fphys.2020.629199

Wilk, M., Krzysztofik, M., Filip, A., Lockie, R. G., and Zajac, A. (2020d). The acute effects of external compression with blood flow restriction on maximal strength and strength-endurance performance of the upper limbs. *Front. Physiol.* 11:567. doi: 10.3389/fphys.2020.00567

Wilk, M., Krzysztofik, M., Filip, A., Zajac, A., Bogdanis, G. C., and Lockie, R. G. (2020e). Short-term blood flow restriction increases power output and bar velocity during the bench press. *J. Strength Cond. Res*. doi: 10.1519/JSC.0000000000003649 [Epub ahead of print].

Wilk, M., Krzysztofik, M., Gepfert, M., Poprzecki, S., Golas, A., and Maszczyk, A. (2018). Technical and training related aspects of resistance training using blood flow restriction in competitive sport – a review. *J. Hum. Kinet.* 65, 249–260. doi: 10.2478/hukin-2018-010100

Wilk, M., Krzysztofik, M., Jarosz, J., Krol, P., Leznicka, K., Zajac, A., et al. (2021b). Impact of ischemic intra-conditioning on power output and bar velocity of the upper limbs. *Front. Physiol.* 12:626915. doi: 10.3389/fphys.2021.626915

Wilk, M., Krzysztofik, M., Maszczyk, A., Chycki, J., and Zajac, A. (2019c). The acute effects of caffeine intake on time under tension and power generated during the bench press movement. *J. Int. Soc. Sports Nutr.* 16, 8. doi: 10.1186/s12970-019-0275-x

Yasuda, T., Fukumura, K., Iida, H., and Nakajima, T. (2015). Effect of low-load resistance exercise with and without blood flow restriction to volitional fatigue on muscle swelling. *Eur. J. Appl. Physiol.* 115, 919–926. doi: 10.1007/s00421-014-3073-9

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Physiology

SYSTEMATIC REVIEW
published: 22 November 2021
doi: 10.3389/fphys.2021.786752

Myoelectric Activity and Fatigue in Low-Load Resistance Exercise With Different Pressure of Blood Flow Restriction: A Systematic Review and Meta-Analysis

Victor Sabino de Queiros[1], Ingrid Martins de França[2], Robert Trybulski[3,4], João Guilherme Vieira[5], Isis Kelly dos Santos[1], Gabriel Rodrigues Neto[6,7], Michal Wilk[8], Dihogo Gama de Matos[9], Wouber Hérickson de Brito Vieira[2], Jefferson da Silva Novaes[10], Piotr Makar[11], Breno Guilherme de Araújo Tinoco Cabral[1,12] and Paulo Moreira Silva Dantas[1,12]**

[1] Graduate Program in Health Sciences, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil, [2] Graduate Program in Physiotherapy, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil, [3] Department of Medical Sciences, The Wojciech Korfanty School of Economics, Katowice, Poland, [4] Provita Zory Medical Center, Zory, Poland, [5] Graduate Program in Physical Education, Federal University of Juiz de Fora (UFJF), Juiz de Fora, Brazil, [6] Graduate Program in Family Health, Faculties of Nursing and Medicine Nova Esperança (FACENE/FAMENE), João Pessoa, Brazil, [7] Coordination of Physical Education, University Center for Higher Education and Development (CESED/UNIFACISA/FCM/ESAC), Campina Grande, Brazil, [8] Institute of Sport Sciences, Jerzy Kukuczka Academy of Physical Education in Katowice, Katowice, Poland, [9] Faculty of Kinesiology and Recreation Management, University of Manitoba, Winnipeg, MB, Canada, [10] Graduate Program at the School of Physical Education and Sport at the Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil, [11] Faculty of Physical Education, Gdańsk University of Physical Education and Sport, Gdańsk, Poland, [12] Graduate Program in Physical Education, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil

Edited by:
*Adam Zajac,
University School of Physical Education in Wrocław, Poland*

Reviewed by:
*Thorsten Rudroff,
The University of Iowa, United States
Fábio Juner Lanferdini,
Federal University of Santa Catarina, Brazil*

***Correspondence:**
*Paulo Moreira Silva Dantas
pgdantas@ufrnnet.br
Victor Sabino de Queiros
victor.sabino.121@ufrn.edu.br*

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *30 September 2021*
Accepted: *26 October 2021*
Published: *22 November 2021*

Citation:
de Queiros VS, de França IM, Trybulski R, Vieira JG, dos Santos IK, Neto GR, Wilk M, Matos DG, Vieira WHB, Novaes JS, Makar P, Cabral BGAT and Dantas PMS (2021) Myoelectric Activity and Fatigue in Low-Load Resistance Exercise With Different Pressure of Blood Flow Restriction: A Systematic Review and Meta-Analysis. Front. Physiol. 12:786752. doi: 10.3389/fphys.2021.786752

Background: Low-load resistance exercise (LL-RE) with blood flow restriction (BFR) promotes increased metabolic response and fatigue, as well as more pronounced myoelectric activity than traditional LL-RE. Some studies have shown that the relative pressure applied during exercise may have an effect on these variables, but existing evidence is contradictory.

Purpose: The aim of this study was to systematically review and pool the available evidence on the differences in neuromuscular and metabolic responses at LL-RE with different pressure of BFR.

Methods: The systematic review and meta-analysis was reported according to PRISMA items. Searches were performed in the following databases: CINAHL, PubMed, Scopus, SPORTDiscus and Web of Science, until June 15, 2021. Randomized or non-randomized experimental studies that analyzed LL-RE, associated with at least two relative BFR pressures [arterial occlusion pressure (AOP)%], on myoelectric activity, fatigue, or metabolic responses were included. Random-effects meta-analyses were performed for MVC torque (fatigue measure) and myoelectric activity. The quality of evidence was assessed using the PEDro scale.

Results: Ten studies were included, all of moderate to high methodological quality. For MVC torque, there were no differences in the comparisons between exercise with

40–50% vs. 80–90% AOP. When analyzing the meta-analysis data, the results indicated differences in comparisons in exercise with 15–20% 1 repetition maximum (1RM), with higher restriction pressure evoking greater MVC torque decline (4 interventions, 73 participants; MD = −5.05 Nm [95%CI = −8.09; −2.01], $p = 0.001$, $I^2 = 0\%$). For myoelectric activity, meta-analyses indicated a difference between exercise with 40% vs. 60% AOP (3 interventions, 38 participants; SMD = 0.47 [95%CI = 0.02; 0.93], $p = 0.04$, $I^2 = 0\%$), with higher pressure of restriction causing greater myoelectric activity. This result was not identified in the comparisons between 40% vs. 80% AOP. In analysis of studies that adopted pre-defined repetition schemes, differences were found (4 interventions, 52 participants; SMD = 0.58 [95%CI = 0.11; 1.05], $p = 0.02$, $I^2 = 27\%$).

Conclusion: The BFR pressure applied during the LL-RE may affect the magnitude of muscle fatigue and excitability when loads between 15 and 20% of 1RM and predefined repetition protocols (not failure) are prescribed, respectively.

Systematic Review Registration: [http://www.crd.york.ac.uk/prospero], identifier [CRD42021229345].

Keywords: KAATSU, vascular occlusion, strength training, metabolic stress, electromyography, muscle excitability, torque, central fatigue

INTRODUCTION

Blood flow restriction (BFR) is a commonly used technique by physical therapists and trainers aiming at physical rehabilitation and neuromuscular adaptations (Nakajima et al., 2006; Patterson and Brandner, 2018; de Queiros et al., 2021). This is certainly justified by the fact that some evidence indicates that low-load {20–40% of 1 repetition maximum [1RM] (Lopez et al., 2021)} resistance training with arterial BFR and venous occlusion artificially induced can promote gains in muscle strength and hypertrophy more pronounced than low-load resistance training without BFR (NO-BFR) (Loenneke et al., 2012) and, in some cases, similar to NO-BFR high-load resistance training (Takarada et al., 2000a; Laurentino et al., 2012). Due to structural and functional adaptations independent of high mechanical stress, BFR resistance training has been recommended for clinical populations with articular limitations for high-load resistance training (Vanwye et al., 2017). In addition, BFR resistance training has been suggested as a training option for athletes seeking to maximize muscle hypertrophy gains (Rolnick and Schoenfeld, 2020).

Low-load resistance exercise with BFR promotes increased blood lactate and intramuscular inorganic phosphate concentrations, and more pronounced intramuscular pH reductions than NO-BFR low-load resistance exercise with equalized training volume (Takarada et al., 2000b; Suga et al., 2009; Sugaya et al., 2011; Wilson et al., 2013). Increased metabolic stress has been postulated as a potential mechanism of muscle hypertrophy arising after BFR resistance training (Loenneke et al., 2011; Jessee et al., 2018a; Rolnick and Schoenfeld, 2020). Accumulation of metabolites appears to accelerate fatigue via stimulation of type III and IV afferent fibers [central fatigue mechanism (Amann et al., 2015)], and to maintain force levels, motor units (MU) of high threshold excitability are recruited, therefore a hypertrophic stimulus would be provided to a greater proportion of muscle fibers (Jessee et al., 2018a). This mechanism has been used to explain the increased myoelectric activity in resistance exercise with BFR, compared to NO-BFR low-load resistance exercise (Rolnick and Schoenfeld, 2020).

Considering a possible association between metabolite-induced fatigue with muscle hypertrophy, some authors have investigated how manipulating the BFR pressure applied during exercise can exert an effect on the level of acute fatigue, measured through of maximum voluntary contraction (MVC) torque analysis (Cook et al., 2007; Yasuda et al., 2009; Counts et al., 2015; Fatela et al., 2016). The results presented so far are divergent. Cook et al. (2007) did not identify differences in the levels of acute fatigue (MVC torque decline) between exercises performed with BFR at a pressure of 160 or 300 mmHg. However, Yasuda et al. (2009), testing the same pressures (i.e., 160 and 300 mmHg), verified that exercise performed with greater occlusion pressure evoked a higher level of acute fatigue. We acknowledge that the studies in question have limitations in the methodology used to generate BFR, given that arbitrary pressures were prescribed. However, this divergence can also be identified among studies that used relative pressures based on arterial occlusion pressure (AOP%) values (Counts et al., 2015; Fatela et al., 2016). Counts et al. (2015) identified no difference in the magnitude of the decrease in MVC torque between exercise performed with BFR at 40 vs. 90% AOP, whereas Fatela et al. (2016) found that a higher occlusion pressure was required (80% vs. 40–60% AOP) for low-load exercise to induce a significant MVC torque decline.

As presented, the studies analyzing the effect of constraint pressure manipulation on neuromuscular fatigue show distinct results and this is possibly justified by the exercise settings [e.g.,

Abbreviations: 1RM, 1 repetition maximum; AOP, arterial occlusion pressure; BFR, blood flow restriction; EMG, electromyography; MVC, maximum voluntary contraction; MU, motor units.

prescribed repetitions scheme and intensity (1RM%)]. In this regard, a robust meta-analysis assigning appropriate weight to each study as part of an integrative analysis becomes important. Therefore, the aim of the present study was to systematically review and meta-analyze the available evidence on the differences in neuromuscular [myoelectric activity and fatigue, here defined by a MVC torque performance reduction (Vøllestad, 1997)] and metabolic responses between low-load resistance exercise with different relative pressure of blood flow restriction. The results of this systematic review may be useful in understanding the effects of different restriction pressures on neuromuscular responses and assist trainers in more appropriate and safer prescription.

METHODS

This systematic review and meta-analysis was reported according to the preferred reporting item guidelines for systematic reviews and meta-analyses (PRISMA) (Page et al., 2021).

Eligibility Criteria

In our analysis we considered studies that adopted the following criteria, population: healthy human beings (18–80 years) of both genders, trained or untrained; intervention and comparative: low load (≤ 40% of 1RM) resistance exercise performed with at least two BFR pressures (at different times) induced by pneumatic cuff and relativized based on AOP values; outcomes: MVC torque (used to identify fatigue), myoelectric activity, blood lactate concentrations, intramuscular metabolic changes [metabolite concentrations (e.g., inorganic phosphate) and changes in intramuscular pH]; study design: randomized or non-randomized experimental studies. Reviews, letters to the editor, animal studies, expert opinion, studies that analyzed aerobic exercise, passive restriction (i.e., no exercise), practical BFR protocols (i.e., BFR induced by elastic bandaging) were not considered for analyses.

Information Sources and Searches

The studies were retrieved from electronic database search and from a comprehensive sweeping in the reference list of the included studies (Horsley et al., 2011). A search was conducted on June 15 2021 in the following databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL - EBSCO), National Library of Medicine (PubMed®), Scopus (Elsevier), SPORTDiscus (EBSCO) and Web of Science (Clarivate Analytics).

Search Strategy

The search strategy combined the following descriptors and Boolean operators (AND/OR): ("blood flow restriction" OR "vascular occlusion" OR KAATSU) AND ("resistance training" OR "strength training" OR "resistance exercise" OR "weightlifting" OR "weight-lifting" OR "weight lifting") AND ("metabolic stress" OR "lactate" OR "fatigue" OR "muscle activation" OR "torque" OR "maximal voluntary isometric contraction" OR "maximal voluntary contraction"). Full details of these supplementary searches can be found in the additional file.

Selection Process

The studies were selected by two independent reviewers (VQ and IF). Disagreements between reviewers were resolved by a third reviewer (IKS). The screening of studies was divided into three steps: elimination of duplicates (Step 1), reading of titles and abstracts (Step 2), reading of the full article (Step 3). We used the Rayyan QCRI® application (Ryyan QCRI, Qatar Computing Research Institute, HBKU, Doha, Qatar) (Ouzzani et al., 2016) to assist in eliminating duplicates and screening from titles and abstracts.

Data Extraction

After reading the full articles, two reviewers (VSQ and IMF) independently performed the data extraction of the included studies, encompassing the prescribed exercise configuration (load, volume, recovery interval), pressures tested, variables analyzed, sample characteristics, and results identified. When results were reported in graphs or were not available in the manuscript, the corresponding author was contacted, via email, to request descriptive data of mean and standard deviations and other relevant information. When data were not available, we used ImageJ software[1] to extract the information directly from the graphs presented in the manuscript.

Assessment of the Risk of Bias of the Included Studies

After the literature search and selection, risk of bias assessment was performed independently by two authors (VSQ and IMF) and disagreements were resolved by a third researcher (IKS) using the Physiotherapy Evidence Database (PEDro) scale, which has been shown to be a valid measure of the methodologic quality of randomized trials (Elkins et al., 2010) and displays acceptable inter-rater reliability (Moseley et al., 2002). Thus, scores on PEDro scale ranged from 0 (high risk of bias) to 10 (low risk of bias). The quality of the studies was used for qualitative assessment, and it was not an exclusion criteria. The methodological quality of the study was categorized as follows: a score ranging from 6 to 10 was indicative of high quality; whereas scores of 4–5 indicated moderate quality; and scores ≤3 indicated low quality (Valkenet et al., 2011).

Data Analysis

Statistical analyses were performed using the Review Manager software, version 5.4 (RevMan 5.4, Cochrane Collaboration). The heterogeneity between the studies was quantified through the I^2 statistic. The heterogeneity was classified according to the following scale: low (< 25%), moderate (25–49%), and high (> 50%) (Higgins and Thompson, 2002). When data were reported on the same scale, a random effects model was used to analyze the mean difference [MD ± 95% confidence interval (95%CI)] (Ahn and Kang, 2018). For torque analyses, the mean

[1] https://imagej.nih.gov/ij/

values and standard deviation (SD) of pre- and post-exercise torque were considered. The SD_{change} was defined by root square $[(SD_{pre2}/N_{pre}) + (SD_{post2}/N_{post})]$ (Borenstein et al., 2021). For the surface electromyography (sEMG) analyses, the mean values and the SD of the last measurement taken were considered. For these analyses, the standardized mean difference (SMD) was considered. Due to the variability of the lower extremity sEMG analyses, the following prioritization order was adopted: vastus medialis > vastus lateralis > rectus femoris. When the study analyzed more than one load (1RM%), the load that most closely matched the other studies was considered. When possible, subgroup analyses were introduced to explore the effects of load and repetition scheme configuration (failure vs. not failure) on the results. It was not possible to analyze publication bias, given that an insufficient number of studies (< 10) were included in our quantitative synthesis (Sterne et al., 2011).

Sensitivity Analysis

We replicated all meta-analyses performed with three studies that showed high heterogeneity, but excluding outliers, defined by the magnitude and direction of the effect, that appeared in the analyses.

Certainty of Evidence

The quality of the evidence was assessed through the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Atkins et al., 2005). Grading of Recommendations Assessment, Development and Evaluation approach suggests the classification of randomized controlled trials initially as high-quality studies (score 4), that go through the specific risk of bias assessments to identify whether their scores need to be reduced to moderate, low, or very low. The following topics were assessed: (1) quality of the original studies; (2) inconsistency of the results (heterogeneity); (3) indirect evidence; (4) imprecision; and (5) publication bias. One point was removed from the quality of the original studies when 50% of the studies in a determined meta-analysis had 1 item (specified in the **Table 1**) assessed as high risk. For inconsistency, we remove a point if statistical heterogeneity was found. The risk of indirect evidence was assessed considering three factors: (1) when the participants differed from the population of interest; (2) when the interventions differed from the specific desired intervention; and (3) when substitute outcomes were used instead of the relevant ones. The imprecision was assessed based on the total sample size < 100 participants. Regarding publication bias, we did not perform any analysis.

RESULTS

Study Selection

A total of 759 studies were identified in the databases. Ten studies were included in this review and seven studies were included in the meta-analysis. The flow diagram of the literature search is presented in **Figure 1**.

TABLE 1 | Methodological quality of the included studies.

Study	1	2	3	4	5	6	7	8	9	10	11	Total (0–10)
Counts et al. (2015)	−	+	−	+	−	−	−	+	+	+	+	6
Loenneke et al. (2015)	−	+	−	+	−	−	−	+	+	+	+	6
Loenneke et al. (2016)	−	+	−	+	−	−	+	+	+	+	+	7
Fatela et al. (2016)	−	+	−	+	−	−	−	+	+	+	+	6
Jessee et al. (2017)	−	+	−	+	−	−	−	+	+	+	+	6
Dankel et al. (2017)	−	+	−	+	−	−	−	+	+	+	+	6
Buckner et al. (2018)	−	+	−	+	−	−	−	+	+	+	+	6
Jessee et al. (2019)	−	+	−	NR	−	−	−	+	+	+	+	5
Ilett et al. (2019)	−	+	−	+	−	−	−	+	+	+	+	6
Singer et al. (2020)	−	−	−	+	−	−	−	+	+	+	+	5

1 – Eligibility criteria specified; 2 – Random allocation; 3 – Concealed allocation; 4 – Groups similar at Baseline; 5 – Participant blinding; 6 – Therapist blinding; 7 – Assessor blinding; 8 – Adequate follow-up; 9 – Intention to-treat analysis; 10 - Between group comparisons; 11 – Point estimates and variability; NR: not reported.

Study Characteristics

Eighty percent (80%) of the included studies adopted a crossover design (Counts et al., 2015; Fatela et al., 2016; Dankel et al., 2017; Jessee et al., 2017, 2019; Buckner et al., 2018; Ilett et al., 2019; Singer et al., 2020) and 20% of the studies used a parallel design (independent groups) (Loenneke et al., 2015, 2016). The studies encompassed a total of 174 participants, with a mean age ranging from 22 to 25 years. Two studies analyzed the same sample (Loenneke et al., 2015, 2016), so only the sample number reported in one of the studies in question was counted. Seventy percent (70%) of the studies analyzed trained individuals (n = 139) (Counts et al., 2015; Loenneke et al., 2015, 2016; Dankel et al., 2017; Jessee et al., 2017, 2019; Buckner et al., 2018) and 30% of the studies considered untrained individuals (n = 35) (Fatela et al., 2016; Ilett et al., 2019; Singer et al., 2020). All studies analyzed a single-joint exercise (knee extension, n = 6; elbow flexion, n = 4). Thirty percent (30%) of the studies analyzed more than one intensity (1RM%) (Loenneke et al., 2015, 2016; Dankel et al., 2017). The characteristics of the participants and studies are presented in detail in **Tables 2**, **3**.

Determination of Blood Flow Restriction Pressure

Seventy percent (70%) of studies determined AOP directly using a vascular Doppler (Counts et al., 2015; Fatela et al., 2016; Dankel et al., 2017; Jessee et al., 2017, 2019; Buckner et al., 2018; Singer et al., 2020), while 10% of studies used an automated tourniquet to determine AOP (Ilett et al., 2019) and 20% of studies estimated AOP from limb circumference (Loenneke et al., 2015, 2016). Sixty percent (60%) of the studies assessed AOP before each exercise session (Dankel et al., 2017; Jessee et al., 2017, 2019; Buckner et al., 2018; Ilett et al., 2019; Singer et al., 2020) and 20% of the studies performed a single measurement on a different day from the experimental session (Counts et al., 2015; Fatela et al., 2016). Sixty percent (60%) of the studies specified that the measurement was performed in the exercise position (Counts et al., 2015; Dankel et al., 2017; Jessee et al., 2017, 2019; Buckner et al., 2018;

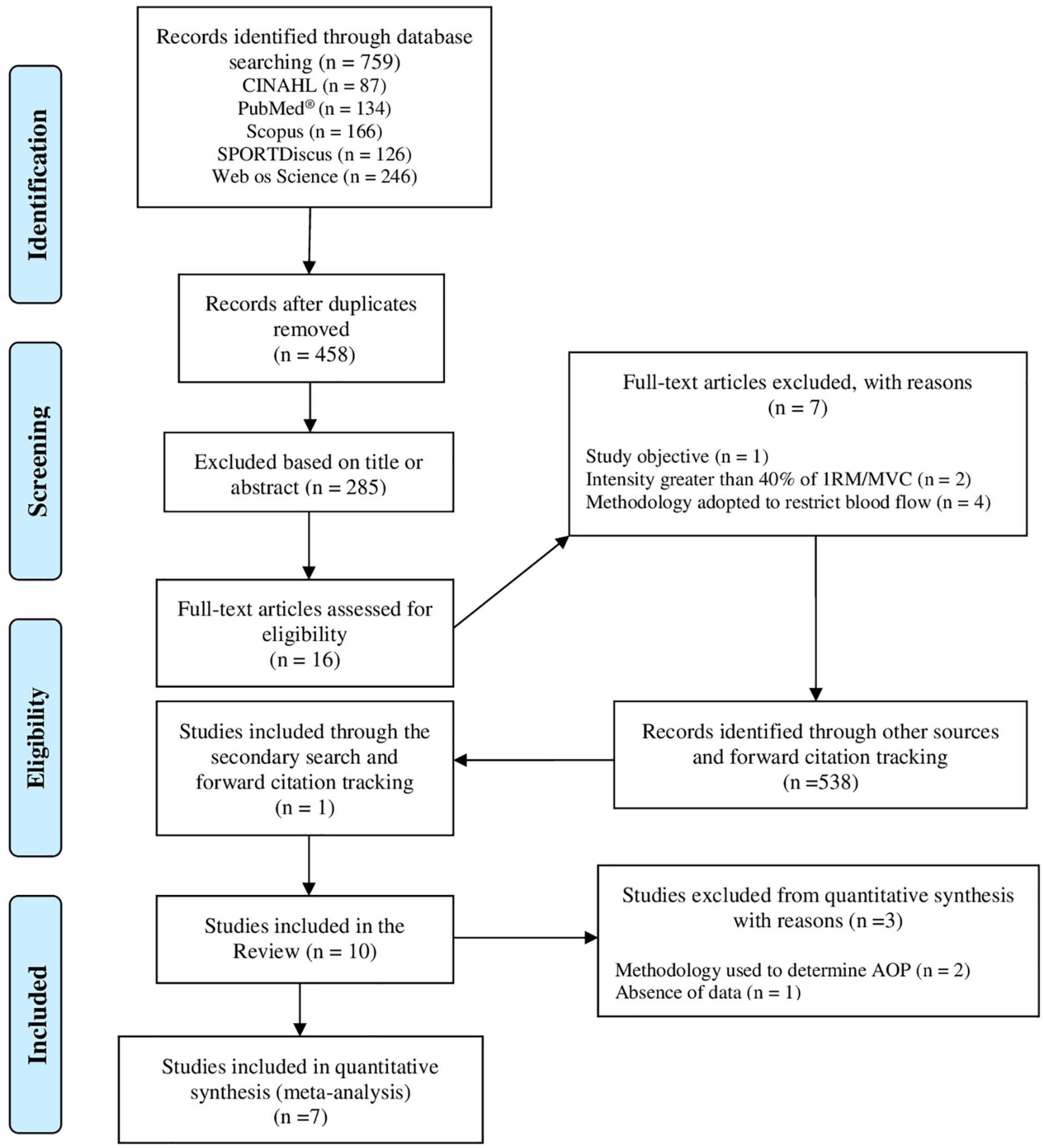

FIGURE 1 | PRISMA flow diagram of study selection.

Singer et al., 2020), while 20% of the studies offered no details about the position adopted for AOP assessments (Fatela et al., 2016; Ilett et al., 2019).

Methodological Quality (Internal Validity)

Eighty percent (80%) of trials received a score between 6 and 10 on the PEDro scale (high methodological quality), while 20% of trials received a score of 5 (moderate methodological quality). Only one study reported blinding of outcome assessors (Loenneke et al., 2016). A single study did not report implementation of randomization (Singer et al., 2020). Although most studies reported use of randomization, none of the studies offered details on how this procedure was performed. In addition, none of the studies reported the existence of a record of the research protocol. The quality ratings for each study included in the review are presented in **Table 1**.

Main Outcomes

Maximum Voluntary Contraction Isometric Torque (Fatigue)

The meta-analysis performed for MVC isometric torque indicated no difference for 40% vs. 60% AOP (MD = −0.73 Nm [95CI% = −4.66; 3.20]; $p = 0.71$; $I^2 = 0\%$) (**Figure 2A**). A trend was identified in comparisons of 40–50% vs. 80–90%

TABLE 2 | Characteristics of the participants.

Study	Participants (n = 174)	Age (years)	Height (cm)	Body mass (kg)	Training status
Counts et al. (2015)	14	24.0 ± 3.0	174.0 ± 6.7	79.7 ± 11.3	Trained
Loenneke et al. (2015)	40	22.3 ± 3.6	176.6 ± 6.3	81.9 ± 13.2	Trained
Loenneke et al. (2016)	40	22.3 ± 3.6	176.6 ± 6.3	81.9 ± 13.2	Trained
Fatela et al. (2016)	14	24.8 ± 5.4	175.2 ± 4.4	71.1 ± 6.9	Untrained
Jessee et al. (2017)	26	22.0 ± 2.6	175.3 ± 10.6	78.7 ± 14.0	Trained
Dankel et al. (2017)	14	24.0 ± 3.8	175.0 ± 11.4	83.0 ± 17.1	Trained
Buckner et al. (2018)	22	22.0 ± 2.0	174.7 ± 10.4	76.0 ± 17.0	Trained
Jessee et al. (2019)	23	22.0 ± 2.7	174.5 ± 10.2	75.7 ± 17.3	Trained
Ilett et al. (2019)	10	25.0 ± 6.0	176.8 ± 5.6	78.1 ± 8.5	Untrained
Singer et al. (2020)	11	25.0 ± 4.0	Not reported	77.8 ± 7.9	Untrained
Mean ± SD	21.4 ± 11.1	23.0 ± 3.7	175.2 ± 8.2	78.4 ± 13.9	—
Range	40.0 – 10.0	25.0 – 22.0	176.8 – 174.0	83.0 – 75.7	—

n = sample size; SD = standard deviation.

AOP (MD = −3.15 Nm [95%CI = −6.50; 0.20]; p = 0.07; I^2 = 55%); subgroup analyses identified that at 15–20% 1RM loading, application of 80-90% AOP promotes greater decrease in torque (MD = −5. 05 Nm [95%CI = −8.09; −2.01]; p = 0.001; I^2 = 0%), results that were not observed in exercise at 30% 1RM (MD = 0.13 Nm [95%CI = −6.01; −6.27]; p = 0.97; I^2 = 80%) (**Figure 2B**). Additionally, exercise with 40–50% AOP or 80–90% AOP was found to induce a greater decrease in isometric torque of the MVC compared to low-load exercise without BFR (0%AOP) (MD = −9.52 Nm [95%CI = −17.95, −1.08]; p = 0.03; I^2 = 89% and MD = −15.04 Nm [95%CI = −25.33; −4.74]; p = 0.004; I^2 = 92%, for exercise with 40–50% and 80–90% AOP, respectively) (**Figure 3**). Details of the GRADE certainty of evidence classification for the analyses in question are reported in detail in **Table 4**.

Sensitivity Analysis

Because of the high heterogeneity identified, sensitivity analyses were implemented for the following comparisons: (i) 40–50% vs. 0% AOP; (ii) 80–90% vs. 0% AOP. After removing one (Buckner et al., 2018) of the three included studies, results remained significant for the comparisons between 80 and 90% vs. 0% AOP (MD = −6.55 Nm [95%CI = −8.96; −4.13]; $p < 0.00001$; I^2 = 0%) and 40-50% vs. 0% of AOP (MD = −3.52 Nm [95%CI = −5.86; −1.17]; p = 0.003; I^2 = 0%), but heterogeneity was reduced.

Surface Electromyography

Electromyography (sEMG) analyses indicated a difference for 40% vs. 60% AOP, in favor of higher pressures (SMD = 0.47 [95%CI = 0.02; 0.93]; p = 0.04; I^2 = 0%) (**Figure 4A**). This result was not identified for 40% vs. 80% AOP (SMD = 0.25 [95%CI = −0.22; 0.72]; p = 0.30; I^2 = 60%); subgroup analyses indicated a difference in these analyses in favor of higher pressures performed not to failure (SMD = 0.58 [95%CI = 0.11; 1.05]; p = 0.02; I^2 = 27%) (**Figure 4B**). We identified no differences for exercise with 40% AOP vs. traditional low-load exercise (SMD = 0.05 [95%CI = −0.34; 0.44]; p = 0.80; I^2 = 0%) (**Figure 5A**) or exercise with 80% AOP vs. traditional low-load exercise (SMD = −0.00 [95%CI = −0.75; 0.74]; p = 0.99; I^2 = 69%) (**Figure 5C**). In contrast, differences were identified for exercise with 40% AOP vs. high-load exercise (SMD = −1.19 [95%CI = −2.37; −0.01]; p = 0.05; I^2 = 84%) (**Figure 5B**), and exercise with 80% AOP (SMD = −0.79 [95%CI = −1.20; −0.38]; p = 0.0001; I^2 = 0%) (**Figure 5D**). Details of the GRADE certainty of evidence classification for the analyses in question are reported in detail in **Table 4**.

Sensitivity Analysis

Sensitivity analyses were performed for the following comparisons: (i) exercise with 80% AOP vs. traditional low-load exercise; (ii) exercise with 40% AOP vs. high-load exercise. After we removed one (Buckner et al., 2018) of the three studies included in the analyses, the results remained significant, but heterogeneity was reduced in the comparisons between exercise with 40% AOP vs. high-load exercise (SMD = −0.49 [95%CI = −0.94; −0.05]; p = 0.03; I^2 = 0%). Similarly, after we removed one (Buckner et al., 2018) of the three studies included in the analyses, the results remained non-significant, but heterogeneity was reduced in the comparisons between exercise with 80% AOP vs. traditional low-load exercise (SMD = −0.37 [95%CI = −0.81; 0.08]; p = 0.11; I^2 = 0%).

DISCUSSION

The purpose of this systematic review and meta-analysis was to analyze neuromuscular responses reported in low-load resistance exercise combined with different BFR pressures (%AOP). With respect to MVC torque decline (fatigue measure), analyses indicated no difference for 40% vs. 60% AOP. A tendency (p = 0.07) was identified for the 40-50% vs. 80–90% AOP comparisons; subgroup analyses indicated that higher pressures (i.e., 80–90% vs. 40–50% AOP) induce more fatigue (MVC torque decline) in exercise at 15–20% of 1RM, but not in exercise at 30% of 1RM. Additionally, exercise at 40–50% or 80–90% appeared to induce more fatigue than traditional low-load exercise (i.e., no BFR; 0% AOP). Regarding sEMG analyses, significant differences were found for 40% vs. 60% AOP and 40% vs. 80% AOP (not to failure) in favor of higher pressures. This result was also identified in the analyses for 40% AOP

TABLE 3 | Summary and characteristics of the studies included in the review.

Study (Year)	Study design	Impact factor	Resistance exercise	Exercise protocol	AOP% (Cuff size)	Outcome measure (s)
Counts et al. (2015)	Crossover	2.5	Elbow flexion	**LL:** 75 reps (30-15-15-15); @30% of 1RM; 30s interval between sets.	40, 50, 60, 70, 80, 90% (5cm)	MVC isometric torque (Nm), sEMG Amplitude (RMS).
Loenneke et al. (2015)	Parallel	2.5	Knee extension	**LL (BFR):** 75 reps (30-15-15-15); @20% and 30% de 1RM; 30s interval between sets. **LL:** 4 sets of muscle failure; @20 and 30% of 1RM; 30s interval between sets. **HL:** 4 sets of 10 reps; @70% of 1RM; 60s interval between sets.	0,40, 50, 60% (5cm)	MVC isometric torque (Nm), sEMG Amplitude (RMS).
Loenneke et al. (2016)	Parallel	1.7	Knee extension	**LL (BFR):** 75 reps (30-15-15-15); @20% and 30% de 1RM; 30s interval between sets. **LL:** 4 sets of muscle failure; @20 and 30% of 1RM; 30s interval between sets. **HL:** 4 sets of 10 reps; @70% of 1RM; 60s interval between sets.	0,40, 50, 60% (5 cm)	Blood lactate (mmol^{-1})
Fatela et al. (2016)	Crossover	2.9	Knee extension	**LL:** 75 reps (30-15-15-15); @20% of 1RM; 30s interval between sets.	40, 60, 80% (13 cm)	MVC isometric torque (Nm), sEMG Amplitude (RMS)
Jessee et al. (2017)	Crossover	1.7	Elbow flexion	**LL:** 75 reps (30-15-15-15); @30% of 1RM; 30s interval between sets	0,10,20,30,50, 90% (5 cm)	MVC isometric torque (Nm), sEMG Amplitude (RMS).
Dankel et al. (2017)	Crossover	1.4	Elbow flexion	**LL:** 75 reps (30-15-15-15); @10%, 15% and 20% of 1RM; 30s interval between sets	40, 80% (5cm)	MVC isometric torque (Nm), sEMG Amplitude (RMS).
Buckner et al. (2018))	Crossover	1.7	Elbow flexion	**LL:** 4 sets of muscle failure; @15% of 1RM; 30s interval between sets. **HL:** 4 sets of muscle failure; @70% of 1RM; 90s interval between sets.	0,40, 80% (5 cm)	MVC isometric torque (Nm), sEMG Amplitude (RMS).
Jessee et al. (2019)	Crossover	1.4	Knee extension	**LL:** 4 sets of muscle failure; @15% of 1RM; 30s interval between sets. **HL:** 4 sets of muscle failure; @70% of 1RM; 90s interval between sets.	0,40, 80% (10 cm)	MVC isometric torque (Nm), sEMG Amplitude (RMS).
Ilett et al. (2019)	Crossover	4.1	Knee extension	**LL:** 75 reps (30-15-15-15); 20% of 1RM; 30s interval between sets. **HL:** 4 sets of 8 reps; @80% 1RM; 150s interval between sets.	0,40, 60, 80% (10.5 cm)	MVC isometric torque (Nm), sEMG Amplitude (RMS), Blood lactate (mmol/L).
Singer et al. (2020)	Crossover	2.9	Knee extension	**LL:** 30 reps (1 set); @30% of peak torque.	0,60, 80, 100% (10 cm)	sEMG Amplitude (RMS)

RM: repetition maximum; AOP: arterial occlusion pressure; BFR: blood flow restriction; sEMG: surface electromyography; HL: high load; LL: low load; MVC: maximum voluntary contraction; RMS: root mean square; @: load used.

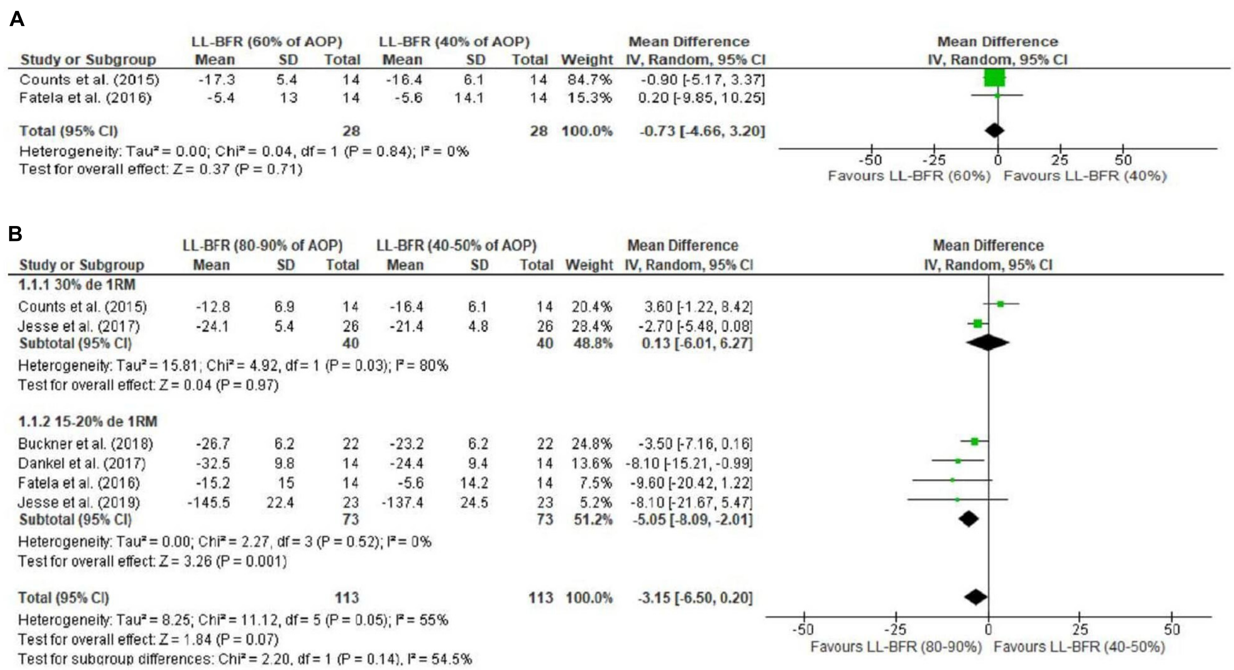

FIGURE 2 | Forest plot illustrating the combined effects for touch MVC torque of: **(A)** LL-RE with BFR pressure of 40% AOP vs. RE-LL with BFR pressure of 60% AOP; **(B)** LL-RE with BFR pressure of 40–50% AOP vs. LL-RE with BFR pressure of 80–90% AOP. 1RM: 1 repetition maximum; 95%CI: Confidence interval; AOP: arterial occlusion pressure; LL-BFR: low load + blood flow restriction; LL: low load; SD: standard deviation.

vs. high-load exercise and 80% AOP vs. NO-BFR high-load resistance exercise, but the results were favorable for NO-BFR high-load resistance exercise.

Maximum Voluntary Contraction Isometric Torque (Fatigue)

Previous studies have found that the application of BFR during low-load exercise maximizes intramuscular metabolic stress (Suga et al., 2009; Sugaya et al., 2011; Yanagisawa and Sanomura, 2017). To illustrate this, Suga et al. (2009) found that low-load (20% of 1RM) plantar flexion exercise with BFR promotes more pronounced inorganic phosphate accumulation and intramuscular pH reductions than NO-BFR low-load exercise and similar to NO-BFR high-load exercise. The accumulation of metabolites may compromise the contractile capacity of skeletal muscle through metabolic stimulation of group III and IV afferents (mechanoreceptors and metaboreceptors, respectively) and, consequently, reduced motoneuron activity (central mechanism) (Boyas and Guével, 2011). Therefore, amplified metabolite accumulation may be a valid justification to explain, at least in part, the more pronounced MVC torque decline in low-load exercise with BFR, relative to NO-BFR low-load exercise. It is worth noting that these results were identified for the analyses of moderate (40–50% AOP) and high (80–90% AOP) BFR pressure.

Previously, a dose-dependent relationship was found between the restriction pressure applied in exercise and intramuscular metabolite accumulation (Sugaya et al., 2011). In this sense, it was expected that exercise with higher relative BFR pressure would induce greater MVC torque decline. Our analyses indicated no difference for 40% vs. 60% AOP. It is possible that an increase from 40 to 60% AOP is not sufficient to induce some sort of metabolic change that amplifies the magnitude of fatigue. The individual findings of Ilett et al. (2019) support this hypothesis, given that the authors found no differences between MVC torque values assessed over multiple knee extension sets for exercise with BFR at pressure 40% and 60% AOP. Additionally, Loenneke et al. (2016) identified that exercise performed at 40% and 60% of the predicted AOP produces similar acute blood lactate changes, i.e., a similar metabolic response.

Our analyses point to a difference in the decline in MVC torque between exercise with BFR at pressure 40–50% vs. 80–90% of AOP, but only for those studies that analyzed exercise with load 15–20% of 1RM. This finding provides evidence that exercise with loads $\leq$ 20% of 1RM may be more influenced by manipulation of constraint pressure, with higher%AOP inducing higher levels of fatigue. In the case of studies with loads $\geq$ 30% of 1RM, it is possible that the applied load itself is sufficient to significantly limit blood flow and therefore the possible effects of constraint pressure manipulation are mitigated Lixandrão et al. (2015). This aspect was used to justify the findings of Lixandrão et al. (2015); the authors found that femoral quadriceps hypertrophy resulting from a 20% 1RM resistance training program is maximized by applying higher BFR pressures (80% vs. 40% AOP), but this dose-dependent effect was not evidenced during resistance training program with load 40% 1RM. Similarly, Counts et al. (2015) did not identify an effect of restriction pressure (40% vs. 90% AOP)

TABLE 4 | Certainty of evidence according to the GRADE.

Outcome	Comparison (%AOP)	Certainty assessment						No of patients		Effect	Certainty
		N° of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	group	group	Absolute(95% CI)	
MVC torque	40% vs. 60%	2	Crossover randomized trials	Serious [a]	Not serious	Not serious	Serious [c]	28	28	−4.66 to 3.20	⊕⊕◯LOW
MVC torque	40% vs. 80%(15–20% 1RM)	4	Crossover randomized trials	Serious [a]	Not serious	Not serious	Serious [c]	73	73	−8.09 to −2.01	⊕⊕◯LOW
MVC torque	40–50% vs. 80–90%(30% 1RM)	2	Crossover randomized trials	Serious [a]	Serious [b]	Not serious	Serious [c]	40	40	−6.01 to 6.27	⊕◯◯VERY LOW
MVC torque	40% vs. 0%	3	Crossover randomized trials	Serious [a]	Serious [b]	Not serious	Serious [c]	71	71	−17.95 to −1.08	⊕◯◯VERY LOW
MVC torque	80% vs. 0%	3	Crossover randomized trials	Serious [a]	Serious [b]	Not serious	Serious[c]	71	71	−25.33 to −4.74	⊕◯◯VERY LOW
EMG	40% vs. 60%	3	Crossover randomized trials	Serious [a]	Not serious	Not serious	Serious[c]	38	38	0.02 to 0.93	⊕⊕◯LOW
EMG	40% vs. 80%(Not failure)	4	Crossover randomized trials	Serious [a]	Not serious	Not serious	Serious[c]	52	52	0.11 to 1.05	⊕⊕◯LOW
EMG	40% vs. 80%(Failure)	2	Crossover randomized trials	Serious [a]	Not serious	Not serious	Serious[c]	40	40	−0.75 to 0.13	⊕⊕◯LOW
EMG	40% vs.0%(Low load)	3	Crossover randomized trials	Serious [a]	Not serious	Not serious	Serious [c]	50	50	−0.34 to 0.44	⊕⊕◯LOW
EMG	40% vs. 0%(High load)	3	Crossover randomized trials	Serious [a]	Serious [b]	Not serious	Serious [c]	50	50	−2.37 to −0.01	⊕◯◯VERY LOW
EMG	80% vs. 0%(Low load)	3	Crossover randomized trials	Serious [a]	Serious [b]	Not serious	Serious[c]	50	50	−0.75 to 0.74	⊕◯◯VERY LOW
EMG	80% vs. 0%(High load)	3	Crossover randomized trials	Serious [a]	Not serious	Not serious	Serious [c]	50	50	−1.20 to −0.38	⊕⊕◯LOW

AOP: Arterial occlusion pressure; CI: Confidence interval.
Explanations:
[a]*Lack of blinding of the result evaluators; Lack of details about the randomization process; Absence of study registration.*
[b]*High and significant heterogeneity.*
[c]*Sample size less than 100 for each group.*

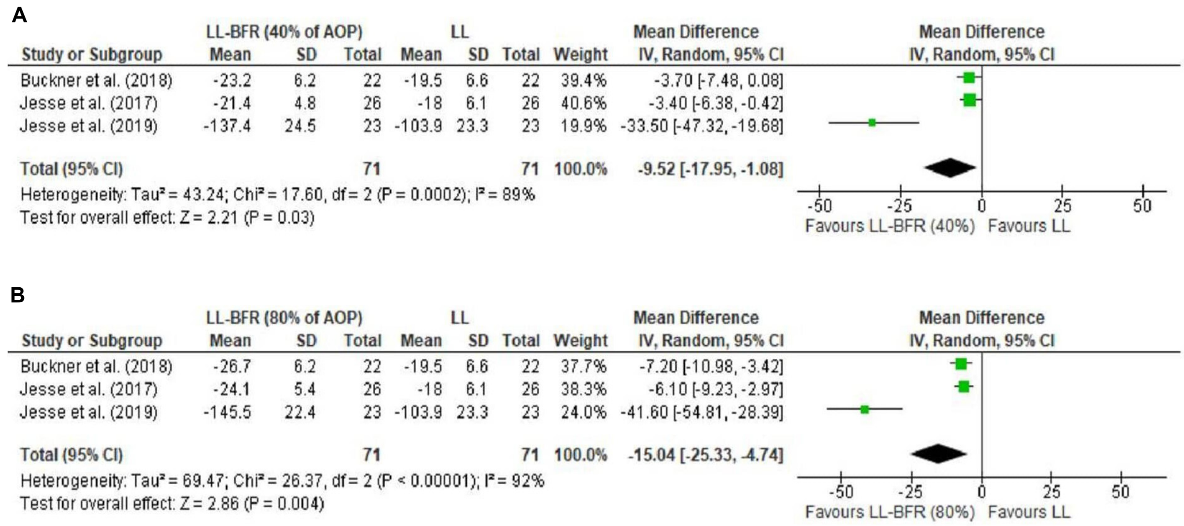

FIGURE 3 | Forest plot illustrating the combined effects for touch MVC of: **(A)** LL-RE with BFR pressure of 40% AOP vs. LL-RE (NO-BFR); **(B)** LL-RE with BFR pressure of 80% AOP vs. LL-RE (NO-BFR). 95%CI: confidence interval; AOP: arterial occlusion pressure; LL-BFR: low load + blood flow restriction; LL: low load; SD: standard deviation.

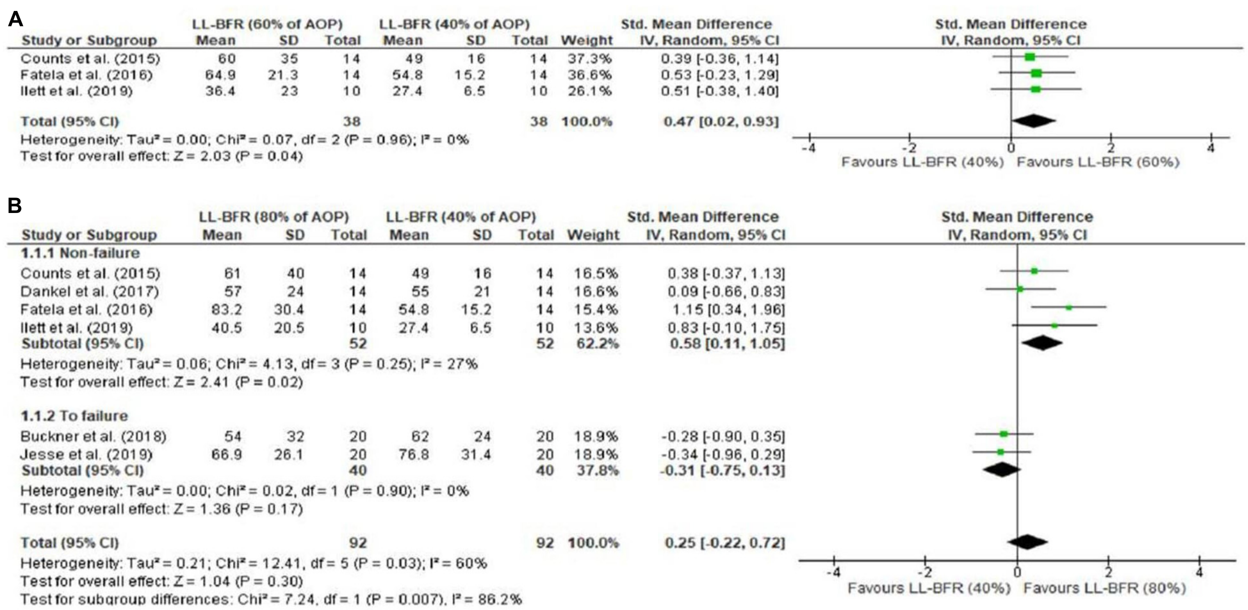

FIGURE 4 | Forest plot illustrating the combined effects for myoelectric activity of: **(A)** LL-RE with BFR pressure of 40% AOP vs. LL-RE with BFR pressure of 60% AOP; **(B)** LL-RE with BFR pressure of 40 AOP vs. LL-RE with BFR pressure of 80% AOP. 95%CI: confidence interval; AOP: arterial occlusion pressure; LL-BFR: low load + blood flow restriction; LL: low load; SD: standard deviation.

on elbow flexor hypertrophy resulting after resistance training program with 30% 1RM load.

Surface Electromyography

A recent meta-analysis identified that under conditions of equalized volume (not failure), myoelectric activity is greater in low-load exercise with BFR than in traditional low-load exercise (Cerqueira et al., 2021). In contrast, in protocols consisting of sets performed to muscle failure this superiority effect of exercise with BFR was non-existent (Cerqueira et al., 2021). Similarly, we identified that in protocols of preset repetition schemes (not failure), muscle excitability is increased by higher BFR pressures (40% vs. 60%; 40% vs. 80% AOP), but this effect was not identified in protocols of repetitions performed to muscle failure. Taken together, these data suggest that the effect of BFR pressure (e.g., 0 vs. 40% vs. 80% AOP) on muscle excitability disappears in

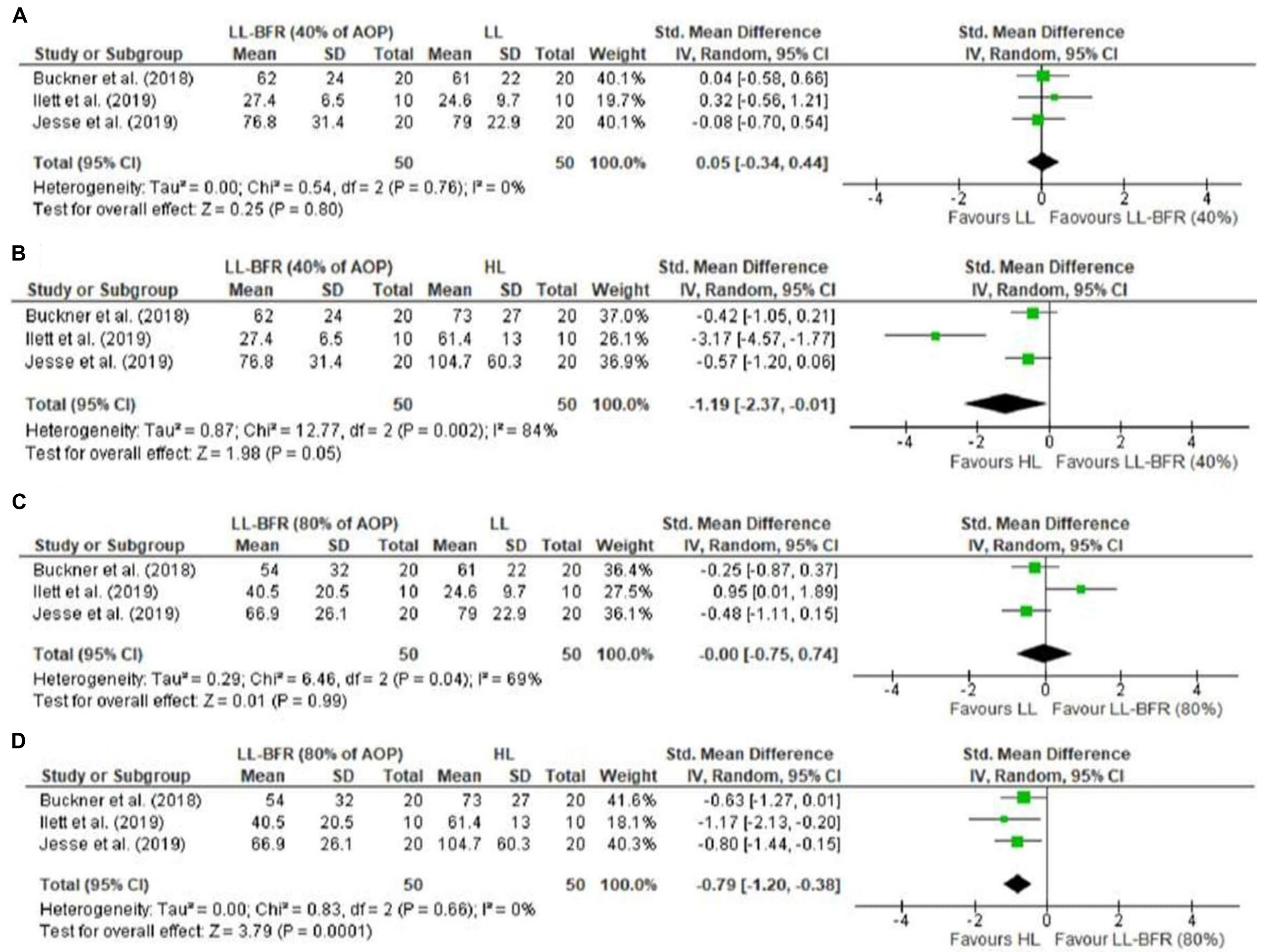

FIGURE 5 | Forest plot illustrating the combined effects for myoelectric activity of: **(A)** LL-RE with BFR pressure of 40% AOP vs. LL-RE (NO-BFR); **(B)** LL-RE with BFR pressure of 40% AOP vs. HL-RE (NO-BFR); **(C)** LL-RE with BFR pressure of 80% AOP vs. LL-RE (NO-BFR); **(D)** LL-RE with BFR pressure of 80% AOP vs. HL-RE (NO-BFR). 95%CI: confidence interval; AOP: arterial occlusion pressure; HL: high load; LL-BFR: low load + blood flow restriction; LL: low load; SD: standard deviation.

protocols performed to muscle failure. This aspect could explain the fact that we did not find differences in the comparisons made for low-load exercise with BFR (40% or 80% AOP) vs. traditional low-load exercise, since most of the studies included in these analyses analyzed sets up to muscle failure. Thus, it is likely that in sets performed to muscle failure, the stimulus provided by exercise with BFR is similar to the stimulus provided by traditional low-load exercise. Perhaps because of this, Jessee et al. (2018b) did not show an effect of BFR (40% or 80% AOP) on the hypertrophic adaptations provided by a low-load RT program (15% of 1RM) composed of exercise performed to muscle failure.

Although the aforementioned theory finds support to some extent, one needs to consider that in the study by Laurentino et al. (2012), a low-load resistance training program combined with BFR promoted hypertrophy similar to a high-load resistance training program (80% of 1RM). Our analyses indicated that the NO-BFR high-load exercise promoted higher myoelectric activity than the low-load exercise with BFR, regardless of the level of restriction (40% or 80% AOP). These results are in line with the results reported by Cerqueira et al. (2021). Considering a primary role of MU recruitment in the hypertrophic adaptations provided by BFR resistance training, one would expect that NO-BFR high-load resistance training programs would induce more hypertrophy than BFR low-load resistance training programs, since sEMG amplitude is lower in the latter. However, two previously published meta-analyses identified that muscle hypertrophy gain is similar between the training models in question (Lixandrão et al., 2018; Centner et al., 2019). Therefore, acute sEMG data may not be good predictors of muscle hypertrophy. Furthermore, sEMG results reported in BFR exercise studies should be interpreted with some level of caution, due to the fact that sEMG amplitude may not necessarily reflect increased MU recruitment (Vigotsky et al., 2018). Finally, we do not rule out the possibility that other mechanisms (e.g., edema) may be involved in the adaptations provided by BFR low-load resistance training, and not just an increase in MU recruitment.

Future Research

Under certain conditions (≤ 20% of 1RM), it has been found that increasing the relative pressure of BFR can maximize fatigue, which in theory may be positive for induction of hypertrophic adaptations arising during and after BFR resistance training. However, these findings may be limited for exercise protocols with continuous restriction. In this type of prescription, the restriction pressure is maintained throughout the exercise, including the recovery intervals between sets. We believe that it would be important for future studies to analyze the effect of modulating the pressure of restraint in intermittent restraint protocols (Wilk et al., 2020), characterized by the release of the restraint pressure during recovery intervals and compare it to continuous restraint models. Additionally, we recommend that future studies analyze the acute effect of restraint pressure modulation in repetition schemes consisting of sets of 15 repetitions. This arbitrary repetition scheme may be a more viable option for studies that propose to analyze no-fail conditions, relative to the protocol consisting of 75 repetitions (30-15-15-15). Finally, we recommend that future studies look for more suitable methods to analyze MU recruitment in exercise protocols with BFR, given that surface EMG presents certain limitations for this type of analysis (Vigotsky et al., 2018), since the amplitude of the sEMG is not only dependent on the recruitment of MU, but also on the firing rate and synchronization of all active muscles fibers under electrode area (Lixandrão et al., 2018).

Limitation

Some aspects should be pointed out for a better understanding of our results. A high heterogeneity was identified for comparisons of torque decline and sEMG between exercise at performed with BFR a pressure 40-50% vs. 80-90% AOP (I^2 = 55% and I^2 = 60% for torque and EMG, respectively), suggesting a certain degree of variability among the studies included in these meta-analyses. However, subgroup analyses were performed in order to isolate the differences and identify possible factors that could account for the different effects. For the torque analyses, a high heterogeneity (I^2 = 80%) was evidenced in the subgroup analyses of the studies that adopted 30% of 1RM load; due to the low number of studies ($n = 2$), we did not perform sensitivity analyses, so these data should be analyzed with caution. Additionally, we identified high heterogeneity among the comparisons performed for exercise with BFR vs. traditional exercise (high-load and low-load). However, we should point out that the results were maintained after our sensitivity analyses.

We pointed out that the quality of evidence was low for all analyses and that the studies had certain important methodological limitations, including lack of blinding of outcome assessors, information about the procedure used for randomization or concealment of this procedure, and information about study registration.

Practical Application

This review provides important information on how the manipulation of BFR pressure (individualized) applied in low-load exercise can affect fatigue. Therefore, our findings can be used to assist trainers and physical therapists in prescribing resistance training with BFR. In particular, we found that exercise with moderate pressures (40–50% AOP) induces a higher level of fatigue than NO-BFR exercise. Therefore, this BFR pressure may be sufficient to induce an adequate stimulus that reflects significant chronic adaptations, in addition to promoting reduced levels of discomfort, compared to higher BFR pressures (Soligon et al., 2018). We point out that, in the case of acute fatigue, exercise with higher loads (30% of 1RM) seems not to be affected by the manipulation of the BFR pressure. Therefore, the application of high pressures may be unnecessary when the exercise is performed with loads between 30 and 40% of 1RM. This aspect could justify the fact that chronic studies (Counts et al., 2015; Lixandrão et al., 2015) that compared resistance training programs combined with different levels of BFR, applying loads of 30 and 40% of 1RM, did not identify the effect of BFR pressure on muscle hypertrophy.

CONCLUSION

In conclusion, the results of this systematic review and meta-analysis demonstrate that low-load resistance exercise with moderate (40–50% AOP) or high (80–90% AOP) blood flow restriction pressure induces more fatigue (decline in neuromuscular function) than NO-BRF low-load resistance exercise. However, applying a high restriction pressure can increase the magnitude of fatigue when loads of 15–20% of 1RM are prescribed. Additionally, we identified that the application of higher restriction pressures can increase muscle excitability in pre-defined repetition schemes (not failure). However, the level of excitability achieved with low-load exercise with moderate or high restriction pressures (40% and 80% AOP, respectively) is still lower than in NO-BFR high-load resistance exercise.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

VQ was responsible for the original idea of the review and wrote the original draft of the manuscript. VQ, IS, GN, BC, and PD were responsible for the study design. VQ and IF performed out the bibliographical research. VQ, IF, and IS participated in the process of screening and evaluating the methodological quality of the studies included in the review. All authors read, critically reviewed, and approved the final version of the manuscript.

FUNDING

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brazil (CAPES), Finance Code 001.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2021.786752/full#supplementary-material

REFERENCES

Ahn, E., and Kang, H. (2018). Introduction to systematic review and meta-analysis. *Korean J. Anesthesiol*. 71, 103–112. doi: 10.4097/kjae.2018.71.2.103

Amann, M., Sidhu, S. K., Weavil, J. C., Mangum, T. S., and Venturelli, M. (2015). Autonomic responses to exercise: group III/IV muscle afferents and fatigue. *Auton. Neurosci.* 188, 19–23. doi: 10.1016/j.autneu.2014.10.018

Atkins, D., Briss, P. A., Eccles, M., Flottorp, S., Guyatt, G. H., Harbour, R. T., et al. (2005). Systems for grading the quality of evidence and the strength of recommendations II: pilot study of a new system. *BMC Health Serv. Res.* 5:25. doi: 10.1186/1472-6963-5-25

Borenstein, M., Hedges, L. V., Higgins, J. P., and Rothstein, H. R. (2021). *Introduction to Meta-Analysis*. Hoboken: John Wiley & Sons.

Boyas, S., and Guével, A. (2011). Neuromuscular fatigue in healthy muscle: underlying factors and adaptation mechanisms. *Ann. Phys. Rehabil. Med.* 54, 88–108.

Buckner, S. L., Jessee, M. B., Dankel, S. J., Mattocks, K. T., Mouser, J. G., Bell, Z. W., et al. (2018). Acute skeletal muscle responses to very low−load resistance exercise with and without the application of blood flow restriction in the upper body. *Clin. Physiol. Funct. Imaging* 39, 201–208. doi: 10.1111/cpf.12557

Centner, C., Wiegel, P., Gollhofer, A., and König, D. (2019). Effects of blood flow restriction training on muscular strength and hypertrophy in older individuals: a systematic review and meta-analysis. *Sports Med.* 49, 95–108. doi: 10.1007/s40279-018-0994-1

Cerqueira, M. S., Maciel, D. G., Barboza, J. A. M., Centner, C., Lira, M., Pereira, R., et al. (2021). Effects of low-load blood flow restriction exercise to failure and non-failure on myoelectric activity: a meta-analysis. *J. Athl. Train.* [Epub ahead of print]

Cook, S. B., Clark, B. C., and Ploutz-Snyder, L. L. (2007). Effects of exercise load and blood-flow restriction on skeletal muscle function. *Med. Sci. Sports Exerc.* 39, 1708–1713. doi: 10.1249/mss.0b013e31812383d6

Counts, B. R., Dankel, S. J., Barnett, B. E., Kim, D., Mouser, J. G., Allen, K. M., et al. (2015). Influence of relative blood flow restriction pressure on muscle activation and muscle adaptation. *Muscle Nerve* 53, 438–445. doi: 10.1002/mus.24756

Dankel, S. J., Jessee, M. B., Buckner, S. L., Mouser, J. G., Mattocks, K. T., and Loenneke, J. P. (2017). Are higher blood flow restriction pressures more beneficial when lower loads are used? *Physiol. Int.* 104, 247–257.

de Queiros, V. S., Dantas, M., Neto, G. R., da Silva, L. F., Assis, M. G., Almeida-Neto, P., et al. (2021). Application and side effects of blood flow restriction technique: a cross-sectional questionnaire survey of professionals. *Medicine* 100:e25794. doi: 10.1097/MD.0000000000025794

Elkins, M. R., Herbert, R. D., Moseley, A. M., Sherrington, C., and Maher, C. (2010). Rating the quality of trials in systematic reviews of physical therapy interventions. *Cardiopulm. Phys. Ther. J.* 21, 20–26.

Fatela, P., Reis, J. F., Mendonca, G. V., Avela, J., and Mil-Homens, P. (2016). Acute effects of exercise under different levels of blood-flow restriction on muscle activation and fatigue. *Eur. J. Appl. Physiol.* 116, 985–995. doi: 10.1007/s00421-016-3359-1

Jessee, M. B., Buckner, S. L., Mattocks, K. T., Dankel, S. J., Mouser, J. G., Bell, Z. W., et al. (2019). Blood flow restriction augments the skeletal muscle response during very low-load resistance exercise to volitional failure. *Physiol. Int.* 106, 180–193.

Jessee, M. B., Mattocks, K. T., Buckner, S. L., Dankel, S. J., Mouser, J. G., Abe, T., et al. (2018a). Mechanisms of blood flow restriction: the new testament. *Tech. Orthop.* 33, 72–79.

Jessee, M. B., Buckner, S. L., Mouser, J. G., Mattocks, K. T., Dankel, S. J., Abe, T., et al. (2018b). Muscle adaptations to high-load training and very low-load training with and without blood flow restriction. *Front. Physiol.* 9:1448. doi: 10.3389/fphys.2018.01448

Jessee, M. B., Mattocks, K. T., Buckner, S. L., Mouser, J. G., Counts, B. R., Dankel, S. J., et al. (2017). The acute muscular response to blood flow−restricted exercise with very low relative pressure. *Clin. Physiol. Funct. Imaging* 2018, 304–311. doi: 10.1111/cpf.12416

Higgins, J. P., and Thompson, S. G. (2002). Quantifying heterogeneity in a meta−analysis. *Stat. Med.* 21, 1539–1558. doi: 10.1002/sim.1186

Horsley, T., Dingwall, O., and Sampson, M. (2011). Checking reference lists to find additional studies for systematic reviews. *Cochrane Database Syst. Rev.* 2011:MR000026. doi: 10.1002/14651858.MR000026.pub2

Ilett, M. J., Rantalainen, T., Keske, M. A., May, A. K., and Warmington, S. A. (2019). The effects of restriction pressures on the acute responses to blood flow restriction exercise. *Front. Physiol.* 10:1018. doi: 10.3389/fphys.2019.01018

Laurentino, G. C., Ugrinowitsch, C., Roschel, H., Aoki, M. S., Soares, A. G., Neves, M. Jr., et al. (2012). Strength training with blood flow restriction diminishes myostatin gene expression. *Med. Sci. Sports Exerc.* 44, 406–412. doi: 10.1249/MSS.0b013e318233b4bc

Lixandrão, M. E., Ugrinowitsch, C., Berton, R., Vechin, F. C., Conceição, M. S., Damas, F., et al. (2018). Magnitude of muscle strength and mass adaptations between high-load resistance training versus low-load resistance training associated with blood-flow restriction: a systematic review and meta-analysis. *Sports Med.* 48, 361–378.

Lixandrão, M. E., Ugrinowitsch, C., Laurentino, G., Libardi, C. A., Aihara, A. Y., Cardoso, F. N., et al. (2015). Effects of exercise intensity and occlusion pressure after 12 weeks of resistance training with blood-flow restriction. *Eur. J. Appl. Physiol.* 115, 2471–2480.

Loenneke, J. P., Fahs, C. A., Wilson, J. M., and Bemben, M. G. (2011). Blood flow restriction: the metabolite/volume threshold theory. *Med. Hypotheses* 77, 748–752. doi: 10.1016/j.mehy.2011.07.029

Loenneke, J. P., Kim, D., Fahs, C. A., Thiebaud, R. S., Abe, T., Larson, R. D., et al. (2016). The influence of exercise load with and without different levels of blood flow restriction on acute changes in muscle thickness and lactate. *Clin. Physiol. Funct. Imaging* 37, 734–740. doi: 10.1111/cpf.12367

Loenneke, J. P., Kim, D., Fahs, C. A., Thiebaud, R. S., Abe, T., Larson, R. D., et al. (2015). Effects of exercise with and without different degrees of blood flow restriction on torque and muscle activation. *Muscle Nerve* 51, 713–721.

Loenneke, J. P., Wilson, J. M., Marín, P. J., Zourdos, M. C., and Bemben, M. G. (2012). Low intensity blood flow restriction training: a meta-analysis. *Eur. J. Appl. Physiol.* 112, 1849–1859.

Lopez, P., Radaelli, R., Taaffe, D. R., Newton, R. U., Galvão, D. A., Trajano, G. S., et al. (2021). Resistance training load effects on muscle hypertrophy and strength gain: systematic review and network meta-analysis. *Med. Sci. Sports Exerc.* 53, 1206–1216. doi: 10.1249/MSS.0000000000002585

Moseley, A. M., Herbert, R. D., Sherrington, C., and Maher, C. G. (2002). Evidence for physiotherapy practice: a survey of the physiotherapy evidence database (PEDro). *Aust. J. Physiother.* 48, 43–49. doi: 10.1016/s0004-9514(14)60281-6

Nakajima, T., Kurano, M., Iida, H., Takano, H., Oonuma, H., Morita, T., et al. (2006). Use and safety of KAATSU training: results of a national survey. *Int. J. KAATSU Train. Res.* 13, 1-9.

Ouzzani, M., Hammady, H., Fedorowicz, Z., and Elmagarmid, A. (2016). Rayyan—a web and mobile app for systematic reviews. *Syst. Rev.* 5:210.

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71 doi: 10.1136/bmj.n71

Patterson, S. D., and Brandner, C. R. (2018). The role of blood flow restriction training for applied practitioners: a questionnaire-based survey. *J. Sports Sci.* 36, 123–130. doi: 10.1080/02640414.2017.1284341

Rolnick, N., and Schoenfeld, B. J. (2020). Blood flow restriction training and the physique athlete: a practical research-based guide to maximizing muscle size. *Strength Cond. J.* 42, 22–36.

Singer, T. J., Stavres, J., Elmer, S. J., Kilgas, M. A., Pollock, B. S., Kearney, S. G., et al. (2020). Knee extension with blood flow restriction: impact of cuff pressure on hemodynamics. *Eur. J. Appl. Physiol.* 120, 79–90.

Sterne, J. A., Sutton, A. J., Ioannidis, J. P., Terrin, N., Jones, D. R., Lau, J., et al. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 343:d4002. doi: 10.1136/bmj.d4002

Soligon, S. D., Lixandrão, M. E., Biazon, T. M. P. C., Angleri, V., Roschel, H., and Libardi, C. A. (2018). Lower occlusion pressure during resistance exercise with blood-flow restriction promotes lower pain and perception of exercise compared to higher occlusion pressure when the total training volume is equalized. *Physiol. Int.* 105, 276–284. doi: 10.1556/2060.105.2018.3.18

Suga, T., Okita, K., Morita, N., Yokota, T., Hirabayashi, K., Horiuchi, M., et al. (2009). Intramuscular metabolism during low-intensity resistance exercise with blood flow restriction. *J. Appl. Physiol.* 106, 1119–1124. doi: 10.1152/japplphysiol.90368.2008

Sugaya, M., Yasuda, T., Suga, T., Okita, K., and Abe, T. (2011). Change in intramuscular inorganic phosphate during multiple sets of blood flow−restricted low−intensity exercise. *Clin. Physiol. Funct. Imaging* 31, 411–413.

Takarada, Y., Takazawa, H., Sato, Y., Takebayashi, S., Tanaka, Y., and Ishii, N. (2000a). Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. *J. Appl. Physiol*. 88, 2097–2106. doi: 10.1152/jappl.2000.88.6.2097

Takarada, Y., Nakamura, Y., Aruga, S., Onda, T., Miyazaki, S., and Ishii, N. (2000b). Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J. Appl. Physiol.* 88, 61–65.

Wilson, J. M., Lowery, R. P., Joy, J. M., Loenneke, J. P., and Naimo, M. A. (2013). Practical blood flow restriction training increases acute determinants of hypertrophy without increasing indices of muscle damage. *J. Strength Cond. Res.* 27, 3068–3075.

Valkenet, K., van de Port, I. G., Dronkers, J. J., de Vries, W. R., Lindeman, E., and Backx, F. J. (2011). The effects of preoperative exercise therapy on postoperative outcome: a systematic review. *Clin. Rehabil.* 25, 99–111. doi: 10.1177/0269215510380830

Vanwye, W. R., Weatherholt, A. M., and Mikesky, A. E. (2017). Blood flow restriction training: implementation into clinical practice. *Int. J. Exerc. Sci*. 10, 649–654.

Vigotsky, A. D., Halperin, I., Lehman, G. J., Trajano, G. S., and Vieira, T. M. (2018). Interpreting signal amplitudes in surface electromyography studies in sport and rehabilitation sciences. *Front. Physiol.* 8:985. doi: 10.3389/fphys.2017.00985

Vøllestad, N. K. (1997). Measurement of human muscle fatigue. *J. Neurosci. Methods* 74, 219–227. doi: 10.1016/s0165-0270(97)02251-6

Wilk, M., Gepfert, M., Krzysztofik, M., Zajac, A., and Bogdanis, G. C. (2020). Acute effects of continuous and intermittent blood flow restriction on movement velocity during bench press exercise against different loads. *Front. Physiol.* 11:569915. doi: 10.3389/fphys.2020.569915

Yanagisawa, O., and Sanomura, M. (2017). Effects of low-load resistance exercise with blood flow restriction on high-energy phosphate metabolism and oxygenation level in skeletal muscle. *Interv. Med. Appl. Sci*. 9, 67–75.

Yasuda, T., Brechue, W. F., Fujita, T., Shirakawa, J., Sato, Y., and Abe, T. (2009). Muscle activation during low-intensity muscle contractions with restricted blood flow. *J. Sports Sci.* 27, 479–489. doi: 10.1080/02640410802626567

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Physiology

REVIEW
published: 02 December 2021
doi: 10.3389/fphys.2021.747759

Check for updates

The Evolution of Blood Flow Restricted Exercise

Eduardo D. S. Freitas[1†], *Murat Karabulut*[2†] *and Michael G. Bemben*[1*†]

[1]Department of Health and Exercise Science, University of Oklahoma, Norman, OK, United States, [2]Department of Health and Human Performance, University of Texas Rio Grande Valley, Brownsville, TX, United States

Edited by:
Adam Zajac,
University School of Physical Education in Wroclaw, Poland

Reviewed by:
Kyle J. Hackney,
North Dakota State University, United States
David Cristóbal Andrade,
University of Antofagasta, Chile

****Correspondence:***
Michael G. Bemben
mgbemben@ou.edu

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *26 July 2021*
Accepted: *10 November 2021*
Published: *02 December 2021*

Citation:
Freitas EDS, Karabulut M and Bemben MG (2021) The Evolution of Blood Flow Restricted Exercise. Front. Physiol. 12:747759. doi: 10.3389/fphys.2021.747759

The use of blood flow restricted (BFR) exercise has become an accepted alternative approach to improve skeletal muscle mass and function and improve cardiovascular function in individuals that are not able to or do not wish to use traditional exercise protocols that rely on heavy loads and high training volumes. BFR exercise involves the reduction of blood flow to working skeletal muscle by applying a flexible cuff to the most proximal portions of a person's arms or legs that results in decreased arterial flow to the exercising muscle and occluded venous return back to the central circulation. Safety concerns, especially related to the cardiovascular system, have not been consistently reported with a few exceptions; however, most researchers agree that BFR exercise can be a relatively safe technique for most people that are free from serious cardiovascular disease, as well as those with coronary artery disease, and also for people suffering from chronic conditions, such as multiple sclerosis, Parkinson's, and osteoarthritis. Potential mechanisms to explain the benefits of BFR exercise are still mostly speculative and may require more invasive studies or the use of animal models to fully explore mechanisms of adaptation. The setting of absolute resistive pressures has evolved, from being based on an individual's systolic blood pressure to a relative measure that is based on various percentages of the pressures needed to totally occlude blood flow in the exercising limb. However, since several other issues remain unresolved, such as the actual external loads used in combination with BFR, the type of cuff used to induce the blood flow restriction, and whether the restriction is continuous or intermittent, this paper will attempt to address these additional concerns.

Keywords: kaatsu, occlusion training, practical BFR, resistance training, aerobic training

INTRODUCTION

Blood flow restricted exercise (BFR) has increasingly been used as an alternative training method for those unable to perform traditional aerobic or resistance exercise protocols, such as individuals with poor strength or endurance, recovering from an injury, or undergoing rehabilitation. BFR training may also serve as a supplemental training technique in combination with traditional exercise protocols to enhance adaptations to training based on the many published studies that demonstrate positive neuromuscular, aerobic, and anaerobic performance parameters (Abe et al., 2010a; Sudo et al., 2017; Amani-Shalamzari et al., 2019). These primary adaptations to BFR exercise include increases in muscle size and strength (Bjørnsen et al., 2019), improved physical function (Abe et al., 2010b), and enhanced endurance capabilities (muscular and cardiorespiratory; Held et al., 2020).

It is also worthwhile noting that the benefits associated with low-load BFR exercise are not limited to healthy young individuals (Abe et al., 2010a), but also middle-aged and elderly (Karabulut et al., 2010; Abe et al., 2010b; Ozaki et al., 2011b). Moreover, several studies have demonstrated the benefits of BFR training to clinical populations, such as post-surgery rehabilitating athletes (Kilgas et al., 2019) and individuals dealing with different forms of chronic inflammation and pain (i.e., arthritis, chronic fatigue syndrome, and fibromyalgia; McCully et al., 2004; Korakakis et al., 2018; Jørgensen et al., 2020). Thus, low-intensity aerobic exercise combined with BFR or low-load resistance exercise with BFR has emerged as potential training alternatives to traditional aerobic and resistance training programs, which are commonly performed at high intensities or using heavy loads, making it difficult for many of the populations already mentioned to withstand the training demands. However, the majority of published studies that explored BFR exercise have been acute interventions, primarily with college-aged males, necessitating the need for prolonged training studies and including females as subjects (Counts et al., 2018).

Although it is commonly accepted that BFR training is effective, there are several topics that need to be addressed to understand the evolution of this training method. First, BFR training has been found to be effective to improve several physiological systems, but improper use of the BFR technique can cause health problems; thus, it requires constant supervision, making its use outside of research and clinical settings difficult and challenging. Second, several studies were performed to understand the underlying mechanisms for BFR-related physiological adaptations, but many details still need further exploration and more invasive studies as well as potential animal models may be necessary to detail the main underlying mechanisms. Third, the devices used to restrict blood flow also varied between studies and have evolved over time. Instead of only the traditional electronically controlled pneumatic cuffs to induce restrictive pressures in a laboratory setting (KAATSU and KAATSU-mini, Sato Sports Plaza, Tokyo, JAP; Hokanson Rapid Cuff Inflation System, Bellevue, WA, United States; and the Delfi Medical Innovations Systems, Vancouver, BC, CAN), there is also a more practical BFR technique (Loenneke et al., 2010) that uses commercially available elastic wraps or bands to reduce blood flow during exercise. Even though having the ability to select different restriction cuffs may be useful, the differences in width and materials of the cuffs used to restrict blood flow can be problematic and result in inconsistencies in the findings. Finally, many previous studies have used different procedures to set restriction pressures and have used numerous different exercise training protocols.

Adding to the confusion, many details about how the cuff pressures were determined [initial pressure/tightness of cuff before inflation vs. final/target pressure – based on the original KAATSU philosophy (Sato, 2005)] are not clear or perhaps are not even reported. Fullana et al. (2005) reported that only a pressure greater than 40 mmHg would change venous diameter at thigh level. In addition, several studies confirmed that the accumulation of some by-products, such as lactate and hydrogen ions, might cause increased afferent signals from intramuscular metaboreceptors resulting in an increased growth hormone response (Takarada et al., 2000a; Goto et al., 2005). Therefore, setting the initial tightness of the cuffs to 40 mmHg or higher will apply some pressure on veins even when the cuffs are deflated, affecting the level of blood and by-product accumulation in the limbs, signals from muscle metaboreceptors, and venous return. A study by Karabulut et al. (2011b) reported supporting evidence of this theory that the session with greater initial tightness of the cuffs resulted in significantly lower tissue hemoglobin oxygen saturations and venous returns. Therefore, it is logical to assume that the lack of clear and descriptive information about BFR protocols has forced many researchers to develop their own specific BFR exercise protocols concerning the which muscle groups to study or what exercises should be used, what the appropriate number of sets or repetitions should be, the length of the rest periods between sets and exercise, etc. This has resulted in little to no consensus of what is the most effective BFR exercise protocol.

This review will describe the safety issues and concerns associated with BFR exercise, a summary of the potential mechanisms for positive adaptations, the types of restrictive devices available for exercise, how restriction protocols and exercise protocols have evolved since the first introduction of BFR exercise in the 1960s and 70s, aerobic and anaerobic exercise with BFR, and the limitations from previous studies and current gaps in the research literature.

SAFETY ISSUES AND CONCERNS

Perhaps the largest and most comprehensive study that examined the safety and efficacy of BFR exercise was completed in Japan in 2005 (Nakajima et al., 2006). Data were collected from 105 out of 195 facilities where BFR exercise was being used. Several types of facilities were surveyed: sports training gyms (27%), osteopathic facilities (24%), hospitals and clinics (22%), acupuncture facilities and other therapeutic massage facilities (10%), and rehabilitative centers (3%). The length of time that each facility had been using BRF exercise ranged from more than 5 years (16%) to less than 1 year (24%), with training sessions ranging from 5 to 30 min, performed 1 to 3 times per week.

The most obvious concerns involve the cardiovascular system since the applied pressure directly affects blood flow return to the heart and central circulation and compressing blood vessels with the restrictive cuffs may also result in thrombosis and/or induce microvascular occlusion that could result in muscle cell damage and necrosis. Most often reported symptoms were dizziness and fainting due to the BFR-related reduced venous return and reduced cardiac preload. Surprisingly, the incidence of side effects reported in this large survey study was minimal and involved only a few incidences of venous thrombus (0.055%), pulmonary embolism (0.008%), and rhabdomyolysis (0.008%), resulting in the authors concluding that BRF exercise was a safe method of training for athletes, healthy individuals, and persons with various physical conditions (Nakajima et al., 2006).

In general, the potential effects of BFR exercise on the cardiovascular system depend on the level of restriction and the mode of exercise. Generally, the increases in heart rate, systolic blood pressure (SBP), and diastolic blood pressure are similar or perhaps even lower than high-load exercises performed with no restriction (Brandner et al., 2014; Mouser et al., 2018). Concerns regarding potentially dangerous spikes in blood pressure triggered by the exercise pressor reflex have also been raised (Spranger et al., 2015). Resistance exercise combined with BFR has been shown to induce robust metabolic alterations in terms of accumulation of several metabolic by-products, such as lactate, inorganic phosphate, dihydrogen phosphate, and hydrogen ions (Suga et al., 2009, 2010). Due to the occlusion of venous return to the central circulation, metabolites are trapped and accumulate locally in the active musculature. Thus, there is some concern regarding the possibility of the elevated exercise-induced metabolic response generating exaggerated increases in blood pressure *via* the exercise pressor reflex (Spranger et al., 2015). However, there is currently no data demonstrating that low-load resistance exercise with BFR elicits such rapid and exaggerated increases in blood pressure. In fact, Pinto et al. (2018) investigated the cardiovascular and metabolic response of hypertensive women to low-load BFR versus traditional high-load resistance exercise and demonstrated that BFR resistance exercise induced neither an exaggerated nor greater cardiovascular or metabolic response compared to traditional resistance exercise. Additionally, studies by Kambič et al. (2019, 2021) have reported that BFR training is safe and is associated with significant improvements in muscle strength and improved muscle function in patients with coronary artery disease (CAD) and that 8 weeks of BFR resistance training can significantly lower systolic and lower diastolic blood pressure with no changes in N-terminal prohormone B-type natriuretic hormone, fibrinogen, and D-dimer values in patients with CAD. Large artery compliance increased the same amount and small artery compliance less than observed with high-load exercise without restriction (Fahs et al., 2012), but another study reported that small arteries stay stiff for a longer period of time following acute vibration exercises in combination with blood flow restriction (Karabulut et al., 2018). With respect to the possible development of a thrombosis (as indicated by an increase in D-dimer) with BFR exercise, no reports have been found in the existing literature (Fry et al., 2010). Also, C-reactive protein, which is linked to clot formation, has also shown to be stable following BFR exercise (Nakajima et al., 2010).

Other potential concerns associated with BFR exercise have included increases in metabolic activity and possible muscle damage. Current findings indicate that BFR exercise does not increase oxidative stress or antioxidant defense (Goldfarb et al., 2008; Petrick et al., 2019). Regarding muscle damage, most studies indicate that BFR exercise does not seem to result in significant muscle damage (Loenneke and Abe, 2012; Karabulut et al., 2013; Thiebaud et al., 2013; Alvarez et al., 2019), probably due to the fact that the low training loads commonly used (i.e., 20 to 50% of 1RM) are not high enough to induce substantial mechanical stress. However, the possibility of muscle damage and even rhabdomyolysis episodes in response to BFR exercise have not been completely been ruled and are still debated in the literature (Loenneke et al., 2014b; Burr et al., 2020; Wernbom et al., 2020). It should be noted that even though serious injuries are not common in the studies that use lab-based BFR units, which can set and control the pressure used during training, the use of elastic bands or wraps that cannot determine, set, or control the pressure can be problematic. Therefore, improper use of field-based, lab-based, or any other BFR techniques that cannot determine the pressure being used may result in serious health issues and can be unsafe if total occlusion occurs.

POTENTIAL MECHANISMS

Although the long-term benefits of BFR exercise, including increased muscular size, strength, muscular endurance, muscular power, and enhanced aerobic capacity, have been extensively reported in the scientific literature (Laurentino et al., 2012; Bjørnsen et al., 2019; Wilk et al., 2020), the underlying mechanisms responsible for these adaptations generally remain speculative. One of the most often referenced occurrence that is thought to be linked to the positive adaptations of BFR exercise is the exercise-induced metabolic stress (Suga et al., 2010; Takada et al., 2012). Although BFR exercise is commonly performed at low loads (20–50% of maximal strength), most studies report a pronounced metabolic response as confirmed by the accumulation of metabolic by-products, such as lactate, di-protonated phosphate, deoxygenated hemoglobin, inorganic phosphate, and hydrogen ions and often at similar levels as those caused by traditional high-load resistance exercise in many studies (Suga et al., 2009, 2012; Yasuda et al., 2010a; Karabulut et al., 2014).

This enhanced metabolic response to BFR exercise is important for several reasons. First, the accumulation of metabolic by-products thought to be associated with the activation of groups III and IV afferent nerve fibers that inhibit the α-motoneurons that innervate slow-twitch motor units, thus requiring the early recruitment of the fast-twitch motor units which are more responsive to hypertrophic adaptations. Additionally, the BFR exercise-induced metabolic response is also linked to the acute release of anabolic hormones like growth hormone (GH) which could then result in an increase in insulin-like growth factor-1 (IGF-1) and ultimately an increase in vascular endothelium growth factor to stimulate vasculogenesis to accommodate the need for a greater blood supply to the increases in muscle mass. In fact, Takarada et al. (2000a) reported an increase in blood lactate levels following a single bout of BFR exercise coupled to an approximately 290 times increase in GH compared to baseline levels.

The central chemoreceptors, located within the ventrolateral medulla, respond to alterations in [H+] and indirectly to CO_2 and peripheral chemoreceptors, located within the carotid and aortic bodies, respond to changes in PaO_2, $PaCO_2$, and pH of the arterial blood. In addition, since baroreceptors sense the changes in blood pressure (Farell et al., 2011), variation in cuff pressure may affect the level of venous return. Therefore, it can be speculated that stimulation of the central and peripheral chemoreceptors by the accumulated metabolites after deflating the BFR cuffs and the reduced end diastolic volume (preload) due to the BFR cuffs-related reduced venous return may be responsible for the changes in several physiological systems and training-related adaptations.

A third potential underlying mechanism to explain the positive adaptations associated with BFR exercise is the muscle swelling that results from the induced exercise demands (Loenneke et al., 2012a). Takarada et al. (2000b) applied a BFR stimulus, without exercise, to patients following anterior cruciate ligament surgery. Each session consisted of 5 sets of BFR application, at pressures between 200 and 260 mmHg, separated by 3-min rest intervals, for 10 days following surgery. They reported a diminished disuse atrophy of the knee extensor muscles compared to a control group (9.4% vs. 20.7%, respectively). Since BFR was applied in the absence of exercise, the contributions of a localized metabolic response or increased muscle activity were unlikely contributors to the adaptations observed (Loenneke et al., 2012c) leading to the speculation that activation of localized chemoreceptors or exercise-induced muscle swelling, commonly observed following BFR exercise, may play a role in the exercise hypertrophic response by shifting the protein balance toward anabolism. This is still speculative since a recent study demonstrated that the application of BFR in the absence of exercise did not increase myofibrillar protein synthesis, except when combined with exercise (Nyakayiru et al., 2019).

A fourth potential mechanism to explain the adaptations associated with BFR exercise is an increased protein synthesis by altering biomolecular pathways, including the mammalian target of rapamycin complex 1 (mTORC1) and the inhibition of atrogenes like Muscle RING Finger1 (MuRF1) and atrogin-1 and the inhibition of the myostatin (MSTN) pathway. Fry et al. (2010) reported that a single bout of BFR exercise at 20% of 1-RM increased muscle protein synthesis by 56% in comparison with pre-exercise levels as well as increasing the phosphorylation of the mTORC1 downstream target ribosomal S6 kinase 1 (S6K1). BFR exercise has also been shown to influence the MSTN pathway, which is a down regulator of muscle growth. In this context, Laurentino et al. (2012) demonstrated that 8 weeks of BFR resistance training resulted in similar muscular size and strength gains similar to traditional high-load resistance training with concomitant decrease in MSTN gene expression.

TYPES OF RESTRICTIVE DEVICES (LAB- AND FIELD-BASED)

The blood flow restriction devices commonly used are basically divided into two major groups: traditional (laboratory-based) and practical (field-based). Traditional laboratory-based BFR devices include the original KAATSU-Master and -Mini (Sato Sports Plaza, Tokyo, Japan), the Delfi Personalized Tourniquet System (Delfi Medical Innovations System, Vancouver, BC, CAN), and the Hokanson rapid cuff inflation system (Hokanson, Inc., Bellevue, WA, United States), with additional models being designed and released as BFR exercise training gains in popularity. KAATSU, Delfi, and Hokanson systems are electronically controlled units. The KAATSU, Hokanson, and Delfi units use standardized cuffs of varying widths and lengths which are physically attached to the devices with cords and provide the capability of precisely controlling the amount of pressure applied to each limb during exercise (McEwen et al., 2019). However, disparities in features between the units results in differences in how the restrictive pressures are set [based on limb occlusion pressure (LOP)]. A study by Weatherholt et al. (2019) compared the Delfi and KAATSU devices to investigate the effects of cuff width on LOP and reported significant differences between units for LOP (Delfi: 239.4 mmHg vs. KAATSU: 500 mmHg). Although these devices are precise and relatively easy to use, they are quite expensive, and somewhat confined to laboratory or clinical settings, making it difficult to perform BFR exercise in more practical settings, such as gyms.

The inability to use traditional BFR in applied settings, like gyms and practice facilities, has stimulated the development of more practical approaches to traditional BFR exercise. Practical BFR exercise consists of using elastic bands or wraps placed around the exercising limbs and not connected to any external pressure controlling device. These techniques are much more affordable and widely available for sale online and require little to no training but have the potential to be over-tightened by those not familiar with the theory of BFR exercise. Since this type of training does not allow for precise control of the pressure that is being applied during exercise, care should be used to ensure that the total occlusion of blood flow does not occur. Wilson et al. (2013) proposed using a perceived tightness scale in an attempt to prescribe the restrictive pressure, although the reliability of this method has been questioned (Bell et al., 2020). Recently, a more practical approach called "capillary refill time (CRT)" has also been used to set and adjust the restriction pressures. CRT is a measure of the time that takes for the capillary bed to regain its color after pressure has been applied. CRT is used in clinical settings to evaluate different populations such as children (Fleming et al., 2016) and the elderly (Schriger and Baraff, 1988) with various health problems like circulatory failure, hemorrhagic fever, and peripheral perfusion (Silverstein and Hopper, 2015; Gallier, 2020). If CRT takes more than a few seconds depending on the population and where it was measured (finger, hand, foot, leg, etc.), it is considered as a health problem or a sign of poor perfusion (Fleming et al., 2015; Silverstein and Hopper, 2015). During BFR exercise training, the CRT is determined by pressing the thumb into the quadriceps muscle immediately above the knee (for the leg pressure cuff) or into the palm of the hands (for the arm pressure cuff) and releasing to see how quickly (in seconds) the blanched (white) area returns to normal color. The pressure that allows the normal color to be regained within 2 to 3 s is then used as the final/target pressure (Amano et al., 2016). However, it should be noted that a study reported that CRT was dependent on patient and environmental factors (Anderson et al., 2008), therefore, even though CRT has been used in clinical settings, using CRT for the purpose of BFR training is new and may need additional research to provide more details regarding this technique.

THE EVOLUTION OF DETERMINING RESTRICTIVE PRESSURES AND EXERCISE PROTOCOLS

The BFR technique originated in Japan by Yoshiaki Sato around the year 1960. The process began with self-experimentation, with Sato using the technique to rehabilitate from a fracture on his leg BFR exercise then gained public notoriety and made its way into research (Sato, 2005). The original research that used the KAATSU-Master device based restrictive pressures on a person's upper body SBP (Wernbom et al., 2006) or simply used arbitrary occlusive pressures around 200 mmHg (Takarada et al., 2000a). For arm BFR exercise, pressures that corresponded to 120% of upper body SBP were used (Arm SBP × 1.2). For leg BFR exercise, an additional 20% restriction was added to the 120% of upper body SBP cuff pressure (Arm SBP × 1.44; Sato et al., 2005; Takano et al., 2005). This essentially resulted in a constant, uniform restriction pressure for all individuals who had similar SBPs, regardless of age, condition, limb size, or limb composition. This approach is similar to suggesting that all individuals should exercise with the same weight or run at the same pace, regardless of an individual's specific characteristics. The use of arbitrary fixed pressures is also currently contraindicated as these may correspond to pressures above the persons' total occlusive pressure, thus increasing the risks of nerve and ischemic injuries (McEwen et al., 2019).

More recently, the basic concept of "individualization" has been used to set the restrictive pressures during traditional BFR exercise to various percentages of the total arterial occlusion pressure for an exercising limb as measured *via* Doppler ultrasound or predicted using standardized equations developed using biometrical measures, such as limb circumference (Laurentino et al., 2018). These pressures are usually in the range of 40 to 60% of the total occlusion pressure for the limb. Additionally, similar long-term neuromuscular adaptations have been reported with restrictive pressures ranging from 40 to 90% of total occlusion (Counts et al., 2016). As a safety concern, prior to formal inclusion into any BFR exercise study, the individual's ankle-brachial index should be assessed to screen for peripheral artery disease and exclusion as a potential subject.

It should be noted that setting the restrictive pressure at 50% of the total occlusion pressure to a given limb does not mean that blood flow to the exercising limb has been reduced to exactly 50% of its normal flow at baseline. Mouser et al. (2017) assessed brachial blood flow in the arms of 45 men and women between the ages of 18 and 40 years, using color flow mode and Doppler velocity waveforms at 10% of total occlusion pressure, 20% total occlusion pressure, and up to 90% total occlusion pressure, increasing each measurement by 10% intervals. Results indicated that blood flow decreased in a nonlinear, stepped fashion but was fairly constant between 40% of total occlusion and 80% of total occlusion. At 40% of total occlusion pressure, flow was about 55% of normal flow, whereas at 80% of total occlusion pressure, flow was at 49.3% of normal flow. This would indicate that there is no added advantage of increasing the restrictive pressure from 40% of total occlusion pressure any higher if blood flow remains essentially the same. This has resulted in most protocols now using 50% of total occlusion pressure as a standard BFR exercise pressure for most study designs.

The inability to set the restrictive pressures based on some standard assessment represents a significant limitation of using an elastic band or some other technique in a field setting since there is no way to reliably replicate conditions from day to day or from person to person and may result in over inflation and a possible increased risk of injury or muscle damage. One method proposed to determine the restrictive pressure that could be used during practical BFR exercise was proposed by Wilson et al. (2013) and consisted of using a perceived pain pressure scale that ranged from 0 to 10. The authors suggested that the elastic band would be tightened around the person's limb until it resulted in a moderate pressure without causing pain. In this same study, the authors demonstrated that practical BFR exercise resulted in the elevations of muscle swelling and increased myoelectric activity, both considered indicators of muscle hypertrophy. Although Wilson's method seemed to work as an effective approach to individualize the restrictive pressure across different individuals, it was not as precise as the method classically performed during traditional BFR exercise that utilizes Doppler ultrasound. Additionally, the reliability and reproducibility of Wilson's scale have been recently questioned (Bell et al., 2020). Current studies are now trying to individualize the pressures to be used during practical BFR exercise based on the person's limb circumference, the length of the elastic band, and CRTs.

For both traditional and practical BFR exercise, a typical protocol commonly consists of 4 sets of 30–15–15–15 repetitions (Wilson et al., 2013; Vechin et al., 2015). However, it should be noted that repetitions performed to failure have also been shown to be effective for inducing some neuromuscular adaptations (Sieljacks et al., 2018; Jessee et al., 2019). This approach highlights additional advantages of low-load BFR exercise over high-load resistance exercise, since there are lower mechanical stresses to the joints because of the lower loads (20% 1RM versus 70% 1RM or greater) and overall lower volume of exercise (load × total repetitions).

In terms of exercise intensity, most BFR exercise protocols include training loads between 20 and 50% 1-RM (Nakajima et al., 2010; Yasuda et al., 2010b), whereas loads higher than 50% 1-RM do not seen to provide any additional advantages (Laurentino et al., 2008). These lower loads used during BFR exercise help to lower or avoid muscle damage and soreness. Therefore, it shortens the time to recover from a single bout of exercise, potentially allowing for an increased training frequency.

The length of the rest interval between sets usually varies from 30 s to 2 min, with 1 min and 1:30 min being the most common rest periods. Two to 5 min of rest have also been used between exercises for protocols that include more than 1 exercise. Traditionally, the cuffs or the elastic wraps remain inflated or tightened during the entire exercise period; in other words, the cuffs or bands are positioned immediately before the first set and removed following completion of the last set of exercise. However, due to the discomfort that BFR exercise induces, new studies have started to investigate the physiological effects of intermittent BFR exercise, in which the cuffs are deflated during the rest intervals between sets. Conflicting results have been reported so far with studies demonstrating that intermittent BFR exercise does not seem to diminish the exercise-induced physiological response (Freitas et al., 2020) while others show otherwise (Suga et al., 2010).

Regarding the muscle groups of interest, due to its the nature, BFR should be applied only to the most proximal portions of the arms and legs. For instance, even if one desires to train the calf muscles using the BFR method, the cuffs or elastic bands should still be applied to the most proximal portion of the leg and not below the knee. Finally, although the application of BFR is limited to arms and legs, previous studies have demonstrated that core muscles may also benefit indirectly from BFR exercise. For instance, Yasuda et al. (2010b) had young males complete 2 weeks of twice a day bench press at 30% of 1-RM with BFR applied to the most proximal portion of both arms and observed a 6% increase bench press 1-RM strength, and 8 and 16% increases in triceps and pectoralis major muscle thicknesses, whereas no significant changes were observed for the control group following training.

AEROBIC EXERCISES WITH BLOOD FLOW RESTRICTION

The basic modes of exercise are either aerobic or anaerobic in nature. Aerobic exercises commonly used in combination with blood flow restriction usually include specific exercises like walking or cycling. The difficulty in setting the workload for aerobically based BFR exercises is the fact that exercise intensity is often based on some percentage of maximal heart rate (Ozaki et al., 2011a). Since blood flow restriction causes a reduction in venous return and a resultant lowering of stroke volume, the ability to maintain cardiac output during exercise is then accomplished by an increased heart rate which may not be the same cardiovascular response that would be expected based on heart rate alone if blood flow restriction was not being used (Renzi et al., 2010). Therefore, perhaps another way to set acute workloads for BFR protocols could be based on perceived exertion to the exercise intensity rather than heart rate.

Traditional aerobic exercise is well known for improving oxygen consumption and consequently endurance performance, without significantly increasing muscle hypertrophy or strength. However, studies investigating the long-term effects of aerobic exercise with BFR have demonstrated that this technique is, surprisingly, effective at enhancing neuromuscular parameters in old and young individuals.

One of the first studies investigating the long-term effects of aerobic exercise with BFR was conducted by Abe et al. (2006), who demonstrated that a walking protocol combined with BFR (160–230 mmHg) twice a day over the course of 3 weeks was effective at increasing muscle cross-sectional area and volume by approximately 6% each in young adults. Such increases in muscle size parameters were also accompanied by increases in maximum dynamic (i.e., 1-RM) and isometric strength. In a follow-up study from the same research group using a similar protocol, the authors were able to replicate the study results, but in this case in a cohort of older individuals aged 60 to 78 years, in addition to improvements in functional parameters also being observed. In another study, Ozaki et al. (2011b) had elderly women (53–73 years) complete 10 weeks of walking combined with BFR, consisting of 20-min sessions performed 4 times a week, with 140 mmHg to 200 mmHg of BFR. After training, the authors reported significant increases in muscle cross-sectional area (~3%) and volume (2.7–3.7%) in the thigh region, as well as in isokinetic strength (~8–22%), and in functional performance measured in the timed up and go test (−10.7%), with concomitant improvements in aerobic capacity (~9%). Furthermore, these adaptations observed with aerobic exercise with BFR are not limited to walking with BFR. Abe et al. (2010a) observed significant increases in skeletal muscle size and volume in the lower body and oxygen uptake following 8 weeks of cycling with BFR, although improvements in muscular strength did not reach statistical significance.

Such findings of walking in combination with BFR eliciting increases in skeletal muscle size and strength are surprising, as traditional aerobic exercise without BFR is well known for improving aerobic capacity but not skeletal muscle size or strength. Some of these increases have been reported to happen as early as after 4 consecutive training days (Abe et al., 2006). Therefore, the findings from the aforementioned studies and others have great implications for individuals unwilling or unable to perform high-intensity resistance exercise and that are seeking to improve neuromuscular parameters, as such training modality may serve as a potential training alternative to resistance training. This is particularly true for those suffering from severe sarcopenia and strength loss, such as frail older individuals and several clinical populations.

Although the findings related to aerobic exercise with BFR present significant clinical relevance, much is yet to be clarified regarding its underlying mechanisms conducing to muscle hypertrophy. The acute release of anabolic hormones has been proposed as one of the potential mechanisms, as Abe et al. (2006) detected significant increases in growth hormone immediately post- and up to 15 min post-exercise, while cortisol levels remained unchanged. On the other hand, Ozaki et al. (2017) observed increases in GH in both BFR and control groups, whereas muscle hypertrophy had previously been observed only in the BFR walk group (Ozaki et al., 2011b). Additionally, there is an intense debate on the contributions of anabolic hormones to the exercise-induced hypertrophic response (Schroeder et al., 2013). It has also been speculated that a potential exercise-induced metabolic response during aerobic exercise with BFR could facilitate the recruitment of the more prone to hypertrophy type II muscle fibers. However, the metabolic response to walking with BFR is either minimal or non-existent according to Loenneke et al. (2012d), although a more pronounced increase was observed by Ozaki et al. (2014). Another suggested mechanism through each aerobic exercise with BFR elicits its positive neuromuscular adaptations is the exercise-induced muscle swelling. The muscle swelling response has long been thought to be one of the mechanisms leading to muscle hypertrophy in the context of resistance exercise with BFR (Loenneke et al., 2012c). Although little is known regarding the effects of aerobic exercise with BFR on muscle swelling, specially concerning walking, Ogawa et al. (2012) reported significant percent change increases in muscle thickness immediately post a single bout of walking with BFR. Lastly, the modulation of biomolecular pathways governing muscle protein turnover, such as Akt/mTOR and myostatin, has also been speculated to contribute to the reported responses to aerobic exercise with BFR. Ozaki et al. (2014) reported significant increases in phosphorylation of Erk1/2 and p38 following a walking protocol with BFR; however, it should be highlighted that increases in p38 were also observed in the non-BFR walking condition; additionally, eEF2 phosphorylation was lower for BFR walking compared to non-BFR walking, no significant changes were observed in Akt and mTOR phosphorylation levels, as well as no differences between conditions for changes in SK1 phosphorylation, and eEF2 phosphorylation was lower for the BFR condition. Nonetheless, these results should be interpreted with caution due to the limited samples size (i.e., 6 participants) and limitations of the study design. Therefore, additional studies are critically needed to further elucidate the mechanism through which aerobic exercise combined with BFR induces muscle hypertrophy.

ANAEROBIC EXERCISES WITH BLOOD FLOW RESTRICTION

For anaerobic-based modalities, that is, resistance exercises, intensities most often will be based on relative loads (percent of maximal strength, % 1RM) rather than absolute loads (Giles et al., 2017). It should be noted that several modes of contraction exist to assess performances to resistance exercise which include isometric contractions (no visible movement of the limb during muscular contraction), isotonic contractions (constant force being generated throughout the entire range of motion as controlled devices like Cybex or KinCom), isokinetic contractions (constant velocity of movement throughout the entire range of motion as controlled by devices like Cybex or KinCom), or dynamic contractions with the use of free weights. In many studies, relative loads of 20 to 30% 1RM with blood flow restriction have been compared to traditional high-intensity (80% 1RM; Laurentino et al., 2008, 2012; Karabulut et al., 2010) resistance training without blood flow restriction but blood flow restriction exercise loads have ranged from 20 to 50% 1RM.

As mentioned above, the original protocols designed for the KAATSU-Master and BFR resistance exercise used loads of 20 to 30% 1RM with 4 sets of exercises composed of 1 set of 30 repetitions followed by 3 sets of 15 repetitions with 1-min rest periods between sets and at a cadence of 1.5 s in both the eccentric and concentric portions of the movement (Freitas et al., 2017; Miller et al., 2018). When multiple exercises are used (usually 2 or 3 total exercises for a given session, like 2 leg press, followed knee extension, and knee flexion), then rest periods between exercises are usually between 3 and 5 min. Normally, the restrictive pressures would be maintained throughout the entire session but recent studies indicate that releasing the pressure in the cuffs between different muscle groups does not seem to diminish the effects of the exercise protocol and are as effective as the continuous restriction protocols (Beaven et al., 2012; Yasuda et al., 2013). Many of the early studies used a single, acute bout of the exercise to explore various physiological responses and then imply that the lower intensity protocols used with blood flow restriction (20–30% 1RM) were as effective as high-intensity (80% 1RM) resistance exercise for gaining strength and promoting muscle hypertrophy. Training protocols using blood flow restriction are fairly limited and usually short in duration, normally lasting between 4 and 8 weeks (Clark et al., 2011; Cook et al., 2014; Conceição et al., 2018; Held et al., 2020; Karabulut et al., 2020; Zhao et al., 2020). Most often, training protocols use 3 training sessions per week with each session separated by 48 h (Clark et al., 2011; Held et al., 2020) but some designs use daily bouts of exercise (5 times per week) and some even use 2 bouts per day for 8 to 10 consecutive days (Iida et al., 2006).

LIMITATIONS FROM PREVIOUS STUDIES AND CURRENT GAPS IN THE RESEARCH LITERATURE

The ability to accurately interpret results from a published paper is often dependent on the clarity of the research design, participant and protocol descriptions, and the clear description of the statistics used to analyze the data. As with most research designs, there are an infinite number of combinations of potentially confounding issues related to participant selection for the protocol, like age, sex, training status, health status, nutritional status, hormonal status, etc., but with blood flow restriction protocols, many other factors must also be considered. These additional factors could include the type of cuff used to induce the restriction pressure (width of the cuff, type of material, pneumatically controlled cuffs or tension wraps or bandages applied based on perceived discomfort; Loenneke et al., 2014c; Buckner et al., 2017; Stray-Gundersen et al., 2020), initial pressure/tightness of the cuffs before inflation (Karabulut et al., 2011a, 2014), the restrictive pressure used (absolute, relative, percent of total restrictive pressure, intermittent pressure, continuous pressure; Murray et al., 2020), the composition (fat and muscle mass; Karabulut et al., 2014) and size (circumference or girth) of the limb being restricted

(Loenneke et al., 2014a), the mode of exercise (walking, cycling, resistance training, absolute loads, relative loads, contraction types – isometric, isotonic, isokinetic), the protocols used if exercise is required (number of repetitions, number of sets, muscle groups, cadence of the concentric and eccentric portions of the movement, time under tension), and if the responses are acute or due to prolonged training (how many sessions, days, weeks, etc.).

Over the past 20 years, most blood flow restriction studies have used male subjects, often college-aged males (18–25 years of age) because of convenience; however, a few studies have also included college-aged females but then failed to separate the sexes when analyzing the data. Only recently, a few studies have focused solely on female participants (Loenneke et al., 2014a). The importance of separating the responses based on sex is grounded in the differences in hormonal status between men and women (testosterone levels, estrogen levels, phase of the menstrual cycle, etc.). As mentioned earlier, many studies have used a college-aged population (Abe et al., 2010a), but some studies have also investigated middle-aged (35–55 years of age) and older subjects (over age 65 years; Abe et al., 2010b; Ozaki et al., 2011a,b), but these studies are much fewer in number.

The training status of participants has not always been reported in many BFR exercise studies, making the interpretation of the results difficult since the more sedentary or deconditioned the subject, the greater the magnitude of change that might be expected. Obviously, health status will also affect the outcome measures of any study, with normal healthy individuals responding very differently than those that have a compromised health status or those having a clinically diagnosed condition like hypertension, diabetes, multiple sclerosis, osteoarthritis, etc. It is also important to examine the nutritional status of participants in research studies since certain supplements (creatine, protein, etc.) or diets deficient in some nutrients (protein, vitamins, etc.) could also affect outcome variables that are being assessed following BFR protocols, like muscle growth or hypertrophy and improvements in muscle strength.

When examining cuff type, factors like cuff width, the material of the cuff, and whether the restriction pressure is carefully set and controlled with a pneumatic device in a laboratory setting or if the pressure is not known because a practical elastic wrap has been used in a community-based setting, also needs to be considered and reported in the literature. The importance of reporting cuff width is critical since the amount of occlusion increases as the cuff width increases at similar restrictive pressures (Loenneke et al., 2012b) resulting in increased brachial and central blood pressures, heart rates, perceived efforts, and perceived pain. The original KAATSU-Master uses an elastic 3 cm wide cuff for the arms and a 5 cm cuff for the legs, while the Hokanson pneumatic device uses a nylon 3.5 cm cuff for the arms and a 13.5 cm nylon cuff for the legs. In general, cuff widths have ranged from 2 cm for the arms to over 20 cm for the legs.

The material of the cuff is also important to report. In general, the differences between elastic and nylon cuffs are minimal with both types resulting in similar numbers of repetitions to fatigue and similar ratings of perceived exertion and discomfort; however, some reports indicate that the arterial occlusion pressures were significantly greater when using the elastic cuff when compared to the nylon cuff. The major issue with elastic wraps (i.e., tensor bandages) used in a community setting is the issue that there is no way to monitor or assess the exact level of occlusion that is occurring since the tightness of the wraps will determine the amount of restriction, so unless a person is very experienced with the technique of blood flow restriction exercise and is very aware of the sensation that should be felt with appropriate restriction, it is generally recommended that the use of elastic wraps should not be used in gym settings because of the tendency to over restrict blood flow or to inadvertently totally occlude blood flow altogether.

The original research that used the KAATSU-Master device used a restrictive pressure of 120% of upper body SBP (Arm SBP × 1.2) for the arms (normally around 140–160 mmHg) and then added an additional 20% to the 120% of upper body SBP cuff pressure (Arm SBP × 1.44) to account for differences in lower body SBP for the legs (usually around 180–240 mmHg). This original research also maintained the constant restrictive pressure for the entire exercise session across all repetitions, sets, and muscle groups, and the pressures were the same for all participants regardless of the size of the limbs that were being exercised. More recent studies have explored the ability to release the restrictive pressure in the cuffs between different muscle groups (after 2 leg press and before knee extensions for example) and have reported similar results to protocols that use pressures that are continuously applied throughout the session (Burgomaster et al., 2003). Also, based on the concept of individualization, researchers have now been determining the pressures needed to totally occlude the legs individually or the arms individually, and then using some relative percentage of the total occlusion pressure for the exercise session (Laurentino et al., 2008). These relative pressures have been around 50% of the pressure needed for total occlusion with the idea that this would result in 50% of the blood flow to the exercising limb would also be restricted; however, studies have indicated that blood flow to the restricted limb (about 50% of normal flow without restriction) is similar for restrictive pressures between 40 and 90% of total occlusion pressure for a given limb when utilizing techniques that can actually measure blood flow, like Doppler ultrasound (Counts et al., 2016).

The concept that limb composition might have an effect of the amount of blood flow restriction that a limb might experience depending on the pressure being used is based on the ability to compress the different tissues of the limb (fat versus muscle). It is logical to think that limbs containing more fat might need more pressure to achieve the desired restriction to blood flow since it was thought that fat would compress and absorb most the pressure without compressing the vasculature that would be closer to the muscle. One study (Karabulut et al., 2011a) reported that thigh composition and size had a significant impact on the effects of initial restrictive pressure. Other studies have investigated the amounts of fat and muscle mass in the limb being restricted and have reported that the circumference of the limb is more predictive of restrictive pressure as compared to the composition of the limb with larger limbs needing greater pressures to achieve a given level of blood flow restriction (Loenneke et al., 2014a).

CONCLUSION

Blood flow restriction exercise remains a relatively safe training strategy for those unable or unwilling to perform high-intensity resistance exercise or endurance exercise, yet wanting to improve neuromuscular parameters, such as muscular strength, power, and function, and improve aerobic endurance. However, considering the complexity of the technique, questions still need to be answered regarding the precise underlying mechanisms responsible for the adaptations to BFR exercise, as well as practical concerns, such as determining the most appropriate restrictive pressures to be applied, the type of restrictive devices to be used, potential risks for clinical populations – especially concerning the cardiovascular system and adequate lengths of time for training and the volumes of low-intensity exercise that need to be performed.

AUTHOR CONTRIBUTIONS

All authors contributed equally to writing and proofreading the manuscript, and also approved the content of the manuscript's final version.

REFERENCES

Abe, T., Fujita, S., Nakajima, T., Sakamaki, M., Ozaki, H., Oga-, R., et al. (2010a). Effects of low-intensity cycle training with restricted leg blood flow on thigh muscle volume and VO 2max in young men. *J. Sports Sci. Med.* 9, 452–458.

Abe, T., Kearns, C. F., and Sato, Y. (2006). Muscle size and strength are increased following walk training with restricted venous blood flow from the leg muscle, Kaatsu-walk training. *J. Appl. Physiol.* 100, 1460–1466. doi: 10.1152/japplphysiol.01267.2005

Abe, T., Sakamaki, M., Fujita, S., Ozaki, H., Sugaya, M., Sato, Y., et al. (2010b). Effects of low-intensity walk training with restricted leg blood flow on muscle strength and aerobic capacity in older adults. *J. Geriatr. Phys. Ther.* 33, 34–40. doi: 10.1152/japplphysiol.01267.2005

Alvarez, I. F., Damas, F., de Biazon, T. M. P., Miquelini, M., Doma, K., and Libardi, C. A. (2019). Muscle damage responses to resistance exercise performed with high-load versus low-load associated with partial blood flow restriction in young women. *Eur. J. Sport Sci.* 20, 125–134. doi: 10.1080/17461391.2019.1614680

Amani-Shalamzari, S., Rajabi, S., Rajabi, H., Gahreman, D. E., Paton, C., Bayati, M., et al. (2019). Effects of blood flow restriction and exercise intensity on aerobic, anaerobic, and muscle strength adaptations in physically active collegiate women. *Front. Physiol.* 10:810. doi: 10.3389/fphys.2019.00810

Amano, S., Ludin, A. F. M., Clift, R., Nakazawa, M., Law, T. D., Rush, L. J., et al. (2016). Effectiveness of blood flow restricted exercise compared with standard exercise in patients with recurrent low back pain: study protocol for a randomized controlled trial. *Trials* 17:81. doi: 10.1186/s13063-016-1214-7

Anderson, B., Kelly, A.-M., Kerr, D., Clooney, M., and Jolley, D. (2008). Impact of patient and environmental factors on capillary refill time in adults. *Am. J. Emerg. Med.* 26, 62–65. doi: 10.1016/j.ajem.2007.06.026

Beaven, C. M., Cook, C. J., Kilduff, L., Drawer, S., and Gill, N. (2012). Intermittent lower-limb occlusion enhances recovery after strenuous exercise. *Appl. Physiol. Nutr. Metab.* 37, 1132–1139. doi: 10.1139/h2012-101

Bell, Z. W., Dankel, S. J., Spitz, R. W., Chatakondi, R. N., Abe, T., and Loenneke, J. P. (2020). The perceived tightness scale does not provide reliable estimates of blood flow restriction pressure. *J. Sport Rehabil.* 29, 516–518. doi: 10.1123/jsr.2018-0439

Bjørnsen, T., Wernbom, M., Løvstad, A., Paulsen, G., D'Souza, R. F., Cameron-Smith, D., et al. (2019). Delayed myonuclear addition, myofiber hypertrophy, and increases in strength with high-frequency low-load blood flow restricted training to volitional failure. *J. Appl. Physiol.* 126, 578–592. doi: 10.1152/japplphysiol.00397.2018

Brandner, C. R., Kidgell, D. J., and Warmington, S. A. (2014). Unilateral bicep curl hemodynamics: low-pressure continuous vs high-pressure intermittent blood flow restriction. *Scand. J. Med. Sci. Sports* 25, 770–777. doi: 10.1111/sms.12297

Buckner, S. L., Dankel, S. J., Counts, B. R., Jessee, M. B., Mouser, J. G., Mattocks, K. T., et al. (2017). Influence of cuff material on blood flow restriction stimulus in the upper body. *J. Physiol. Sci.* 67, 207–215. doi: 10.1007/s12576-016-0457-0

Burgomaster, K. A., Moore, D. R., Schofield, L. M., Phillips, S. M., Sale, D. G., and Gibala, M. J. (2003). Resistance training with vascular occlusion: metabolic adaptations in human muscle. *Med. Sci. Sports Exerc.* 35, 1203–1208. doi: 10.1249/01.MSS.0000074458.71025.71

Burr, J. F., Hughes, L., Warmington, S., Scott, B. R., Owens, J., Abe, T., et al. (2020). Response: commentary: can blood flow restricted exercise cause muscle damage? Commentary on blood flow restriction exercise: considerations of methodology, application, and safety. *Front. Physiol.* 11:574633. doi: 10.3389/fphys.2020.574633

Clark, B. C., Manini, T. M., Hoffman, R. L., Williams, P. S., Guiler, M. K., Knutson, M. J., et al. (2011). Relative safety of 4 weeks of blood flow-restricted resistance exercise in young, healthy adults. *Scand. J. Med. Sci. Sports* 21, 653–662. doi: 10.1111/j.1600-0838.2010.01100.x

Conceição, M. S., Junior, E. M., Telles, G. D., Libardi, C. A., Castro, A., Andrade, A. L. L., et al. (2019). Augmented anabolic responses after 8-wk cycling with blood flow restriction. *Med. Sci. Sports Exerc.* 51, 84–93. doi: 10.1249/MSS. 0000000000001755

Cook, C. J., Kilduff, L. P., and Beaven, C. M. (2014). Improving strength and power in trained athletes with 3 weeks of occlusion training. *Int. J. Sports Physiol. Perform.* 9, 166–172. doi: 10.1123/ijspp.2013-0018

Counts, B. R., Dankel, S. J., Barnett, B. E., Kim, D., Mouser, J. G., Allen, K. M., et al. (2016). Influence of relative blood flow restriction pressure on muscle activation and muscle adaptation. *Muscle Nerve* 53, 438–445. doi: 10.1002/mus.24756

Counts, B. R., Rossow, L. M., Mattocks, K. T., Mouser, J. G., Jessee, M. B., Buckner, S. L., et al. (2018). Let's talk about sex: where are the young females in blood flow restriction research? *Clin. Physiol. Funct. Imaging* 38, 1–3. doi: 10.1111/cpf.12394

Fahs, C. A., Rossow, L. M., Loenneke, J. P., Thiebaud, R. S., Kim, D., Bemben, D. A., et al. (2012). Effect of different types of lower body resistance training on arterial compliance and calf blood flow. *Clin. Physiol. Funct. Imaging* 32, 45–51. doi: 10.1111/j.1475-097X.2011.01053.x

Farell, P. A., Joyner, M. J., and Caiozzo, V. J. (2011). *ACSM's advanced exercise physiology*. Wolters Kluwer Health Adis (ESP).

Fleming, S., Gill, P., Jones, C., Taylor, J. A., Van den Bruel, A., Heneghan, C., et al. (2015). The diagnostic value of capillary refill time for detecting serious illness in children: a systematic review and meta-analysis. *PLoS One* 10:e0138155. doi: 10.1371/journal.pone.0138155

Fleming, S., Gill, P. J., Van den Bruel, A., and Thompson, M. (2016). Capillary refill time in sick children: a clinical guide for general practice. *Br. J. Gen. Pract.* 66:587. doi: 10.3399/bjgp16X687925

Freitas, E. D. S., Bemben, M. G., Silva, A. S., Aniceto, R. R., Ferreira-Junior, J. B., and Cirilo-Sousa, M. S. (2017). Resistance exercise performed at different degrees of arterial occlusion pressure does not induce prolonged oxidative stress or muscle damage. *Int. J. Sports Exerc. Med.* 3, 1–9. doi: 10.23937/2469-5718/1510075

Freitas, E. D. S., Miller, R. M., Heishman, A. D., Ferreira-Júnior, J. B., Araújo, J. P., and Bemben, M. G. (2020). Acute physiological responses to resistance exercise with continuous versus intermittent blood flow restriction: a randomized controlled trial. *Front. Physiol.* 11:132. doi: 10.3389/fphys.2020.00132

Fry, C. S., Glynn, E. L., Drummond, M. J., Timmerman, K. L., Fujita, S., Abe, T., et al. (2010). Blood flow restriction exercise stimulates mTORC1 signaling and muscle protein synthesis in older men. *J. Appl. Physiol.* 108, 1199–1209. doi: 10.1152/japplphysiol.01266.2009

Fullana, J. M., Cros, F., Becker, F., Ouchene, A., and Partsch, H. (2005). The venous return simulator: an effective tool for investigating the effects of external compression on the venous hemodynamics–first results after thigh compression. *Vasa* 34, 19–23. doi: 10.1024/0301-1526.34.1.19

Gallier, J. (2020). How to measure capillary refill time in patient's who are acutely ill. *Nurs. Times* 116, 29–30.

Giles, L., Webster, K. E., McClelland, J., Cook, J. L., and Giles, I. L. (2017). Quadriceps strengthening with and without blood flow restriction in the treatment of patellofemoral pain: a double-blind randomised trial. *Br. J. Sports Med.* 51, 1688–1694. doi: 10.1136/bjsports-2016-096329

Goldfarb, A. H., Garten, R. S., Chee, P. D. M., Cho, C., Reeves, G. V., Hollander, D. B., et al. (2008). Resistance exercise effects on blood glutathione status and plasma protein carbonyls: influence of partial vascular occlusion. *Eur. J. Appl. Physiol.* 104, 813–819. doi: 10.1007/s00421-008-0836-1

Goto, K., Ishii, N., Kizuka, T., and Takamatsu, K. (2005). The impact of metabolic stress on hormonal responses and muscular adaptations. *Med. Sci. Sports Exerc.* 37, 955–963. doi: 10.1249/01.mss.0000170470.98084.39

Held, S., Behringer, M., and Donath, L. (2020). Low intensity rowing with blood flow restriction over 5 weeks increases VO2max in elite rowers: a randomized controlled trial. *J. Sci. Med. Sport* 23, 304–308. doi: 10.1016/j.jsams.2019.10.002

Iida, H., Kurano, M., Takano, H., Oonuma, H., Imuta, H., Kubota, N., et al. (2006). Can KAATSU be used for an orthostatic stress in astronauts?: a case study. *Int. J. KAATSU Train. Res.* 2, 45–52. doi: 10.3806/ijktr.2.45

Jessee, M. B., Buckner, S. L., Mattocks, K. T., Dankel, S. J., Mouser, J. G., Bell, Z. W., et al. (2019). Blood flow restriction augments the skeletal muscle response during very low-load resistance exercise to volitional failure. *Physiol. Int.* 106, 180–193. doi: 10.1556/2060.106.2019.15

Jørgensen, S. L., Bohn, M. B., Aagaard, P., and Mechlenburg, I. (2020). Efficacy of low-load blood flow restricted resistance EXercise in patients with knee osteoarthritis scheduled for total knee replacement (EXKnee): protocol for a multicentre randomised controlled trial. *BMJ Open* 10:e034376. doi: 10.1136/bmjopen-2019-034376

Kambič, T., Novaković, M., Tomažin, K., Strojnik, V., Božič-Mijovski, M., and Jug, B. (2021). Hemodynamic and hemostatic response to blood flow restriction resistance exercise in coronary artery disease. *J. Cardiovasc. Nurs.* 36, 507–516. doi: 10.1097/JCN.0000000000000699

Kambič, T., Novaković, M., Tomažin, K., Strojnik, V., and Jug, B. (2019). Blood flow restriction resistance exercise improves muscle strength and hemodynamics, but not vascular function in coronary artery disease patients: a pilot randomized controlled trial. *Front. Physiol.* 10:656. doi: 10.3389/fphys.2019.00656

Karabulut, M., Abe, T., Sato, Y., and Bemben, M. G. (2010). The effects of low-intensity resistance training with vascular restriction on leg muscle strength in older men. *Eur. J. Appl. Physiol.* 108, 147–155. doi: 10.1007/s00421-009-1204-5

Karabulut, M., Bemben, D. A., Sherk, V. D., Anderson, M. A., Abe, T., and Bemben, M. G. (2011a). Effects of high-intensity resistance training and low-intensity resistance training with vascular restriction on bone markers in older men. *Eur. J. Appl. Physiol.* 111, 1659–1667. doi: 10.1007/s00421-010-1796-9

Karabulut, U., Karabulut, M., and James, E. G. (2018). Small arteries stay stiff for a longer period following vibration exercises in combination with blood flow restriction. *Clin. Physiol. Funct. Imaging* 38, 1000–1007. doi: 10.1111/cpf.12516

Karabulut, M., Leal, J. A., Garcia, S. D., Cavazos, C., and Bemben, M. (2014). Tissue oxygenation, strength and lactate response to different blood flow restrictive pressures. *Clin. Physiol. Funct. Imaging* 34, 263–269. doi: 10.1111/cpf.12090

Karabulut, M., Lopez, J. A., and Karabulut, U. (2020). Aerobic training session length affects arterial elasticity. *Clin. Physiol. Funct. Imaging* 40, 14–20. doi: 10.1111/cpf.12596

Karabulut, M., McCarron, J., Abe, T., Sato, Y., and Bemben, M. (2011b). The effects of different initial restrictive pressures used to reduce blood flow and thigh composition on tissue oxygenation of the quadriceps. *J. Sports Sci.* 29, 951–958. doi: 10.1080/02640414.2011.572992

Karabulut, M., Sherk, V. D., Bemben, D. A., and Bemben, M. G. (2013). Inflammation marker, damage marker and anabolic hormone responses to resistance training with vascular restriction in older males. *Clin. Physiol. Funct. Imaging* 33, 393–399. doi: 10.1111/cpf.12044

Kilgas, M. A., Lytle, L. L. M., Drum, S. N., and Elmer, S. J. (2019). Exercise with blood flow restriction to improve quadriceps function long after ACL reconstruction. *Int. J. Sports Med.* 40, 650–656. doi: 10.1055/a-0961-1434

Korakakis, V., Whiteley, R., and Giakas, G. (2018). Low load resistance training with blood flow restriction decreases anterior knee pain more than resistance training alone. A pilot randomised controlled trial. *Phys. Ther. Sport* 34, 121–128. doi: 10.1016/j.ptsp.2018.09.007

Laurentino, G. C., Loenneke, J. P., Mouser, J. G., Buckner, S. L., Counts, B. R., Dankel, S. J., et al. (2018). Validity of the handheld Doppler to determine lower-limb blood flow restriction pressure for exercise protocols. *J. Strength Cond. Res.* 34, 2693–2696. doi: 10.1519/JSC.0000000000002665

Laurentino, G., Ugrinowitsch, C., Aihara, A. Y., Fernandes, A. R., Parcell, A. C., Ricard, M., et al. (2008). Effects of strength training and vascular occlusion. *Int. J. Sports Med.* 29, 664–667. doi: 10.1055/s-2007-989405

Laurentino, G. C., Ugrinowitsch, C., Roschel, H., Aoki, M. S., Soares, A. G., Neves, M., et al. (2012). Strength training with blood flow restriction diminishes myostatin gene expression. *Med. Sci. Sports Exerc.* 44, 406–412. doi: 10.1249/MSS.0b013e318233b4bc

Loenneke, J. P., and Abe, T. (2012). Does blood flow restricted exercise result in prolonged torque decrements and muscle damage? *Eur. J. Appl. Physiol.* 112, 3445–3449. doi: 10.1007/s00421-012-2312-1

Loenneke, J. P., Allen, K. M., Mouser, J. G., Thiebaud, R. S., Kim, D., Abe, T., et al. (2014a). Blood flow restriction in the upper and lower limbs is predicted by limb circumference and systolic blood pressure. *Eur. J. Appl. Physiol.* 115, 397–405. doi: 10.1007/s00421-014-3030-7

Loenneke, J. P., Fahs, C. A. A., Rossow, L. M. M., Abe, T., and Bemben, M. G. G. (2012a). The anabolic benefits of venous blood flow restriction training may be induced by muscle cell swelling. *Med. Hypotheses* 78, 151–154. doi: 10.1016/j.mehy.2011.10.014

Loenneke, J. P., Fahs, C. A., Rossow, L. M., Sherk, V. D., Thiebaud, R. S., Abe, T., et al. (2012b). Effects of cuff width on arterial occlusion: implications for blood flow restricted exercise. *Eur. J. Appl. Physiol.* 112, 2903–2912. doi: 10.1007/s00421-011-2266-8

Loenneke, J., Fahs, C., Thiebaud, R., Rossow, L., Abe, T., Ye, X., et al. (2012c). The acute muscle swelling effects of blood flow restriction. *Acta Physiol. Hung.* 99, 400–410. doi: 10.1556/APhysiol.99.2012.4.4

Loenneke, J. P., Kearney, M. L., Thrower, A. D., Collins, S., and Pujol, T. J. (2010). The acute response of practical occlusion in the knee extensors. *J. Strength Cond. Res.* 24, 2831–2834. doi: 10.1519/JSC.0b013e3181f0ac3a

Loenneke, J. P., Thiebaud, R. S., and Abe, T. (2014b). Does blood flow restriction result in skeletal muscle damage? A critical review of available evidence. *Scand. J. Med. Sci. Sports* 24, e415–e422. doi: 10.1111/sms.12210

Loenneke, J. P., Thiebaud, R. S., Fahs, C. A., Rossow, L. M., Abe, T., and Bemben, M. G. (2014c). Blood flow restriction: effects of cuff type on fatigue and perceptual responses to resistance exercise. *Acta Physiol. Hung.* 101, 158–166. doi: 10.1556/APhysiol.101.2014.2.4

Loenneke, J. P., Thrower, A. D., Balapur, A., Barnes, J. T., and Pujol, T. J. (2012d). Blood flow-restricted walking does not result in an accumulation of metabolites. *Clin. Physiol. Funct. Imaging* 32, 80–82. doi: 10.1111/j.1475-097X.2011.01059.x

McCully, K. K., Smith, S., Rajaei, S., Leigh, J. S., and Natelson, B. H. (2004). Muscle metabolism with blood flow restriction in chronic fatigue syndrome. *J. Appl. Physiol.* 96, 871–878. doi: 10.1152/japplphysiol.00141.2003

McEwen, J. A., Owens, J. G., and Jeyasurya, J. (2019). Why is it crucial to use personalized occlusion pressures in blood flow restriction (BFR) rehabilitation? *J. Med. Biol. Eng.* 39, 173–177. doi: 10.1007/s40846-018-0397-7

Miller, R. M., Keeter, V. M., Freitas, E. D. S., Heishman, A. D., Knehans, A. W., Bemben, D. A., et al. (2018). Effects of blood-flow restriction combined with postactivation potentiation stimuli on jump performance in recreationally active men. *J. Strength Cond. Res.* 32, 1869–1874. doi: 10.1519/JSC.0000000000002110

Mouser, J. G., Ade, C. J., Black, C. D., Bemben, D. A., and Bemben, M. G. (2017). Brachial blood flow under relative levels of blood flow restriction is decreased in a nonlinear fashion. *Clin. Physiol. Funct. Imaging* 38, 425–430. doi: 10.1111/cpf.12432

Mouser, G. J., Mattocks, K. T., Dankel, S. J., Buckner, S. L., Jessee, M. B., Bell, Z. W., et al. (2018). Very low load resistance exercise in the upper body with and without blood flow restriction: cardiovascular outcomes. *Appl. Physiol. Nutr. Metab.* 44, 288–292. doi: 10.1139/apnm-2018-0325

Murray, J., Bennett, H., Boyle, T., Williams, M., and Davison, K. (2020). Approaches to determining occlusion pressure for blood flow restricted exercise training: systematic review. *J. Sports Sci.* 39, 663–672. doi: 10.1080/02640414.2020.1840734

Nakajima, T., Kurano, M., Iida, H., Takano, H., Oonuma, H., Morita, T., et al. (2006). Use and safety of KAATSU training: results of a national survey. *Int. J. KAATSU Train. Res.* 2, 5–13. doi: 10.3806/ijktr.2.5

Nakajima, T., Kurano, M., Sakagami, F., Iida, H., Fukumura, K., Fukuda, T., et al. (2010). Effects of low-intensity KAATSU resistance training on skeletal muscle size/strength and endurance capacity in patients with ischemic heart disease. *Int. J. KAATSU Train. Res.* 6, 1–7. doi: 10.3806/ijktr.6.1

Nyakayiru, J., Fuchs, C. J., Trommelen, J., Smeets, J. S. J., Senden, J. M., Gijsen, A. P., et al. (2019). Blood flow restriction only increases myofibrillar protein synthesis with exercise. *Med. Sci. Sports Exerc.* 51, 1137–1145. doi: 10.1249/MSS.0000000000001899

Ogawa, M., Loenneke, J. P., Yasuda, T., Fahs, C. A., Lindy, M., Thiebaud, R. S., et al. (2012). Time course changes in muscle size and fatigue during walking with restricted leg blood flow in young men. *J. Phys. Educ. Sport Manag.* 3, 14–19. doi: 10.5897/JPESM12.002

Ozaki, H., Kakigi, R., Kobayashi, H., Loenneke, J. P., Abe, T., and Naito, H. (2014). Effects of walking combined with restricted leg blood flow on mTOR and MAPK signalling in young men. *Acta Physiol.* 211, 97–106. doi: 10.1111/apha.12243

Ozaki, H., Loenneke, J. P., and Abe, T. (2017). Blood flow-restricted walking in older women: does the acute hormonal response associate with muscle hypertrophy? *Clin. Physiol. Funct. Imaging* 37, 379–383. doi: 10.1111/cpf.12312

Ozaki, H., Miyachi, M., Nakajima, T., and Abe, T. (2011a). Effects of 10 weeks walk training with leg blood flow reduction on carotid arterial compliance and muscle size in the elderly adults. *Angiology* 62, 81–86. doi: 10.1177/0003319710375942

Ozaki, H., Sakamaki, M., Yasuda, T., Fujita, S., Ogasawara, R., Sugaya, M., et al. (2011b). Increases in thigh muscle volume and strength by walk training with leg blood flow reduction in older participants. *J. Gerontol. A Biol. Sci. Med. Sci.* 66, 257–263. doi: 10.1093/gerona/glq182

Petrick, H. L., Pignanelli, C., Barbeau, P. A., Churchward-Venne, T. A., Dennis, K. M. J. H., van Loon, L. J. C., et al. (2019). Blood flow restricted resistance exercise and reductions in oxygen tension attenuate mitochondrial H2O2 emission rates in human skeletal muscle. *J. Physiol.* 15, 3985–3997. doi: 10.1113/JP277765

Pinto, R. R., Karabulut, M., Poton, R., and Polito, M. D. (2018). Acute resistance exercise with blood flow restriction in elderly hypertensive women: haemodynamic, rating of perceived exertion and blood lactate. *Clin. Physiol. Funct. Imaging* 38, 17–24. doi: 10.1111/cpf.12376

Renzi, C. P., Tanaka, H., and Sugawara, J. (2010). Effects of leg blood flow restriction during walking on cardiovascular function. *Med. Sci. Sports Exerc.* 42, 726–732. doi: 10.1249/MSS.0b013e3181bdb454

Sato, Y. (2005). The history and future of KAATSU training. *Int. J. KAATSU Train. Res.* 1, 1–5. doi: 10.3806/ijktr.1.1

Sato, Y., Yoshitomi, A., and Abe, T. (2005). Acute growth hormone response to low-intensity KAATSU resistance exercise: comparison between arm and leg. *Int. J. KAATSU Train. Res.* 1, 45–50. doi: 10.3806/ijktr.1.45

Schriger, D. L., and Baraff, L. (1988). Defining normal capillary refill: variation with age, sex, and temperature. *Ann. Emerg. Med.* 17, 932–935. doi: 10.1016/S0196-0644(88)80675-9

Schroeder, E. T., Villanueva, M., West, D. D. W., and Phillips, S. M. (2013). Are acute post-resistance exercise increases in testosterone, growth hormone, and IGF-1 necessary to stimulate skeletal muscle anabolism and hypertrophy? *Med. Sci. Sports Exerc.* 45, 2044–2051. doi: 10.1249/MSS.0000000000000147

Sieljacks, P., Degn, R., Hollaender, K., Wernbom, M., and Vissing, K. (2018). Non-failure blood flow restricted exercise induces similar muscle adaptations and less discomfort than failure protocols. *Scand. J. Med. Sci. Sports* 29, 336–347. doi: 10.1111/sms.13346

Silverstein, D., and Hopper, K. (2014). *Small animal critical care medicine-E-Book*. Elsevier Health Sciences.

Spranger, M. D., Krishnan, A. C., Levy, P. D., O'Leary, D. S., and Smith, S. A. (2015). Blood flow restriction training and the exercise pressor reflex: a call for concern. *Am. J. Physiol. Heart Circ. Physiol.* 309, H1440–H1452. doi: 10.1152/ajpheart.00208.2015

Stray-Gundersen, S., Wooten, S., and Tanaka, H. (2020). Walking with leg blood flow restriction: wide-rigid cuffs vs. narrow-elastic bands. *Front. Physiol.* 11:568. doi: 10.3389/fphys.2020.00568

Sudo, M., Ando, S., and Kano, Y. (2017). Repeated blood flow restriction induces muscle fiber hypertrophy. *Muscle Nerve* 55, 274–276. doi: 10.1002/mus.25415

Suga, T., Okita, K., Morita, N., Yokota, T., Hirabayashi, K., Horiuchi, M., et al. (2009). Intramuscular metabolism during low-intensity resistance exercise with blood flow restriction. *J. Appl. Physiol.* 106, 1119–1124. doi: 10.1152/japplphysiol.90368.2008

Suga, T., Okita, K., Morita, N., Yokota, T., Hirabayashi, K., Horiuchi, M., et al. (2010). Dose effect on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *J. Appl. Physiol.* 108, 1563–1567. doi: 10.1152/japplphysiol.00504.2009

Suga, T., Okita, K., Takada, S., Omokawa, M., Kadoguchi, T., Yokota, T., et al. (2012). Effect of multiple set on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *Eur. J. Appl. Physiol.* 112, 3915–3920. doi: 10.1007/s00421-012-2377-x

Takada, S., Okita, K., Suga, T., Omokawa, M., Kadoguchi, T., Sato, T., et al. (2012). Low-intensity exercise can increase muscle mass and strength proportionally to enhanced metabolic stress under ischemic conditions. *J. Appl. Physiol.* 113, 199–205. doi: 10.1152/japplphysiol.00149.2012

Takano, H., Morita, T., Iida, H., Kato, M., Uno, K., Hirose, K., et al. (2005). Effects of low-intensity "KAATSU" resistance exercise on hemodynamic and growth hormone responses. *Int. J. KAATSU Train. Res.* 1, 13–18. doi: 10.3806/ijktr.1.13

Takarada, Y., Nakamura, Y., Aruga, S., Onda, T., Miyazaki, S., and Ishii, N. (2000a). Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J. Appl. Physiol.* 88, 61–65. doi: 10.1152/jappl.2000.88.1.61

Takarada, Y., Takazawa, H., and Ishii, N. (2000b). Applications of vascular occlusion diminish disuse atrophy of knee extensor muscles. *Med. Sci. Sports Exerc.* 32, 2035–2039. doi: 10.1097/00005768-200012000-00011

Thiebaud, R. S., Yasuda, T., Loenneke, J. P., and Abe, T. (2013). Effects of low-intensity concentric and eccentric exercise combined with blood flow restriction on indices of exercise-induced muscle damage. *Interv. Med. Appl. Sci.* 5, 53–59. doi: 10.1556/IMAS.5.2013.2.1

Vechin, F. C., Libardi, C. A., Conceição, M. S., Damas, F. R., Lixandrão, M. E., Berton, R. P. B., et al. (2015). Comparisons between low-intensity resistance training with blood flow restriction and high-intensity resistance training on quadriceps muscle mass and strength in elderly. *J. Strength Cond. Res.* 29, 1071–1076. doi: 10.1519/JSC.0000000000000703

Weatherholt, A. M., Vanwye, W. R., Lohmann, J., and Owens, J. G. (2019). The effect of cuff width for determining limb occlusion pressure: a comparison of blood flow restriction devices. *Int. J. Exerc. Sci.* 12, 136–143.

Wernbom, M., Augustsson, J., and Thomeé, R. (2006). Effects of vascular occlusion on muscular endurance in dynamic knee extension exercise at different submaximal loads. *J. Strength Cond. Res.* 20, 372–377. doi: 10.1519/R-16884.1

Wernbom, M., Schoenfeld, B. J., Paulsen, G., Bjørnsen, T., Cumming, K. T., Aagaard, P., et al. (2020). Commentary: can blood flow restricted exercise cause muscle damage? Commentary on blood flow restriction exercise: considerations of methodology, application, and safety. *Front. Physiol.* 11:243. doi: 10.3389/fphys.2020.00243

Wilk, M., Krzysztofik, M., Filip, A., Zajac, A., Bogdanis, G. C., and Lockie, R. G. (2020). Short-term blood flow restriction increases power output and bar velocity during the bench press. *J. Strength Cond. Res.* doi: 10.1519/JSC.0000000000003649 [Epub ahead of print].

Wilson, J. M., Lowery, R. P., Joy, J. M., Loenneke, J. P., and Naimo, M. A. (2013). Practical blood flow restriction training increases acute determinants of hypertrophy without increasing indices of muscle damage. *J. Strength Cond. Res.* 27, 3068–3075. doi: 10.1519/JSC.0b013e31828a1ffa

Yasuda, T., Abe, T., Brechue, W. F., Iida, H., Takano, H., Meguro, K., et al. (2010a). Venous blood gas and metabolite response to low-intensity muscle contractions with external limb compression. *Metabolism* 59, 1510–1519. doi: 10.1016/j.metabol.2010.01.016

Yasuda, T., Fujita, S., Ogasawara, R., Sato, Y., and Abe, T. (2010b). Effects of low-intensity bench press training with restricted arm muscle blood flow on chest muscle hypertrophy: a pilot study. *Clin. Physiol. Funct. Imaging* 30, 338–343. doi: 10.1111/j.1475-097X.2010.00949.x

Yasuda, T., Loenneke, J. P., Ogasawara, R., and Abe, T. (2013). Influence of continuous or intermittent blood flow restriction on muscle activation during low-intensity multiple sets of resistance exercise. *Acta Physiol. Hung.* 100, 419–426. doi: 10.1556/APhysiol.100.2013.4.6

Zhao, Y., Lin, A., and Jiao, L. (2020). Eight weeks of resistance training with blood flow restriction improve cardiac function and vascular endothelial function in healthy young Asian males. *Int. Health* 13, 471–479. doi: 10.1093/inthealth/ihaa089

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Physiology

ORIGINAL RESEARCH
published: 03 February 2022
doi: 10.3389/fphys.2022.837697

Muscle Adaptations to Heavy-Load and Blood Flow Restriction Resistance Training Methods

Anthony K. May, Aaron P. Russell, Paul A. Della Gatta and Stuart A. Warmington*

Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Geelong, VIC, Australia

OPEN ACCESS

Edited by:
Adam Zajac, University School of Physical Education in Wroclaw, Poland

Reviewed by:
Michał Krzysztofik, Jerzy Kukuczka Academy of Physical Education in Katowice, Poland
Masatoshi Nakamura, Niigata University of Health and Welfare, Japan

***Correspondence:**
Anthony K. May
a.may@deakin.edu.au

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *16 December 2021*
Accepted: *11 January 2022*
Published: *03 February 2022*

Citation:
May AK, Russell AP, Della Gatta PA and Warmington SA (2022) Muscle Adaptations to Heavy-Load and Blood Flow Restriction Resistance Training Methods. Front. Physiol. 13:837697. doi: 10.3389/fphys.2022.837697

Resistance-based blood flow restriction training (BFRT) improves skeletal muscle strength and size. Unlike heavy-load resistance training (HLRT), there is debate as to whether strength adaptations following BFRT interventions can be primarily attributed to concurrent muscle hypertrophy, as the magnitude of hypertrophy is often minor. The present study aimed to investigate the effect of 7 weeks of BFRT and HLRT on muscle strength and hypertrophy. The expression of protein growth markers from muscle biopsy samples was also measured. Male participants were allocated to moderately heavy-load training (HL; $n=9$), low-load BFRT (LL+BFR; $n=8$), or a control (CON; $n=9$) group to control for the effect of time. HL and LL+BFR completed 21 training sessions (3 d.week^{-1}) comprising bilateral knee extension and knee flexion exercises (HL=70% one-repetition maximum (1-RM), LL+BFR=20% 1-RM+blood flow restriction). Bilateral knee extension and flexion 1-RM strength were assessed, and leg muscle CSA was measured *via* peripheral quantitative computed tomography. Protein growth markers were measured in vastus lateralis biopsy samples taken pre- and post the first and last training sessions. Biopsy samples were also taken from CON at the same time intervals as HL and LL+BFR. Knee extension 1-RM strength increased in HL (19%) and LL+BFR (19%) but not CON (2%; $p<0.05$). Knee flexion 1-RM strength increased similarly between all groups, as did muscle CSA (50% femur length; HL=2.2%, LL+BFR=3.0%, CON=2.1%; TIME main effects). 4E-BP1 (Thr37/46) phosphorylation was lower in HL and LL+BFR immediately post-exercise compared with CON in both sessions ($p<0.05$). Expression of other growth markers was similar between groups ($p>0.05$). Overall, BFRT and HLRT improved muscle strength and size similarly, with comparable changes in intramuscular protein growth marker expression, both acutely and chronically, suggesting the activation of similar anabolic pathways. However, the low magnitude of muscle hypertrophy was not significantly different to the non-training control suggesting that strength adaptation following 7 weeks of BFRT is not driven by hypertrophy, but rather neurological adaptation.

Keywords: hypertrophy, strength, vascular occlusion, skeletal muscle, growth markers

INTRODUCTION

Blood flow restriction training (BFRT) generally comprises periods of low-intensity resistance or aerobic exercise with blood flow restriction (BFR) applied to the working limbs *via* pneumatic or elastic cuffs. Resistance-based BFRT can increase skeletal muscle strength and induce muscle hypertrophy to a greater degree than equal-intensity training without the application of BFR (Kubo et al., 2006; Takada et al., 2012). Such muscle adaptation without utilizing large mechanical loads has positioned BFRT as a potential alternative or complementary training method to heavy-load resistance training (HLRT), particularly for lower physical functioning populations, such as those undergoing musculoskeletal rehabilitation or the frail elderly.

BFRT utilizes lighter external loads than HLRT (BFRT = 20–30% one-repetition maximum (1-RM); HLRT >60% 1-RM), induces reduced-to-similar adaptations to muscle strength (Lixandrão et al., 2018; Grønfeldt et al., 2020), and comparable hypertrophy (Lixandrão et al., 2018). Enhanced muscle force generating capacity following HLRT is largely due to neuromuscular adaptation, rather than hypertrophy (Kraemer et al., 1996). Indeed, the causative role of hypertrophy in resistance training-based strength adaptations in humans is still questioned (Dankel et al., 2018). However, the contributions of hypertrophy vs. neuromuscular adaptation to strength gains following BFRT are less clear. BFRT induces muscle hypertrophy within 2 weeks (Abe et al., 2006; Hill et al., 2018) and can induce hypertrophy without changes to neural activation (Kubo et al., 2006). These findings, combined with some observations of similar percentage changes in muscle strength and hypertrophy (Kubo et al., 2006; Martín-Hernández et al., 2013; Ozaki et al., 2013), suggest that hypertrophy may be a major factor contributing to BFRT-induced strength gains. In contrast, pronounced BFRT-induced strength adaptations may be incongruent with minor/no muscle hypertrophy (Laurentino et al., 2012; Lixandrão et al., 2015; Vechin et al., 2015; Cook et al., 2018). For example, BFRT and HLRT increased leg extension 1-RM strength similarly (23.5% average) when compared to an untrained control group (Cook et al., 2018), but meaningful muscle hypertrophy did not occur as the change in muscle volume (4.5%) was not different to an untrained control group. This suggests that if hypertrophic adaptation is induced following BFRT, it may have minimal contribution to strength change; the latter most likely driven by neurological adaptations (Jessee et al., 2018).

Mechanical tension is the dominant primary stimulus for anabolic activity during HLRT (Pearson and Hussain, 2015). Comparatively, BFRT produces less mechanical tension due to lower loads but induces enhanced metabolic stress (Pearson and Hussain, 2015). It is therefore possible that regulation of intramuscular signaling pathways differs between training methods. Protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway signaling increases protein synthesis (Rommel et al., 2001; Wang and Proud, 2006) and is responsive to chronic (Léger et al., 2006) and single-bout (acute) HLRT (Dreyer et al., 2006, 2008, 2010), as well as acute BFRT (Fujita et al., 2007; Fry et al., 2010; Gundermann et al., 2012; Wernbom et al., 2013). As such, similar cell signaling events may regulate muscle growth following HLRT and BFRT. Comparatively, anabolic mitogen-activated protein kinase (MAPK) cascade activity in BFRT is somewhat uncharacterized. MAPKs generally activate following traditional resistance exercise (Boppart et al., 1999; Martineau and Gardiner, 2001; Williamson et al., 2003; Deldicque et al., 2008), but extracellular signal-regulated kinase (ERK) 1/2 activation has been unchanged following BFRT (Gundermann et al., 2012, 2014). In addition, c-Jun N-terminal kinase (JNK) appears sensitive to mechanical tension and muscle damage (Aronson et al., 1997), which appear lower in BFRT, though has not been investigated. Furthermore, the acute response to BFRT following a training program (i.e., the chronic effect of training) is yet to be investigated. Activation of key translation initiation proteins appears preserved in young adult muscle following traditional resistance training (Farnfield et al., 2012), but it is unclear if this is also the case following BFRT.

This study aimed to compare the effect of 7 weeks of BFRT and HLRT on changes in muscle strength and size to investigate the role of muscle hypertrophy in BFRT-induced strength adaptation. A secondary aim was to investigate the mechanisms of BFRT-induced hypertrophy *via* intracellular signaling proteins that affect muscle growth by confirming the role of Akt, and exploring the role of other potential pathways, both acutely and chronically.

MATERIALS AND METHODS

Participants

Twenty-six untrained young men were recruited for this study. Participants were matched for bilateral leg extension 1-RM strength then randomly allocated to either a low-load resistance BFRT group (LL + BFR; $n = 8$), a moderately heavy-load resistance training group without BFR (HL; $n = 9$), or a passive non-training control group (CON; $n = 9$). All participants had not undertaken any regular resistance exercise within the previous 6 months and did not present with any musculoskeletal, neurological, or vascular disease/injury. Prior to inclusion in the study, all participants provided written informed consent and underwent a pre-screening procedure including a health questionnaire. Participants were excluded if presenting with diagnosed diabetes mellitus, hypertension, or if taking medication prescribed for blood pressure control. In addition, participants at increased risk of complications due to muscle biopsies, such as those with blood clotting disorders or prescribed with blood thinning medications, were also excluded. This study was carried out in accordance with the recommendations of the Deakin University Human Ethics Advisory Group. All participants gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Deakin University Human Ethics Advisory Group (Project number 2014-229).

Experimental Design

The overall experimental design is displayed in **Figure 1**. All participants first completed a familiarization session, followed by a testing session at least 3 days later (PRE). PRE included

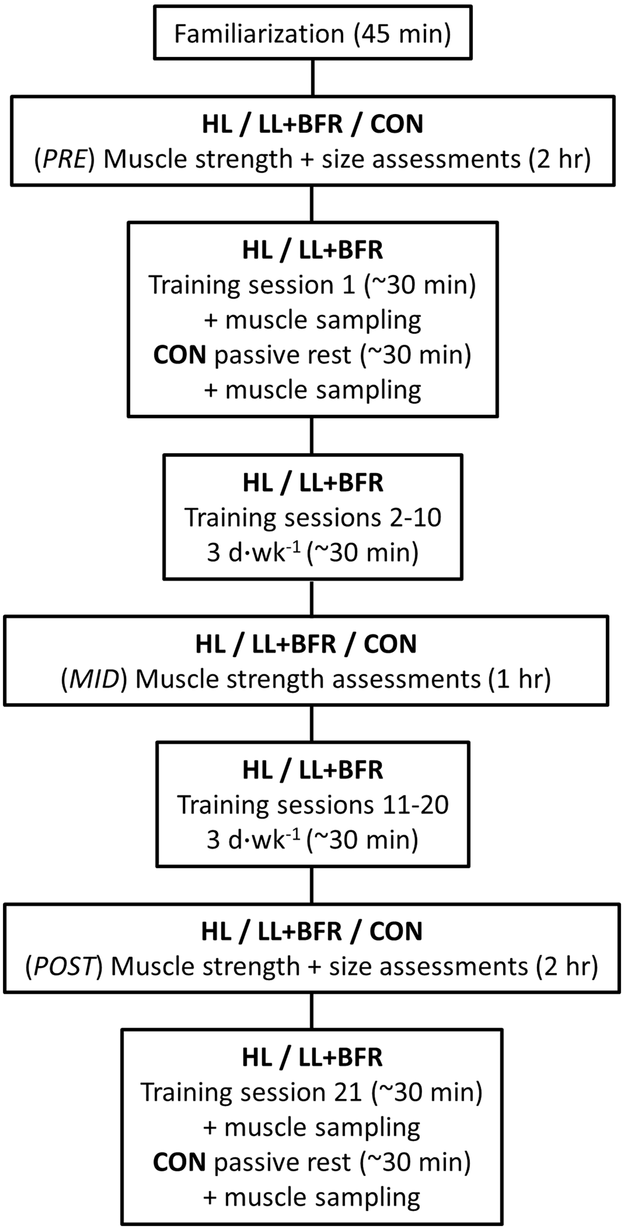

FIGURE 1 | Experimental protocol. HL, heavy-load resistance training group; LL + BFR, blood flow restriction training group; and CON, non-training control group.

a muscle cross-sectional area (CSA) measurement of the dominant leg, followed by 1-RM strength assessments of the lower body. One week following PRE, HL and LL + BFR performed 20 training sessions (3 d.week^{-1}) over 7 weeks. Training sessions comprised bilateral knee extension and knee flexion exercises. During training, LL + BFR had blood flow restricted by pressurized cuffs. The initial session (Session 1) of the training program, or passive rest in the case of CON, included an excision of muscle *via* percutaneous muscle biopsies for growth marker protein analysis. Attendance from CON was not required for any other session in the training block. Muscle strength was assessed following completion of 10 training sessions (MID), and both muscle strength and size were assessed on a final occasion 3–5 days following completion of the last (20th) training session (POST). One week following the final muscle size and strength assessment, all participant groups attended the laboratory for a final exercise session (for HL and LL + BFR) involving muscle sampling (Session 21). A single researcher performed all testing and biochemical analyses and was not blinded to participant grouping allocations.

Familiarization

After an initial pre-screening process, participants were familiarized with the laboratory and machinery used throughout the program. Participants were then instructed on exercises used within the study, which was followed by an initial familiarization with BFRT that comprised light bilateral dumbbell bicep curl exercises where the dominant arm had BFR applied and the non-dominant arm did not. This was performed to inform participants of the unique sensations expected during BFRT. This BFR familiarization was not performed in the legs, which would be trained with BFR applied if the participant were later allocated to LL + BFR, to minimize any influences on lifting performance in future.

Training Protocol

Allocated exercise loads in the first 10 training sessions were calculated as a percentage of 1-RM measured during PRE strength testing and sessions 11–20 from the MID strength testing. In addition, loads for Session 21 were calculated using results from POST.

Training sessions began with a general 5-min warm-up on a cycle ergometer. Participants in HL then performed four sets of knee flexion and knee extension exercises at a repetition velocity of 2 s eccentric, 2 s concentric phase, guided by a metronome. Exercises were performed at 70% 1-RM without BFR applied and comprised eight repetitions each set. Rest periods were 2 min each as per recommendations for muscle strength and hypertrophy adaptations (American College of Sports Medicine, 2009). Participants in LL + BFR performed four sets of lower-body exercises at 20% 1-RM with BFR applied to the most proximal portion of the upper legs. Training sessions comprised a set of 30 repetitions, followed by three sets of 15 repetitions. 30-s rest periods with continuous cuff inflation were utilized as is standard practice for BFRT to increase metabolic stress (Scott et al., 2015). Repetition velocity matched that of HL. The order of knee flexion/extension exercises alternated every training session. CON did not perform any resistance training during the training period but continued their daily habits. During study participation, all groups were not permitted to perform any structured resistive exercise outside of laboratory sessions.

Muscle Strength

Bilateral knee flexion and knee extension strength were measured *via* 1-RM assessments utilizing pneumatic resistance machinery; a seated bilateral knee extension machine (Keiser Air200 leg extension, Keiser Corporation, Fresno, United States) and a prone knee flexion machine (Keiser Air200 leg curl, Keiser Corporation, Fresno, United States). The same machinery was also utilized for training sessions for HL and LL + BFR.

All 1-RM strength testing followed the American College of Sports Medicine (ACSM) guidelines for maximal muscle strength assessment (Thompson et al., 2010). 1-RM tests were preceded by a general 5-min warm-up on a cycle ergometer, then a specific resistance submaximal warm-up for both following 1-RM exercises. Successful attempts required the participant to lift the resistance through a full range of motion with control. Participants were permitted to grip the handles of the machines in training and testing sessions. Fixation belts were not utilized.

Muscle Cross-Sectional Area

Muscle CSA of the dominant leg was measured at PRE and POST *via* peripheral quantitative computed tomography (pQCT; Stratec XCT3000, Stratec Medizintechnik, Baden-Württemberg, Germany). Scans were performed at 25 and 50% femur length in the dominant leg (Seynnes et al., 2007). All measurements were performed by the same researcher with the participant laying supine and the scanned limb positioned through the center of the pQCT gantry. Participants were asked to remain still and to breathe normally during scans, which were acquired with a voxel size of 0.5 mm. pQCT images were analyzed using the BoneJ plugin for ImageJ (Doube et al., 2010). Muscle tissue was defined as voxels with a density >40 and <200 mg/cm^2 (Rantalainen et al., 2014); then, total muscle CSA was calculated for all soft tissue within those thresholds. CSA of grouped knee flexor and extensor muscles were also independently analyzed at 25% of femur length but not 50% femur length due to unclear separation of muscles at those sites with the resolution available.

Blood Flow Restriction

LL + BFR performed the training protocol with blood flow to the lower-body restricted using cuffs (86 cm length, 10.5 cm width, 8 cm bladder width, nylon material) attached to an automatic tourniquet system (Zimmer ATS 4000, Zimmer Biomet, Warsaw, United States). BFR cuffs were applied to the most proximal portion of both upper legs and inflated immediately prior to commencement of the first set of exercises (either knee flexion or extension). Cuffs remained inflated continuously throughout all training sessions until completion of the final set of subsequent lower-body exercises (roughly 14-min inflation per session).

On arriving at the laboratory for Session 1, prior to administration of anesthetic, individualized limb occlusion pressure (LOP) of the lower limbs, the pressure required to completely occlude peripheral tissue blood flow, was assessed (**Table 1**) using previously reported methods (May et al., 2018). The BFR restriction pressure for the following 10 training sessions was set to 60% LOP. Assessment of LOP was also repeated prior to commencement of the 11th training session (Session 11) and 60% LOP was utilized as the restriction pressure for all remaining sessions.

TABLE 1 | Participant anthropometry, and limb occlusion pressure (LOP) in heavy-load resistance training (HL), blood flow restriction training (LL + BFR), and non-training control (CON) groups.

Variable	HL	LL + BFR	CON
Age (years)	24.1 ± 3.8	24.1 ± 4.0	21.2 ± 2.2
Height (cm)	179.8 ± 8.7	185.3 ± 9.4	181.3 ± 4.3
Session 1 Body mass (kg)	78.8 ± 16.7	85.3 ± 16.2	85.1 ± 23.2
Session 21 Body mass (kg)	79.4 ± 16.2	85.2 ± 16.2	86.7 ± 24.3*
Session 1 BMI (kg•m^{-2})	24.3 ± 4.4	24.7 ± 3.8	25.7 ± 6.2
Session 21 BMI (kg•m^{-2})	24.5 ± 4.3	24.7 ± 3.8	26.2 ± 6.5*
Session 1 LOP (mmHg)	-	215 ± 19	-
Training session 1–10 restriction pressure (60% LOP; mmHg)	-	129 ± 11	-
Session 11 LOP (mmHg)	-	212 ± 17	-
Training session 11–20 restriction pressure (60% LOP; mmHg)	-	127 ± 10	-

*Data are mean ± SD. BMI, body mass index; BFR, blood flow restriction. *Different from Session 1 ($p < 0.05$).*

Muscle Biopsy Sessions

Skeletal muscle sampling *via* muscle biopsies occurred during Session 1 and Session 21, both of which required all participants to report to the laboratory on two consecutive days. These sessions each involved four biopsies of the vastus lateralis muscle (**Figure 2**). Exercise was not permitted on the day of muscle sampling sessions, or the day prior. Participants commenced the sessions at roughly the same time of day (<1-h variation) in a fasted state. Standard dinners were consumed the night before any muscle sampling days. Meals consisted of: energy, 12,090 kJ; protein, 20.2 g; fat (total), 9.6 g; fat (saturated), 4.2 g; carbohydrate (total), 32.0 g; carbohydrate (sugars), 5.4 g; and sodium, 1,060 mg.

Using a Bergström needle (Bergström, 1962), with applied suction (Evans et al., 1982), muscle biopsies were taken from the vastus lateralis of participants under local anesthesia (1% Xylocaine). Generally, 100–200 mg of sample was obtained for each muscle biopsy then immediately frozen in liquid nitrogen and stored at −80°C for protein extraction and analysis. Serial biopsy samples were taken on opposite legs (i.e., left, right, left, and right) and collected at least 2 cm from previous biopsy sites.

After the initial muscle biopsy on Session 1 and Session 21, participants allocated to CON then passively sat or lay supine for 30 min. Participants allocated to HL and LL + BFR immediately began the exercise session (following ~30 s walking to exercise machinery). After completion of a 5-min warm-up

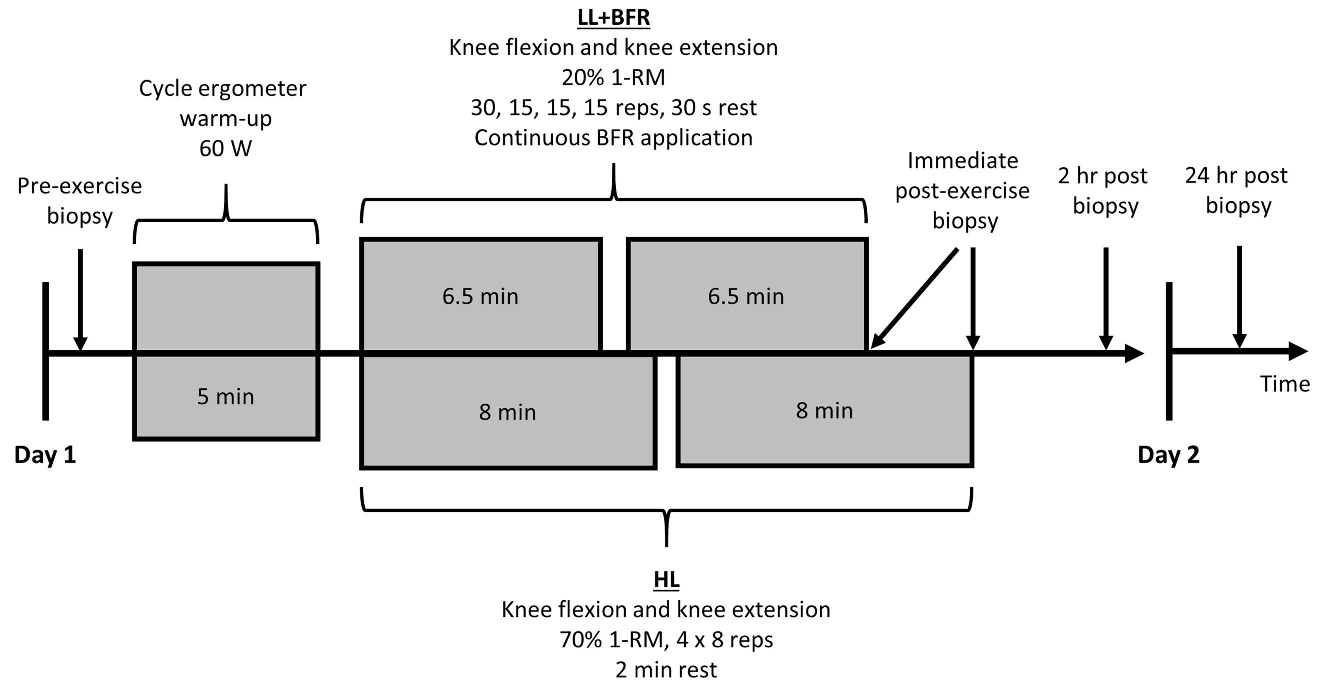

FIGURE 2 | Skeletal muscle sampling sessions for heavy-load resistance training (HL) and blood flow restriction training (LL + BFR) groups. A non-training control group (CON) also performed 30 min passive rest between the first and second biopsies. 1-RM, one-repetition maximum and BFR, blood flow restriction.

on a cycle ergometer at 60 watts, allocated training programs were performed under supervision. Knee extension exercises were performed before knee flexion exercises on both Session 1 and 21. Within 2 min of exercise completion, an immediate post-exercise muscle biopsy occurred. CON also had a sample taken following the passive rest period. All participants then rested passively for 2 h, after which another muscle biopsy occurred. Sampling sites were then covered, and participants were provided with a standard lunch to ensure consistent post-exercise diets. Participants reported back to the laboratory in a fasted state for one final muscle biopsy 24 h following exercise completion or in the case of CON, 24 h following the second muscle biopsy. In total, eight muscle biopsy samples were obtained from all participants over the two sampling sessions.

Protein Extraction and Western Blots

Total protein from biopsy samples was extracted using RIPA buffer (Merck, Kilsyth, Australia) with 1 μL.ml^{-1} protease inhibitor cocktail (Sigma-Aldrich, Castle Hill, Australia) and 10 μL.ml^{-1} phosphatase inhibitor cocktail (Thermo Fisher Scientific, Scoresby, Australia). Total protein content was determined using a BCA protein assay kit (Thermo Fisher Scientific, Scoresby, Australia).

Equal amounts of protein were separated on 4–15% Criterion™ TGX Stain-Free™ precast gels (Bio-Rad, Gladesville, Australia) in 10% Tris/Glycine/SDS buffer solution. Proteins were then transferred for 30 min into Immobilin-FL PVDF membranes (Millipore, Billerica, United States) and membranes were scanned to quantify total protein transferred in individual wells using a Bio-Rad Gel Doc™ XR+ (Bio-Rad Laboratories, Hercules, United States). Membranes were then blocked for 1 h at room temperature in 5% skim milk powder/10% Tris-buffered saline with 0.1% Tween 20 (TBST).

After blocking, blots were cut and separated, which was followed by overnight incubation with gentle agitation at 4°C in 5% bovine serum albumin/TBST combined with primary antibodies. The following antibodies were purchased from Cell Signaling Technology (Danvers, United States): Phospho-mTOR (Ser2448), Phospho-eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1; Thr37/46), Phospho-ERK 1/2 (Thr202/Tyr204), Phospho-Stress-activated protein kinase (SAPK)/JNK (Thr183/Tyr185), total mTOR, total ribosomal S6 kinase 1 (S6K1), total 4E-BP1, total ERK 1/2, and total SAPK/JNK. In addition, total muscle RING finger protein-1 (MuRF-1) was purchased from Taylor Bio-Medical (Ashfield, Australia). All antibodies were used in a dilution of 1:1,000 except Total 4E-BP1 (1:500) and Phospho-ERK 1/2 (Thr202/Tyr204; 1:2,000). Only phosphorylation data are shown in this article. All other results are shown in **Supplementary Material**.

Following overnight incubation, membranes were washed in 10% TBST for 3 × 5-min periods then incubated with gentle agitation for 1 h at room temperature with an appropriate secondary antibody (1:15,000) in a 5% bovine serum albumin/TBST solution. Following incubation, blots were washed again in 10% TBST then exposed on an Odyssey® Infrared Imaging System (LI-COR Biosciences, Lincoln, United States) and individual protein band optical densities were determined using Image Studio Lite (V5.2.5; LI-COR Biosciences, Lincoln, United States). All blots were normalized to the total protein load and an internal control.

Data Presentation and Statistical Analysis

Power analyses indicated that 24 participants (eight participants per group) were required to detect differences in 1-RM strength, muscle CSA, and acute mTOR (Ser2448) phosphorylation, with 80% power. Thirty participants were recruited and four dropped out citing muscle biopsy concerns (13% attrition). Unless otherwise stated, data are presented as mean ± SD. Normality of data distribution was assessed *via* Shapiro-Wilk tests. Participant age and height were compared for GROUP (HL; LL + BFR; CON) *via* a one-way analysis of variance (ANOVA). Body mass and body mass index (BMI) were analyzed *via* mixed-model ANOVA comparing for GROUP × SESSION (Session 1; Session 21). LOP and training restriction pressures for LL + BFR were compared between sessions *via* paired t-tests. 1-RM strength data were analyzed with a mixed-model ANOVA comparing for GROUP (HL; LL + BFR; CON) and TIME (PRE; MID; POST). Muscle CSA data were analyzed *via* mixed-model ANOVA comparing for GROUP × TIME (PRE; POST).

The ratio of phosphorylated forms to total content (phospho/total) of analyzed intramuscular proteins was also expressed as fold change and analyzed by two-way ANOVA within sessions (Session 1 and Session 21, separately) comparing for GROUP × TIME [Pre-exercise (Pre); immediately post-exercise (0 h); 2 h post-exercise (2 h); 24 h post-exercise (24 h)]. A separate two-way ANOVA was performed within individual groups comparing for SESSION × TIME.

For all significant main effects or interactions within ANOVAs, specific differences were further examined using Tukey-Kramer *post-hoc* tests. For all statistical tests, the significance level was set to $p < 0.05$. All analyses were conducted using Stata/SE 14 (StataCorp LLC, Texas, United States).

RESULTS

Anthropometric measures were not significantly different between groups (**Table 1**; $p > 0.05$). Body mass and BMI were both significantly greater in CON during Session 21 compared with Session 1 (both measures $p < 0.001$). For LL + BFR, LOP and training restriction pressure measurements were not different between Session 1 and Session 11 ($p = 0.32$).

Muscle Strength

Mixed-model ANOVA indicated a GROUP × TIME interaction for knee extension 1-RM strength (**Figure 3A**; $p < 0.05$). Post-hoc analysis revealed that strength at MID increased significantly in HL (10%) and LL + BFR (9%) when compared to PRE ($p < 0.001$). This was greater at MID in LL + BFR when compared to CON (1%; $p = 0.04$). At POST, knee extension strength increased in HL (19%) and LL + BFR (19%; $p < 0.001$), but not CON (2%; $p > 0.05$). This increase was greater in both HL and LL + BFR compared with CON ($p < 0.01$).

For knee flexion 1-RM strength, there was a main effect for TIME such that strength increased from PRE to MID for ALL groups (**Figure 3B**; $p < 0.01$), and again at POST (HL = 16%, LL + BFR = 11%, CON = 5%; $p < 0.01$). There was no GROUP main effect or interaction.

Muscle Cross-Sectional Area

There was no GROUP × TIME interaction ($p > 0.05$) or GROUP main effect ($p > 0.05$) for any muscle CSA measure. A main effect for TIME occurred for total muscle CSA at 25 and 50% femur length, and knee flexor CSA (25% length) indicating an increase at POST for all groups ($p < 0.01$; **Table 2**). There was no interaction or main effects for knee extensor muscle CSA at 25% femur length ($p > 0.05$).

Growth Marker Protein Expression

No interactions, GROUP, TIME, or SESSION main effects, were identified for mTOR (Ser2448) phosphorylation (expressed as fold change) by two-way ANOVAs (**Figure 4A**; $p > 0.05$).

For 4E-BP1 (Thr37/46) phosphorylation during both Session 1 and Session 21, two-way ANOVAs indicated GROUP × TIME interactions (**Figure 4B**; $p < 0.05$). Post-hoc testing identified

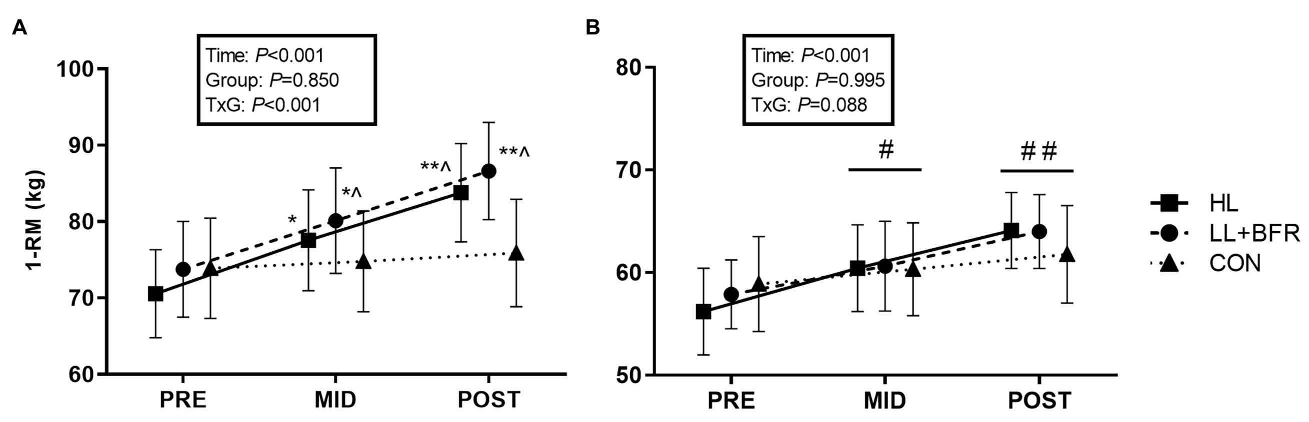

FIGURE 3 | One-repetition maximum (1-RM) strength for bilateral knee extension **(A)** and knee flexion exercises **(B)** in heavy-load resistance training (HL), blood flow restriction training (LL + BFR), and non-training control (CON) groups. Data are mean ± SEM. * Different from PRE ($p < 0.001$); ** different from PRE and MID ($p < 0.001$); ^ different from CON ($p < 0.01$); # different from PRE (TIME main effect; $p < 0.01$); and ## different from PRE and MID (TIME main effect; $p < 0.01$).

TABLE 2 | Muscle cross-sectional area (CSA) in heavy-load resistance training (HL), blood flow restriction training (LL + BFR), and non-training control (CON) groups.

Cross-section	Site	Group	PRE	POST	Change (%)
		HL	85.9 ± 11.2	87.7 ± 10.3#	2.4 ± 6.0
	Total muscle CSA (cm^2)	LL + BFR	84.1 ± 11.4	87.5 ± 10.7#	4.2 ± 2.7
		CON	87.5 ± 20.3	89.0 ± 20.1#	1.9 ± 2.4
		HL	48.5 ± 8.2	48.7 ± 7.1	0.8 ± 5.3
25% femur length	Knee extensor muscle CSA (cm^2)	LL + BFR	46.6 ± 7.6	47.9 ± 7.9	3.0 ± 4.1
		CON	49.2 ± 12.6	49.9 ± 12.9	1.4 ± 3.4
		HL	25.9 ± 3.2	27.5 ± 3.6#	6.0 ± 5.3
	Knee flexor muscle CSA (cm^2)	LL + BFR	25.9 ± 5.2	27.3 ± 4.6#	5.8 ± 4.8
		CON	26.7 ± 6.9	27.1 ± 6.7#	1.8 ± 3.2
		HL	145.8 ± 17.1	148.9 ± 16.7#	2.2 ± 2.9
50% femur length	Total muscle CSA (cm^2)	LL + BFR	147.6 ± 24.6	151.7 ± 23.7#	3.0 ± 3.0
		CON	139.6 ± 33.4	141.8 ± 35.2#	2.1 ± 2.7

Data are mean ± SD. #Main effect for TIME ($p < 0.01$).

that in Session 1, 4E-BP1 (Thr37/46) phosphorylation at 0 h (immediately post-exercise) reduced in HL (0.4 ± 0.3 AU) compared with Pre ($p < 0.001$). This was also lower than for 2 h (0.9 ± 0.3 AU; $p = 0.002$) and 24 h (0.9 ± 0.2 AU; $p = 0.026$). 4E-BP1 (Thr37/46) phosphorylation at 0 h for LL + BFR (0.6 ± 0.3 AU) did not reduce compared with Pre ($p = 0.062$), though was lower than 24 h (1.3 ± 0.4 AU; $p < 0.001$). HL and LL + BFR were both lower than CON at 0 h (1.0 ± 0.3 AU; $p < 0.05$). In Session 21, there was no significant change in 4E-BP1 (Thr37/46) phosphorylation for any group. Although, 4E-BP1 (Thr37/46) phosphorylation at 0 h for both HL and LL + BFR was lower than for CON ($p < 0.05$). No SESSION × TIME interaction, SESSION or TIME main effects were identified *via* two-way ANOVA between Session 1 and 21 ($p > 0.05$).

For ERK 1/2 (Thr202/Tyr204) phosphorylation during Session 1, there was no GROUP × TIME interaction or main effects (**Figure 4C**; $p > 0.05$). Two-way ANOVA identified a TIME main effect within Session 21. Subsequent post-hoc testing revealed Pre was lower overall compared with 2 h ($p = 0.006$). There were no GROUP main effects or interactions for Session 21, and two-way ANOVA between sessions did not identify any SESSION × TIME interaction, SESSION, or TIME main effects ($p > 0.05$).

Two-way ANOVAs for JNK (Thr183/Tyr185) phosphorylation identified TIME main effects for both Session 1 and Session 21 (**Figure 4D**; $p < 0.05$). Post-hoc analyses revealed that during Session 1, Pre was lower compared with 24 h ($p = 0.029$), and 0 h was lower than 2 h ($p = 0.014$). In Session 21, *post-hoc* tests indicated JNK (Thr183/Tyr185) phosphorylation was lower at Pre compared with 2 h ($p = 0.007$) and 24 h ($p = 0.019$), and was lower at 0 h compared with 2 h ($p = 0.033$). No GROUP main effects or interactions occurred, and there was no SESSION × TIME interaction, SESSION, or TIME main effects identified *via* two-way ANOVA between sessions ($p > 0.05$).

DISCUSSION

This study aimed to measure and compare the effect of 7 weeks of BFRT and moderately heavy-load resistance training on skeletal muscle adaptations. A non-exercising control group was also included to control for the effect of time. Several key observations were made. Firstly, BFRT and HLRT increased knee extension strength to a similar extent, independently of a meaningful concurrent increase to muscle CSA. This indicates strength adaptations to both resistance training methods were driven by a neuromuscular response. In addition, potential intramuscular mechanisms for protein expression following BFRT appeared similar to those for HLRT, despite differences in primary anabolic stimuli (e.g., training load and metabolic stress).

Muscle Strength and Cross-Sectional Area

The magnitude of strength adaptation following BFRT has historically been variable due to differences in methodology, though the increase in bilateral knee extension strength observed in the present study following the LL + BFR intervention (19%) is supported by previous literature (Karabulut et al., 2009; Cook et al., 2017, 2018). Knee extension 1-RM strength (and knee flexion strength) also increased similarly to that for HL. This indicates the benefit of BFRT for healthy untrained males and supports its potential as a low mechanical stress alternative to HLRT to induce muscle adaptations for low physical functioning populations. This is particularly applicable for these populations given that safe isolated joint exercises were prescribed, and pneumatic resistance machinery was utilized, which appears to be gaining popularity as a possible training method for older adults and for musculoskeletal rehabilitation. Knee extension 1-RM strength adaptation can be pronounced during BFRT, although the similar adaptation between resistance training groups was somewhat surprising given that improvements to BFRT can sometimes be half that for HLRT (Martín-Hernández et al., 2013; Cook et al., 2017, 2018). It is still unclear if BFRT is as effective as HLRT for strength adaptation (Lixandrão et al., 2018; Grønfeldt et al., 2020), though benefits to BFRT compared with HLRT are likely dependent on factors, such as the training population, exercise selection, and domains of strength (i.e., isometric and isotonic).

Bilateral knee flexion 1-RM strength increased similarly between all groups (TIME main effect). The magnitude of change was lowest for the passive control group (5%),

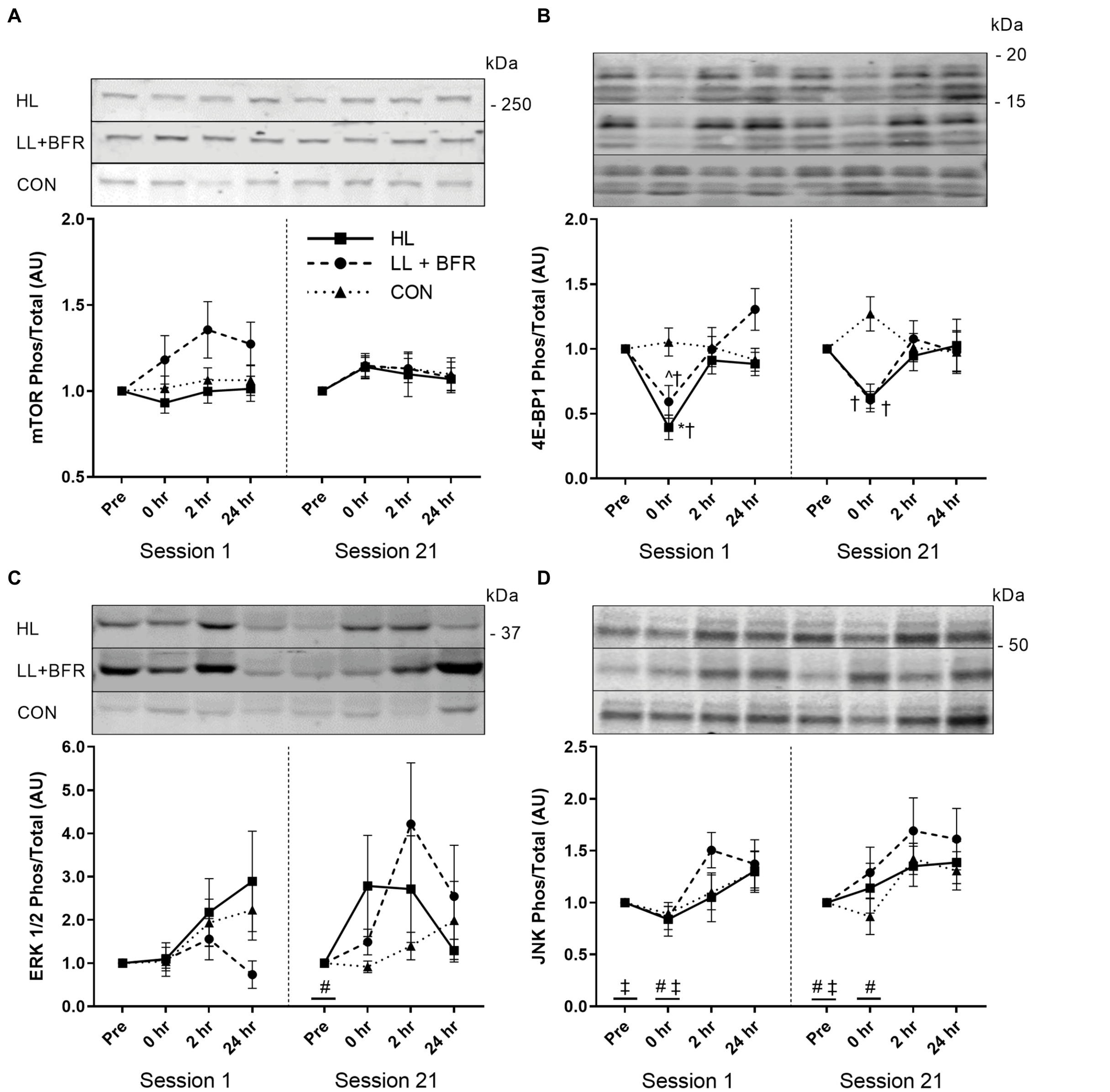

FIGURE 4 | Ratio of phosphorylated to total mTOR (Ser2448; **A**), 4E-BP1 (Thr37/46; **B**), ERK 1/2 (Thr202/Tyr204; **C**), and JNK (Thr183/Tyr185; **D**) sampled pre-exercise (Pre), immediately following (0h), 2h following (2h), and 24h following (24h) knee extension and flexion exercise in heavy-load resistance training (HL), blood flow restriction training (LL+BFR), and non-training control (CON) groups during the first (Session 1) and last (Session 21) training sessions of a program. Representative blots also shown. Data are mean ± SEM in arbitrary units (AU; fold change). * Different from all other time points ($p<0.05$); † different from CON ($p<0.05$); ^ different from 24h ($p<0.01$); # different from 2h (TIME main effect; $p<0.05$); and ‡ different from 24h (TIME main effect; $p<0.05$). mTOR, mammalian target of rapamycin; 4E-BP1, 4E-binding protein 1; ERK, extracellular signal-regulated kinase; and JNK, c-Jun N-terminal kinase.

although the main effect for TIME suggests a learning effect on strength adaptation for all groups. The increase in bilateral knee flexion 1-RM strength for LL + BFR (11%; 8 kg) is similar to a previous investigation in women (Seo et al., 2016), though was somewhat less than a previous report from our laboratory with a similar population and training protocol (18%; May et al., 2018). This may have been influenced due to differences in knee flexion exercises (i.e., prone knee flexion in the present study vs. seated previously) as the magnitude of hamstrings muscle adaptation appears influenced long muscle lengths (Maeo et al., 2021). Although, knee extension 1-RM strength was also lower than we have previously shown despite similar baseline strength. Overall, this may be attributable to differences in utilized exercise machinery for resistance exercises; pneumatic resistance machinery was used in the present study for training and testing versus traditional plate-loaded machinery for our previous investigation. There is little information available on comparable effectiveness of these training methods for muscle adaptation. Although, plate-loaded machinery utilizing traditional resistance training (non-BFRT) appears to elicit greater muscle power adaptation in older adults (Balachandran et al., 2017) and induces greater peripheral and central fatigue for inducing strength/hypertrophy adaptation (Peltonen et al., 2013). It is currently unclear how utilizing different exercise machinery would influence results for BFRT.

Training protocols in the current study did not induce meaningful skeletal muscle hypertrophy. The increase in muscle CSA was similar for all groups including CON (TIME main effect; **Table 2**). Across the two measurement slices (25 and 50% femur length), BFRT increased total muscle CSA on average by 3.6%, HLRT by 2.3%, and passive rest by 2%. Interestingly, the majority of this minor change occurred in the knee flexors, rather than the knee extensors where total muscle mass is greatest and largest strength adaptations were observed. This indicates that the contribution of hypertrophy to strength adaptation following BFRT was negligible and suggests that muscle groups may have different predispositions to hypertrophy in response to BFRT. Distribution of muscle fiber types is variable between different skeletal muscles (Elder et al., 1982). The hamstrings are predominantly composed of fast-twitch fibers (Evangelidis et al., 2017), and BFRT has been suggested to have enhanced activation of fast-twitch fibers, despite the low training load (Pearson and Hussain, 2015). Therefore, this fiber type distribution may be a contributing factor to the preferential hypertrophy of the knee flexors in LL + BFR within this study. It should also be noted that in CON only, body weight and BMI significantly increased from Session 1 to Session 21 (**Table 1**). Potentially, inactivity in CON participants during over the 7-week training period resulted in accumulation of fat mass. Increases to fat mass and muscle fat free mass can occur concurrently in untrained populations (Bray et al., 2012), potentially due to a requirement for greater muscle mass to support movement of an overall heavier body mass.

The failure of training interventions in this study to induce meaningful skeletal muscle hypertrophy despite significant strength improvement provides further evidence that BFRT, like HLRT, increases strength mostly *via* neurological mechanisms. This was somewhat expected as strength adaptations following BFRT can outweigh hypertrophy (Laurentino et al., 2012; Lixandrão et al., 2015). However, the exact neurological mechanisms by which skeletal muscle strength adaptations occur following BFRT remain unclear. To illustrate, strength adaptations have been observed following BFRT without increased central activation (Kubo et al., 2006; Cook et al., 2018), nerve conduction velocity (Clark et al., 2011), spinal excitability (Takarada et al., 2000b), or peripheral neuromuscular adaptation (*via* electrically evoked torque; Cook et al., 2018). Although, our laboratory has previously found increased motor-evoked potential following BFRT (Brandner et al., 2015). In addition, metabolic stress/accumulation has been suggested to drive BFRT-induced muscle hypertrophy (Pearson and Hussain, 2015). However, this may also be associated with neurological mechanisms for strength adaptation due to a suggested capacity for metabolic accumulation to augment muscle activation (Dankel et al., 2017).

Growth Marker Activation and Content

Post-exercise mTOR (Ser2448) phosphorylation was similar between acute HLRT and BFRT, and did not change at any time point. Therefore, different exposures to primary anabolic stimuli (i.e., mechanical tension and metabolic stress) *via* HLRT and BFRT had little influence on local mTOR activation. Unchanged post-exercise mTOR (Ser2448) phosphorylation supports some previous evidence for BFRT (Fujita et al., 2007; Wernbom et al., 2013). Although mTOR (Ser2448) activation may increase 1–2 h post-HLRT (Dreyer et al., 2006, 2008; Camera et al., 2010), which we did not observe. As such, the present intramuscular responses support the similar low rates of muscle hypertrophy. However, post-exercise mTOR (Ser2448) phosphorylation has also previously increased at 3 h post-exercise, and not during 1–2 h post-exercise (Fry et al., 2010; Gundermann et al., 2012), suggesting that the chosen biopsy intervals may not have been as optimal for this specific marker as for the others assessed.

4E-BP1 (Thr37/46) phosphorylation is often reduced during the catabolic state induced by resistance exercise (Dreyer et al., 2006, 2008; Deldicque et al., 2008). This reduction immediately post-exercise for HL was consistent with prior studies (Dreyer et al., 2006, 2008, 2010; Camera et al., 2010). Reduced 4E-BP1 (Thr37/46) phosphorylation during exercise is thought to stimulate tissue remodeling following exercise completion (Kraemer and Ratamess, 2005). As such, this downstream factor of the mTOR pathway likely has an anabolic effect following HLRT. 4E-BP1 (Thr37/46) phosphorylation in Session 1 for LL + BFR also followed the trend of the literature as it did not reduce immediately post-exercise (Fry et al., 2010; Gundermann et al., 2012). There are numerous mechanisms for activation of the mTOR pathway influenced by mechanical tension, including insulin-like growth factor-1 signaling and stretch-activated calcium ion channels and integrins (Philp et al., 2011). Potentially, the unchanged 4E-BP1 (Thr37/46) phosphorylation for LL + BFR may be related to insufficient mechanical tension during BFRT. However, it should be noted that 4E-BP1 (Thr37/46) phosphorylation immediately post-exercise in LL + BFR was significantly lower than CON and similar to HL. As such, an effect of BFRT cannot be discounted.

ERK 1/2 is activated through numerous sources; broadly including growth factors, hormones, cytokines, and integrins (Widegren et al., 2001). HLRT can increase ERK 1/2 (Thr202/Tyr204) phosphorylation immediately post-exercise (Karlsson et al., 2004; Deldicque et al., 2008; Drummond et al., 2008). In contrast, acute BFRT has only trended ($p < 0.1$) toward increasing ERK 1/2 (Thr202/Tyr204) phosphorylation

(Gundermann et al., 2012, 2014). Phosphorylation within the present study was similar in all groups as only a main effect for TIME (Session 21) was observed, suggesting the high mechanical loads of HL did not induce optimal ERK 1/2 signaling. Similarities in ERK 1/2 (Thr202/Tyr204) phosphorylation between HL and LL + BFR may be associated with the influence of an anabolic hormonal stimulus of BFRT (Takarada et al., 2000a), or the high variability that was observed in ERK 1/2 (Thr202/Tyr204) activation. In addition, this TIME main effect also reflects an upward trend in CON activation indicating an influence separate from resistance training. Multiple muscle biopsies, when taken from the same site, increase ERK1/2 (and JNK) phosphorylation (Aronson et al., 1998). While our biopsies were taken from different sites, the third and fourth biopsies were taken distally (~2 cm apart) from the first and second biopsies, respectively. It is possible that the localized biopsy damage to the muscle may be somewhat causative for the increased phosphorylation over time (TIME main effects) seen for MAPKs within this study.

JNK is linked to mRNA expression of transcription factors that modulate cell proliferation and DNA repair (Schoenfeld, 2010), and appears to increase in activation with rising muscle force output (Martineau and Gardiner, 2001). Although, the role of JNK in HLRT-induced hypertrophy is not yet established (Schoenfeld, 2016), minor increases to phosphorylation for all groups (TIME main effect) suggest JNK activity was not strongly dependent on the magnitude of mechanical tension/loading. Muscle damage appears to be an alternate stimulus for JNK activation and subsequent DNA repair (Schoenfeld, 2010). Muscle damage is negligible during BFRT (Loenneke et al., 2014), and JNK (Thr183/Tyr185) phosphorylation is much lower in concentric vs. eccentric resistance exercise (Boppart et al., 1999). As such, similarities to JNK activation between groups may have occurred due to low muscle damage induced by both resistance exercise modes during the sampling sessions.

To our knowledge, this is the first study to investigate the change in acute intramuscular growth marker signaling after completion of a BFRT program compared to pre-intervention. Phosphorylation of all chosen growth markers for LL + BFR did not differ between Session 1 and 21. This indicates that the response to exercise is preserved/consistent following a program of BFRT. However, 4E-BP1 (Thr37/46) phosphorylation immediately post-exercise in HL during Session 21 was lower than CON but, unlike Session 1, remained similar to pre-exercise. This is the only study we are aware of in which a traditional resistance training program inhibited the post-exercise reduction in 4E-BP1 (Thr37/46) phosphorylation in skeletal muscle. Dreyer et al. (2006) suggested catabolic activity increases during HLRT because protein synthesis requires ATP that is prioritized for muscle contraction. Resistance training can increase availability of ATP, creatine phosphate, and glycogen within muscle (MacDougall et al., 1977). HL may have increased ATP availability, reducing the requirement for ATP sparing and catabolic activity during exercise. Therefore, the greater phosphorylation of 4E-BP1 (Thr37/46) during Session 21 may suggest that the HLRT program may have reduced the stimulus for tissue remodeling, subsequently resulting in a low rate of muscle hypertrophy. Conversely, though progressive overload was enforced in this study, it is possible that the mechanical stress of HLRT simply reduced as participants became more familiar with the knee flexion and extension exercises.

Limitations

The observed growth marker protein activation was minor. This can be attributed to minor muscle hypertrophy within the present study and so may not be representative of the intramuscular environment of training protocols with greater physical muscle adaptation. The reported protein activation is also dependent on selection of the vastus lateralis as the chosen site of muscle biopsies. The measured intramuscular activation of growth marker proteins is only a representative snapshot of activity within the knee extensors, where knee extensor muscle CSA remained unchanged at 25% femur length. Furthermore, this was only a preliminary time course comparison of protein growth marker signaling between training groups. Changes to intramuscular signaling may be more clearly observed in future if the Akt pathway was further characterized. For example, post-exercise changes to activation of growth marker proteins within the downstream FoxO pathway were not assessed despite these signaling cascades having a major role in catabolic activity within skeletal muscle (Accili and Arden, 2004).

The minor skeletal muscle hypertrophy for training groups observed in the present study reflects a likely neurological mechanism for strength adaptation during shorter training programs. However, the low magnitude of change was not expected. We identified four participants across training groups that were non-responders across multiple measurement sites (i.e., 25% length, 50% length, flexors, and extensors). As global non-responders to exercise are unlikely to exist but rather benefit from a more individualized response (Pickering and Kiely, 2019), our study protocol was perhaps overly rigid. Exercise prescription may have benefited from greater flexibility in programming variables, such as rest period durations, the applied BFR pressure, and progressive overload.

CONCLUSION

This study found that the magnitudes and mechanisms for strength adaptation and intramuscular anabolic activity following a 7-week BFRT program are similar to those for moderately heavy-load resistance training. Minor hypertrophy with large strength adaptation reaffirms the contribution of the neuromuscular system in driving strength adaptation in response to resistance exercise of differing forms. This occurred despite differences in the nature of training methods, such as exercise load or induced metabolic stress, indicating consistent mechanisms by which muscle adapts to resistance-based exercise programs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Deakin University Human Ethics Advisory Group − Deakin University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM, SW, PG, and AR conceived and designed the research, wrote, edited, and approved the manuscript. AM conducted the experiments. AM and SW analyzed the data. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported only by local funds made available by the School of Exercise and Nutrition Sciences, Faculty of Health, Deakin University, Victoria, Australia.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2022.837697/full#supplementary-material

REFERENCES

Abe, T., Kearns, C. F., and Sato, Y. (2006). Muscle size and strength are increased following walk training with restricted venous blood flow from the leg muscle, Kaatsu-walk training. *J. Appl. Physiol.* 100, 1460–1466. doi: 10.1152/japplphysiol.01267.2005

Accili, D., and Arden, K. C. (2004). FoxOs at the crossroads of cellular metabolism, differentiation, and transformation. *Cell* 117, 421–426. doi: 10.1016/S0092-8674(04)00452-0

American College of Sports Medicine (2009). Progression models in resistance training for healthy adults. *Med. Sci. Sports Exerc.* 41, 687–708. doi: 10.1249/MSS.0b013e3181915670

Aronson, D., Violan, M. A., Dufresne, S. D., Zangen, D., Fielding, R. A., and Goodyear, L. J. (1997). Exercise stimulates the mitogen-activated protein kinase pathway in human skeletal muscle. *J. Clin. Invest.* 99, 1251–1257. doi: 10.1172/JCI119282

Aronson, D., Wojtaszewski, J. F. P., Thorell, A., Nygren, J., Zangen, D., Richter, E. A., et al. (1998). Extracellular-regulated protein kinase cascades are activated in response to injury in human skeletal muscle. *Am. J. Phys. Cell Physiol.* 275, C555–C561. doi: 10.1152/ajpcell.1998.275.2.C555

Balachandran, A. T., Gandia, K., Jacobs, K. A., Streiner, D. L., Eltoukhy, M., and Signorile, J. F. (2017). Power training using pneumatic machines vs. plate-loaded machines to improve muscle power in older adults. *Exp. Gerontol.* 98, 134–142. doi: 10.1016/j.exger.2017.08.009

Bergström, J. (1962). Muscle electrolytes in man - determined by neutron activation analysis on needle biopsy specimens - study on normal subjects, kidney patients, and patients with chronic diarrhoea. *Scand. J. Clin. Lab. Invest.* 14(Suppl. 68), 1–110.

Boppart, M. D., Aronson, D., Gibson, L., Roubenoff, R., Abad, L. W., Bean, J., et al. (1999). Eccentric exercise markedly increases c-Jun NH(2)-terminal kinase activity in human skeletal muscle. *J. Appl. Physiol.* 87, 1668–1673. doi: 10.1152/jappl.1999.87.5.1668

Brandner, C. R., Warmington, S. A., and Kidgell, D. J. (2015). Corticomotor excitability is increased following an acute bout of blood flow restriction resistance exercise. *Front. Hum. Neurosci.* 9:652. doi: 10.3389/fnhum.2015.00652

Bray, G. A., Smith, S. R., de Jonge, L., Xie, H., Rood, J., Martin, C. K., et al. (2012). Effect of dietary protein content on weight gain, energy expenditure, and body composition during overeating: a randomized controlled trial. *JAMA* 307, 47–55. doi: 10.1001/jama.2011.1918

Camera, D. M., Edge, J., Short, M. J., Hawley, J. A., and Coffey, V. G. (2010). Early time course of Akt phosphorylation after endurance and resistance exercise. *Med. Sci. Sports Exerc.* 42, 1843–1852. doi: 10.1249/MSS.0b013e3181d964e4

Clark, B. C., Manini, T. M., Hoffman, R. L., Williams, P. S., Guiler, M. K., Knutson, M. J., et al. (2011). Relative safety of 4 weeks of blood flow-restricted resistance exercise in young, healthy adults. *Scand. J. Med. Sci. Sports* 21, 653–662. doi: 10.1111/j.1600-0838.2010.01100.x

Cook, S. B., LaRoche, D. P., Villa, M. R., Barile, H., and Manini, T. M. (2017). Blood flow restricted resistance training in older adults at risk of mobility limitations. *Exp. Gerontol.* 99, 138–145. doi: 10.1016/j.exger.2017.10.004

Cook, S. B., Scott, B. R., Hayes, K. L., and Murphy, B. G. (2018). Neuromuscular adaptations to low-load blood flow restricted resistance training. *J. Sports Sci. Med.* 17, 66–73.

Dankel, S. J., Buckner, S. L., Jessee, M. B., Grant Mouser, J., Mattocks, K. T., Abe, T., et al. (2018). Correlations do not show cause and effect: not even for changes in muscle size and strength. *Sports Med.* 48, 1–6. doi: 10.1007/s40279-017-0774-3

Dankel, S. J., Mattocks, K. T., Jessee, M. B., Buckner, S. L., Mouser, J. G., and Loenneke, J. P. (2017). Do metabolites that are produced during resistance exercise enhance muscle hypertrophy? *Eur. J. Appl. Physiol.* 117, 2125–2135. doi: 10.1007/s00421-017-3690-1

Deldicque, L., Atherton, P., Patel, R., Theisen, D., Nielens, H., Rennie, M. J., et al. (2008). Decrease in Akt/PKB signalling in human skeletal muscle by resistance exercise. *Eur. J. Appl. Physiol.* 104, 57–65. doi: 10.1007/s00421-008-0786-7

Doube, M., Klosowski, M. M., Arganda-Carreras, I., Cordelieres, F. P., Dougherty, R. P., Jackson, J. S., et al. (2010). BoneJ: free and extensible bone image analysis in ImageJ. *Bone* 47, 1076–1079. doi: 10.1016/j.bone.2010.08.023

Dreyer, H. C., Drummond, M. J., Pennings, B., Fujita, S., Glynn, E. L., Chinkes, D. L., et al. (2008). Leucine-enriched essential amino acid and carbohydrate ingestion following resistance exercise enhances mTOR signaling and protein synthesis in human muscle. *Am. J. Physiol. Endocrinol. Metab.* 294, e392–e400. doi: 10.1152/ajpendo.00582.2007

Dreyer, H. C., Fujita, S., Cadenas, J. G., Chinkes, D. L., Volpi, E., and Rasmussen, B. B. (2006). Resistance exercise increases AMPK activity and reduces 4E-BP1 phosphorylation and protein synthesis in human skeletal muscle. *J. Physiol.* 576, 613–624. doi: 10.1113/jphysiol.2006.113175

Dreyer, H. C., Fujita, S., Glynn, E. L., Drummond, M. J., Volpi, E., and Rasmussen, B. B. (2010). Resistance exercise increases leg muscle protein synthesis and mTOR signalling independent of sex. *Acta Physiol (Oxford)* 199, 71–81. doi: 10.1111/j.1748-1716.2010.02074.x

Drummond, M. J., Dreyer, H. C., Pennings, B., Fry, C. S., Dhanani, S., Dillon, E. L., et al. (2008). Skeletal muscle protein anabolic response to resistance exercise and essential amino acids is delayed with aging. *J. Appl. Physiol.* 104, 1452–1461. doi: 10.1152/japplphysiol.00021.2008

Elder, G. C., Bradbury, K., and Roberts, R. (1982). Variability of fiber type distributions within human muscles. *J. Appl. Physiol.* 53, 1473–1480. doi: 10.1152/jappl.1982.53.6.1473

Evangelidis, P. E., Massey, G. J., Ferguson, R. A., Wheeler, P. C., Pain, M. T. G., and Folland, J. P. (2017). The functional significance of hamstrings composition: is it really a "fast" muscle group? *Scand. J. Med. Sci. Sports* 27, 1181–1189. doi: 10.1111/sms.12786

Evans, W. J., Phinney, S. D., and Young, V. R. (1982). Suction applied to a muscle biopsy maximizes sample size. *Med. Sci. Sports Exerc.* 14, 101–102.

Farnfield, M. M., Breen, L., Carey, K. A., Garnham, A., and Cameron-Smith, D. (2012). Activation of mTOR signalling in young and old human skeletal muscle in response to combined resistance exercise and whey protein ingestion. *Appl. Physiol. Nutr. Metab.* 37, 21–30. doi: 10.1139/h11-132

Fry, C. S., Glynn, E. L., Drummond, M. J., Timmerman, K. L., Fujita, S., Abe, T., et al. (2010). Blood flow restriction exercise stimulates mTORC1 signaling and muscle protein synthesis in older men. *J. Appl. Physiol.* 108, 1199–1209. doi: 10.1152/japplphysiol.01266.2009

Fujita, S., Abe, T., Drummond, M. J., Cadenas, J. G., Dreyer, H. C., Sato, Y., et al. (2007). Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *J. Appl. Physiol.* 103, 903–910. doi: 10.1152/japplphysiol.00195.2007

Grønfeldt, B. M., Lindberg Nielsen, J., Mieritz, R. M., Lund, H., and Aagaard, P. (2020). Effect of blood-flow restricted vs heavy-load strength training on muscle strength: systematic review and meta-analysis. *Scand. J. Med. Sci. Sports* 30, 837–848. doi: 10.1111/sms.13632

Gundermann, D. M., Fry, C. S., Dickinson, J. M., Walker, D. K., Timmerman, K. L., Drummond, M. J., et al. (2012). Reactive hyperemia is not responsible for stimulating muscle protein synthesis following blood flow restriction exercise. *J. Appl. Physiol.* 112, 1520–1528. doi: 10.1152/japplphysiol.01267.2011

Gundermann, D. M., Walker, D. K., Reidy, P. T., Borack, M. S., Dickinson, J. M., Volpi, E., et al. (2014). Activation of mTORC1 signaling and protein synthesis in human muscle following blood flow restriction exercise is inhibited by rapamycin. *Am. J. Physiol. Endocrinol. Metab.* 306, e1198–e1204. doi: 10.1152/ajpendo.00600.2013

Hill, E. C., Housh, T. J., Keller, J. L., Smith, C. M., Schmidt, R. J., and Johnson, G. O. (2018). Early phase adaptations in muscle strength and hypertrophy as a result of low-intensity blood flow restriction resistance training. *Eur. J. Appl. Physiol.* 118, 1831–1843. doi: 10.1007/s00421-018-3918-8

Jessee, M. B., Mattocks, K. T., Buckner, S. L., Dankel, S. J., Mouser, J. G., Abe, T., et al. (2018). Mechanisms of blood flow restriction: The new testament. *Tech. Orthop.* 33, 72–79. doi: 10.1097/BTO.0000000000000252

Karabulut, M., Abe, T., Sato, Y., and Bemben, M. G. (2009). The effects of low-intensity resistance training with vascular restriction on leg muscle strength in older men. *Eur. J. Appl. Physiol.* 108, 147–155. doi: 10.1007/s00421-009-1204-5

Karlsson, H. K., Nilsson, P. A., Nilsson, J., Chibalin, A. V., Zierath, J. R., and Blomstrand, E. (2004). Branched-chain amino acids increase p70S6k phosphorylation in human skeletal muscle after resistance exercise. *Am. J. Physiol. Endocrinol. Metab.* 287, e1–e7. doi: 10.1152/ajpendo.00430.2003

Kraemer, W. J., Fleck, S. J., and Evans, W. J. (1996). Strength and power training: physiological mechanisms of adaptation. *Exerc. Sport Sci. Rev.* 24, 363–397.

Kraemer, W. J., and Ratamess, N. A. (2005). Hormonal responses and adaptations to resistance exercise and training. *Sports Med.* 35, 339–361. doi: 10.2165/00007256-200535040-00004

Kubo, K., Komuro, T., Ishiguro, N., Tsunoda, N., Sato, Y., Ishii, N., et al. (2006). Effects of low-load resistance training with vascular occlusion on the mechanical properties of muscle and tendon. *J. Appl. Biomech.* 22, 112–119. doi: 10.1123/jab.22.2.112

Laurentino, G. C., Ugrinowitsch, C., Roschel, H., Aoki, M. S., Soares, A. G., Neves, M., et al. (2012). Strength training with blood flow restriction diminishes myostatin gene expression. *Med. Sci. Sports Exerc.* 44, 406–412. doi: 10.1249/MSS.0b013e318233b4bc

Léger, B., Cartoni, R., Praz, M., Lamon, S., Dériaz, O., Crettenand, A., et al. (2006). Akt signalling through GSK-3β, mTOR and Foxo1 is involved in human skeletal muscle hypertrophy and atrophy. *J. Physiol.* 576, 923–933. doi: 10.1113/jphysiol.2006.116715

Lixandrão, M. E., Ugrinowitsch, C., Berton, R., Vechin, F. C., Conceição, M. S., Damas, F., et al. (2018). Magnitude of muscle strength and mass adaptations between high-load resistance training versus low-load resistance training associated with blood-flow restriction: a systematic review and meta-analysis. *Sports Med.* 48, 361–378. doi: 10.1007/s40279-017-0795-y

Lixandrão, M. E., Ugrinowitsch, C., Laurentino, G., Libardi, C. A., Aihara, A. Y., Cardoso, F. N., et al. (2015). Effects of exercise intensity and occlusion pressure after 12 weeks of resistance training with blood-flow restriction. *Eur. J. Appl. Physiol.* 115, 2471–2480. doi: 10.1007/s00421-015-3253-2

Loenneke, J. P., Thiebaud, R. S., and Abe, T. (2014). Does blood flow restriction result in skeletal muscle damage? A critical review of available evidence. *Scand. J. Med. Sci. Sports* 24, E415–E422. doi: 10.1111/sms.12210

MacDougall, J. D., Ward, G. R., Sale, D. G., and Sutton, J. R. (1977). Biochemical adaptation of human skeletal muscle to heavy resistance training and immobilization. *J. Appl. Physiol. Respir. Environ. Exerc. Physiol.* 43, 700–703. doi: 10.1152/jappl.1977.43.4.700

Maeo, S., Huang, M., Wu, Y., Sakurai, H., Kusagawa, Y., Sugiyama, T., et al. (2021). Greater hamstrings muscle hypertrophy but similar damage protection after training at long versus short muscle lengths. *Med. Sci. Sports Exerc.* 53, 825–837. doi: 10.1249/MSS.0000000000002523

Martineau, L. C., and Gardiner, P. F. (2001). Insight into skeletal muscle mechanotransduction: MAPK activation is quantitatively related to tension. *J. Appl. Physiol.* 91, 693–702. doi: 10.1152/jappl.2001.91.2.693

Martín-Hernández, J., Marín, P. J., Menéndez, H., Ferrero, C., Loenneke, J. P., and Herrero, A. J. (2013). Muscular adaptations after two different volumes of blood flow-restricted training. *Scand. J. Med. Sci. Sports* 23, e114–e120. doi: 10.1111/sms.12036

May, A. K., Russell, A. P., and Warmington, S. A. (2018). Lower body blood flow restriction training may induce remote muscle strength adaptations in an active unrestricted arm. *Eur. J. Appl. Physiol.* 118, 617–627. doi: 10.1007/s00421-018-3806-2

Ozaki, H., Yasuda, T., Ogasawara, R., Sakamaki-Sunaga, M., Naito, H., and Abe, T. (2013). Effects of high-intensity and blood flow-restricted low-intensity resistance training on carotid arterial compliance: role of blood pressure during training sessions. *Eur. J. Appl. Physiol.* 113, 167–174. doi: 10.1007/s00421-012-2422-9

Pearson, S. J., and Hussain, S. R. (2015). A review on the mechanisms of blood-flow restriction resistance training-induced muscle hypertrophy. *Sports Med.* 45, 187–200. doi: 10.1007/s40279-014-0264-9

Peltonen, H., Häkkinen, K., and Avela, J. (2013). Neuromuscular responses to different resistance loading protocols using pneumatic and weight stack devices. *J. Electromyogr. Kinesiol.* 23, 118–124. doi: 10.1016/j.jelekin.2012.08.017

Philp, A., Hamilton, D. L., and Baar, K. (2011). Signals mediating skeletal muscle remodeling by resistance exercise: PI3-kinase independent activation of mTORC1. *J. Appl. Physiol.* 110, 561–568. doi: 10.1152/japplphysiol.00941.2010

Pickering, C., and Kiely, J. (2019). Do non-responders to exercise exist-and if so, what should we do about them? *Sports Med.* 49, 1–7. doi: 10.1007/s40279-018-01041-1

Rantalainen, T., Duckham, R. L., Suominen, H., Heinonen, A., Alen, M., and Korhonen, M. T. (2014). Tibial and fibular mid-shaft bone traits in young and older sprinters and non-athletic men. *Calcif. Tissue Int.* 95, 132–140. doi: 10.1007/s00223-014-9881-4

Rommel, C., Bodine, S. C., Clarke, B. A., Rossman, R., Nunez, L., Stitt, T. N., et al. (2001). Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. *Nat. Cell Biol.* 3, 1009–1013. doi: 10.1038/ncb1101-1009

Schoenfeld, B. J. (2010). The mechanisms of muscle hypertrophy and their application to resistance training. *J. Strength Cond. Res.* 24, 2857–2872. doi: 10.1519/JSC.0b013e3181e840f3

Schoenfeld, B. (2016). *Science and Development of Muscle Hypertrophy*. Champaign, IL: Human Kinetics.

Scott, B. R., Loenneke, J. P., Slattery, K. M., and Dascombe, B. J. (2015). Exercise with blood flow restriction: an updated evidence-based approach for enhanced muscular development. *Sports Med.* 45, 313–325. doi: 10.1007/s40279-014-0288-1

Seo, D.-I., So, W.-Y., and Sung, D. J. (2016). Effect of a low-intensity resistance exercise programme with blood flow restriction on growth hormone and insulin-like growth factor-1 levels in middle-aged women. *S. Afr. J. Sports Med.* 38, 167–177.

Seynnes, O. R., de Boer, M., and Narici, M. V. (2007). Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training. *J. Appl. Physiol.* 102, 368–373. doi: 10.1152/japplphysiol.00789.2006

Takada, S., Okita, K., Suga, T., Omokawa, M., Kadoguchi, T., Sato, T., et al. (2012). Low-intensity exercise can increase muscle mass and strength proportionally to enhanced metabolic stress under ischemic conditions. *J. Appl. Physiol.* 113, 199–205. doi: 10.1152/japplphysiol.00149.2012

Takarada, Y., Nakamura, Y., Aruga, S., Onda, T., Miyazaki, S., and Ishii, N. (2000a). Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J. Appl. Physiol.* 88, 61–65. doi: 10.1152/jappl.2000.88.1.61

Takarada, Y., Takazawa, H., Sato, Y., Takebayashi, S., Tanaka, Y., and Ishii, N. (2000b). Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. *J. Appl. Physiol.* 88, 2097–2106. doi: 10.1152/jappl.2000.88.6.2097

Thompson, W., Gordon, N., and Pescatello, L. (2010). *ACSM's Guidelines for Exercise Testing and Prescription*. Philadelphia: Lippincott Williams & Wilkins.

Vechin, F. C., Libardi, C. A., Conceição, M. S., Damas, F. R., Lixandrão, M. E., Berton, R. P. B., et al. (2015). Comparisons between low-intensity resistance training with blood flow restriction and high-intensity resistance training on quadriceps muscle mass and strength in elderly. *J. Strength Cond. Res.* 29, 1071–1076. doi: 10.1519/JSC.0000000000000703

Wang, X., and Proud, C. G. (2006). The mTOR pathway in the control of protein synthesis. *Physiology (Bethesda)* 21, 362–369. doi: 10.1152/physiol.00024.2006

Wernbom, M., Apro, W., Paulsen, G., Nilsen, T. S., Blomstrand, E., and Raastad, T. (2013). Acute low-load resistance exercise with and without blood flow restriction increased protein signalling and number of satellite cells in human skeletal muscle. *Eur. J. Appl. Physiol.* 113, 2953–2965. doi: 10.1007/s00421-013-2733-5

Widegren, U., Ryder, J. W., and Zierath, J. R. (2001). Mitogen-activated protein kinase signal transduction in skeletal muscle: effects of exercise and muscle contraction. *Acta Physiol. Scand.* 172, 227–238. doi: 10.1046/j.1365-201x.2001.00855.x

Williamson, D., Gallagher, P., Harber, M., Hollon, C., and Trappe, S. (2003). Mitogen-activated protein kinase (MAPK) pathway activation: effects of age and acute exercise on human skeletal muscle. *J. Physiol.* 547, 977–987. doi: 10.1113/jphysiol.2002.036673

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Physiology

ORIGINAL RESEARCH
published: 11 March 2022
doi: 10.3389/fphys.2022.800155

Physiological Responses to Acute Cycling With Blood Flow Restriction

Matthew A. Kilgas[1,2], Tejin Yoon[3], John McDaniel[4,5], Kevin C. Phillips[2] and Steven J. Elmer[2]*

[1]School of Health and Human Performance, Northern Michigan University, Marquette, MI, United States, [2]Department of Kinesiology and Integrative Physiology, Michigan Technological University, Houghton, MI, United States, [3]Department of Physical Education, Kangwon National University, Chuncheon, South Korea, [4]Department of Exercise Physiology, Kent State University, Kent, OH, United States, [5]Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, OH, United States

Aerobic exercise with blood flow restriction (BFR) can improve muscular function and aerobic capacity. However, the extent to which cuff pressure influences acute physiological responses to aerobic exercise with BFR is not well documented. We compared blood flow, tissue oxygenation, and neuromuscular responses to acute cycling with and without BFR. Ten participants completed four intermittent cycling (6 × 2 min) conditions: low-load cycling (LL), low-load cycling with BFR at 60% of limb occlusion pressure (BFR60), low-load cycling with BFR at 80% of limb occlusion pressure (BFR80), and high-load cycling (HL). Tissue oxygenation, cardiorespiratory, metabolic, and perceptual responses were assessed during cycling and blood flow was measured during recovery periods. Pre- to post-exercise changes in knee extensor function were also assessed. BFR60 and BFR80 reduced blood flow (~33 and ~50%, respectively) and tissue saturation index (~5 and ~15%, respectively) when compared to LL (all $p < 0.05$). BFR60 resulted in lower VO_2, heart rate, ventilation, and perceived exertion compared to HL (all $p < 0.05$), whereas BFR80 resulted in similar heart rates and exertion to HL (both $p > 0.05$). BFR60 and BFR80 elicited greater pain compared to LL and HL (all $p < 0.05$). After exercise, knee extensor torque decreased by ~18 and 40% for BFR60 and BFR80, respectively (both $p < 0.05$), and was compromised mostly through peripheral mechanisms. Cycling with BFR increased metabolic stress, decreased blood flow, and impaired neuromuscular function. However, only BFR60 did so without causing very severe pain (>8 on pain intensity scale). Cycling with BFR at moderate pressure may serve as a potential alternative to traditional high-intensity aerobic exercise.

Keywords: vascular occlusion, Kaatsu, aerobic exercise, fatigue, arterial blood flow, functional near inferred spectroscopy

OPEN ACCESS

Edited by:
Adam Zajac,
University School of Physical Education in Wroclaw, Poland

Reviewed by:
Bruce Paton,
Institute of Sport Exercise and Health, United Kingdom
Michael E. Tschakovsky,
Queen's University, Canada

****Correspondence:***
Matthew A. Kilgas
mkilgas@nmu.edu

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *22 October 2021*
Accepted: *15 February 2022*
Published: *11 March 2022*

Citation:
Kilgas MA, Yoon T, McDaniel J, Phillips KC and Elmer SJ (2022) Physiological Responses to Acute Cycling With Blood Flow Restriction. Front. Physiol. 13:800155. doi: 10.3389/fphys.2022.800155

INTRODUCTION

Exercise with blood flow restriction (BFR) offers an alternative method for increasing muscle size and strength (Nakajima et al., 2006; Loenneke et al., 2012b). This exercise uses a pressurized cuff or tourniquet to restrict blood flow to and from the working muscles (Scott et al., 2015). While BFR is usually combined with low-load resistance exercise (e.g., 20–30% of one repetition maximum; Patterson and Brandner, 2017), it has also been used with low-intensity aerobic exercise (e.g., <50% of VO_{2peak}). Aerobic exercise with BFR increases muscle size and strength as well as VO_{2peak}, time until exhaustion, and onset of blood lactate accumulation (Abe et al., 2010; Corvino et al., 2014; De Oliveira et al., 2016). Thus, aerobic exercise with BFR may offer a unique stimulus for improving both muscular function and aerobic capacity.

Selection of cuff pressure is critical for administering exercise with BFR safely and effectively. According to a recent BFR position stand (Patterson et al., 2019), cuff pressures between 40 and 80% of an individual's resting limb occlusion pressure are recommended. Application of pressure within this range is thought to improve muscular and cardiovascular function by augmenting metabolite accumulation and local hypoxia (Scott et al., 2014; Cayot et al., 2016), and inducing cell swelling (Loenneke et al., 2014). It has been proposed that these metabolic changes accelerate fatigue leading to preferential type II fiber recruitment (Yasuda et al., 2009), increase serum growth hormone (Pierce et al., 2006), and stimulate angiogenesis, mitochondrial biogenesis (Conceicao et al., 2019), and increase arterial diameter (Christiansen et al., 2020). While cuff pressures are typically set as a percentage of resting limb occlusion pressure, the impact they have on the magnitude of blood flow during exercise and intermittent recovery periods is not well established. We previously assessed changes in blood flow (*via* Doppler ultrasound) and tissue oxygenation (*via* near-infrared spectroscopy) while performing rhythmic handgrip (Kilgas et al., 2019) and knee extension (Singer et al., 2020) contractions across a range of cuff pressures. Our results indicated that pressures of 60 and 80% of limb occlusion pressure decreased blood flow and tissue saturation and increased concentrations of deoxyhemoglobin. Together, these findings support the notion that moderate cuff pressures increase metabolic stress and metabolite accumulation without completely occluding blood flow and compromising individual safety. It is unclear if these changes for resistance-based exercise with BFR can be applied to aerobic exercise with BFR because of differences in blood pressure, cardiac output, muscle mass, cyclical nature of the movement, and time under occlusion between the two exercise modes.

Reductions in blood flow during BFR exercise also contribute to the development of neuromuscular fatigue (i.e., reduction in maximal voluntary torque; Bigland-Ritchie and Woods, 1984). These reductions in maximal voluntary torque could be due to factors that reside in the brain and spinal column (central fatigue), the muscles themselves (peripheral fatigue), and/or some combination of the two (central and peripheral fatigue). Typically, greater neuromuscular fatigue is associated with increased growth hormone concentrations which may play a role in training adaptations (Hakkinen and Pakarinen, 1993; Pierce et al., 2006). Previous authors (Karabulut et al., 2010; Cook et al., 2013; Husmann et al., 2018) have reported impairments in neuromuscular function following knee extension exercise with BFR which were attributed to both central and peripheral mechanisms. Changes in neuromuscular function following aerobic exercise with BFR, however, are mixed with some authors reporting reduced knee extensor torque after submaximal (Kim et al., 2015) and supramaximal (Willis et al., 2018) cycling but not after walking (Ogawa et al., 2012). Given these varied results and the task-specific nature of fatigue (Bigland-Ritchie et al., 1995), more work is needed to confirm how cuff pressure influences the development of fatigue during aerobic exercise with BFR.

To date, the extent to which cuff pressure influences acute physiological responses to aerobic exercise with BFR is not well understood. Therefore, the purpose of this study was to compare changes in blood flow, tissue oxygenation, and neuromuscular function to acute cycling exercise with and without BFR. We hypothesized that cycling with BFR (60% of limb occlusion pressure) would decrease blood flow and tissue saturation index and increase concentrations of deoxyhemoglobin. These responses would be further exacerbated by increased cuff pressure (80% of limb occlusion pressure). We also hypothesized that cycling with BFR would impair end exercise maximal knee extensor isometric torque. Based on previous reports (Karabulut et al., 2010; Cook et al., 2013; Husmann et al., 2018), we hypothesized that these impairments in neuromuscular function would be to central and peripheral mechanisms. Finally, with these anticipated physiological changes, we also expected that perceived exertion and muscle pain would increase during cycling with BFR.

MATERIALS AND METHODS

Participants

Ten active men between 18 and 44 years volunteered to participate in this study (**Table 1**). All participants self-reported that they performed aerobic exercise at moderate to high-intensity for at least 150 min/week, which is consistent with ACSM guidelines (Garber et al., 2011). Body composition and lower limb lean mass were assessed using dual-energy X-ray absorptiometry (Discovery Wi, Hologic Inc., Marlborough, MA, United States). Participants were excluded from the study if they used nicotine products, had diabetes, or had any cardiopulmonary disorders. Based on pilot data, *a priori* power analysis revealed a sample of 10 participants was adequate to detect a change in blood flow between the BFR conditions (effect size $d = 0.57$) given an alpha of 0.05, with a power of 0.8. Following the initial screening, participants were informed of the purpose of the study, the risks involved, and gave informed written consent. This study was approved by the Institutional Review Board at Michigan Technological University.

TABLE 1 | Participant characteristics.

Height (cm)	179 ± 6
Body mass (kg)	79 ± 8
Age (year)	26 ± 6
Body fat (%)	18 ± 4
Lower limb lean mass (kg)	21 ± 2
VO_{2peak} (ml/kg/min)	53 ± 6
Heart rate peak (b/min)	191 ± 9
Limb occlusion pressure (mmHg)	208 ± 19

Values are expressed as mean ± SD. LLLM, Lower limb lean mass.

Study Overview

In this investigation, we used a single group repeated measures design. Participants reported to the laboratory on five separate days separated by at least 48 h. Participants were instructed to avoid vigorous physical activity for 24 h prior to each session. All laboratory visits were performed at approximately the same time of day, in a thermoneutral environment. During the initial laboratory visit, participants were familiarized with the measurement of neuromuscular function, performed a submaximal cycling protocol, and completed a graded exercise test for the determination of peak oxygen consumption (VO_{2peak}). For the remaining experimental laboratory visits, participants completed one of the four cycling conditions in a randomized order (i.e., simple randomization). The conditions consisted of: (1) low-load cycling at 40% VO_{2peak} without BFR (LL), (2) low-load cycling at 40% VO_{2peak} with BFR set at 60% limb occlusion pressure (BFR60), (3) low-load cycling at 40% VO_{2peak} with BFR set at 80% occlusion pressure (BFR80), and (4) high-load cycling at 80% VO_{2peak} without BFR (HL). These conditions were chosen as they are representative of current guidelines for aerobic exercise with and without BFR (Garber et al., 2011; Patterson et al., 2019) and are similar to previous investigations which have been shown to improve muscular function and aerobic capacity following cycling training with BFR (Abe et al., 2010; Corvino et al., 2014; De Oliveira et al., 2016). Prior to each cycling trial, baseline neuromuscular function was assessed, and limb occlusion pressure was identified. Participants then completed an intermittent cycling protocol (six sets of 2 min cycling intervals with 1 min recovery between sets). Tissue oxygenation and gas exchange data were recorded throughout the cycling trial. Blood flow was measured during the recovery periods. Immediately after the cycling trial, neuromuscular function was assessed again (**Figure 1**).

Oxygen Consumption and Peak Aerobic Power

To establish a linear relationship between steady-state VO_2 and power output, participants completed a submaximal cycling protocol on an electromagnetically braked cycle ergometer (Velotron Elite; RacerMate Inc., Seattle, WA, United States). Specifically, participants cycled at 40, 80, 120, and 160 W for 4 min using a self-selected pedaling rate. Gas exchange data were measured continuously using open-circuit spirometry (True Max 2,400; Parvo Medics, Sandy, UT, United States). The metabolic measurement system was calibrated with a 3 L calibration syringe and medical gases of known concentrations (16.00% O_2, 4.00% CO_2, and balanced N_2). Heart rate was measured continuously using a Polar transmitter (Polar Electro OY, Kempele, Finland). Gas exchange and heart data were averaged every 15 s throughout the test. After a 15 min break, participants then performed a graded exercise test until task failure as described by Lucia et al. (1999). The protocol began at 40 W and increased 5 W every 12 s. The test was terminated voluntarily by the participant, or when pedaling rate could no longer be maintained above 70 rpm, despite verbal encouragement. The highest 30 s average of VO_2 and heart rate achieved during the test were recorded. Power outputs that elicited 40 and 80% of VO_{2peak} were estimated by interpolating the linear relationship between VO_2 and power output.

Cycling Exercise

Prior to the intermittent cycling protocol, participants rested on the cycle ergometer for 5 min for collection of baseline responses. Following this baseline period, the cuff was inflated to 60 or 80% limb occlusion pressure (BFR conditions only) while participants rested for 1 min. Note that, for the LL and HL cycling conditions, 1 min of rest was also provided. Subsequently, participants completed six sets of 2 min cycling intervals with 1 min between sets. An intermittent cycling protocol was selected because previous research suggests that work-rest periods while keeping the pressure cuff inflated has benefits over continuous cycling with BFR (Corvino et al., 2017). For the BFR cycling conditions, blood flow was restricted in each leg using a 10 cm wide nylon pneumatic cuff (Hokanson, Belleview, WA, United States) wrapped around the thigh at the most proximal location. The cuff pressure was set and maintained using a rapid cuff inflator (Hokanson, Belleview, WA, United States). This system is commonly used for administering BFR and its important to acknowledge that pressure set on the system can differ slightly from the actual cuff-to-limb interface pressure (Hughes et al., 2018b). The pressure in the cuff was sustained throughout the entire cycling protocol and deflated immediately after the participant completed the last set of cycling.

Blood Flow

Blood flow was measured in the superficial femoral artery just distal to the pressure cuff. Blood velocity (V_{mean}) and vessel diameter (V_d) were measured with a Logiq *E* ultrasound system (General Electric Medical Systems, Milwaukee, WI, United States) equipped with a linear array transducer operating at an imaging frequency of 12 MHz and Doppler frequency of 5 MHz. Doppler pulse wave spectrum and ultrasound images were continuously recorded throughout each time period. Vessel diameters were determined by averaging the perpendicular distance between the superficial and deep walls of the superficial femoral artery at three nonconsecutive R waves during the last 15 s of each recording. Measurements of V_{mean} were obtained with the probe positioned to maintain an insonation angle of ≤60°. Mean blood velocity was averaged across 15 s intervals throughout the recording. Importantly, blood velocity data obtained with Doppler ultrasound are reliable (Nyberg et al., 2018) which is notable given the complex nature of blood velocity during dynamic muscle contractions. Using arterial diameter (V_d) and mean blood velocity (V_{mean}), blood flow was calculated as $\text{Blood flow} = V_{mean} \times \pi \times \frac{V_d}{2} \times 60$ as described by Wray et al. (2011). Blood flow was averaged throughout the 1 min recovery interval.

Limb occlusion pressure was determined while the participant was seated on the cycle ergometer. Their right foot was positioned on a stool next to the ergometer. Their hip was abducted slightly and their knee angle was ~90°. The pressure cuff was wrapped

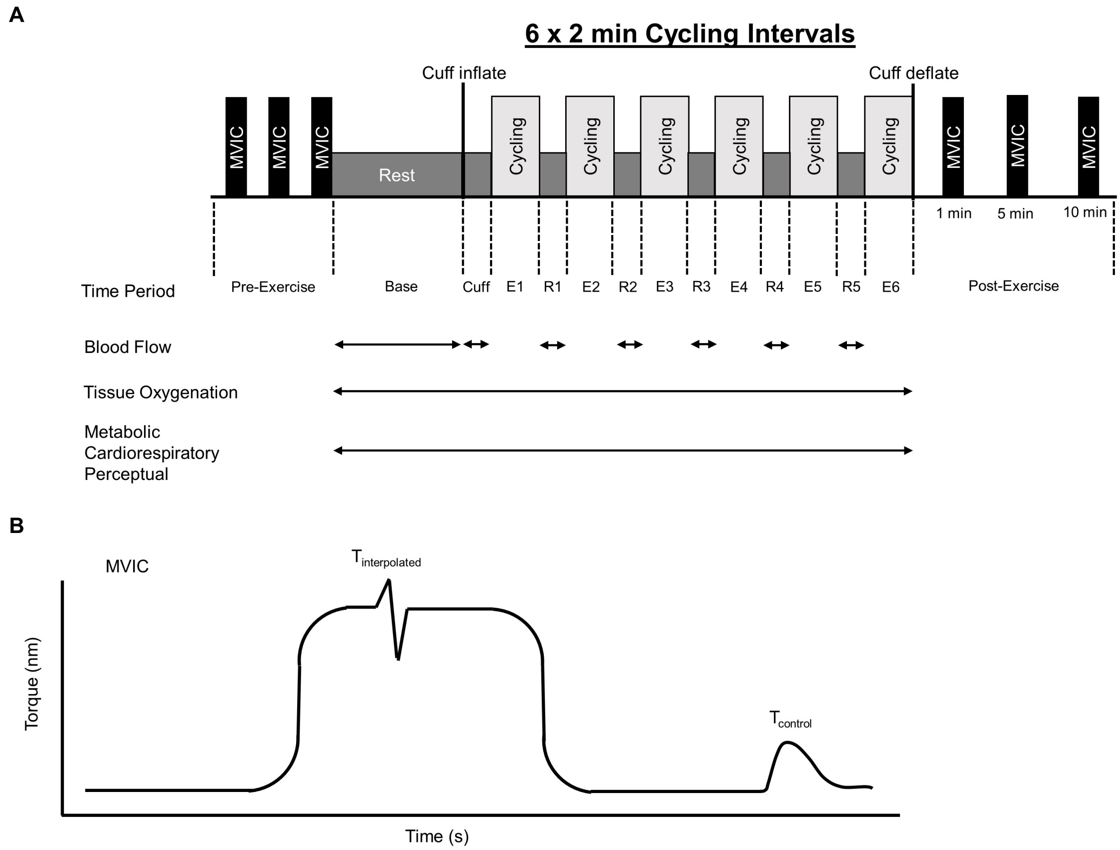

FIGURE 1 | Overview of intermittent cycling protocol which consisted of 6 × 2 min intervals **(A)**. Base, Cuff, E, and R denote baseline, cuff inflate, exercise interval, and recovery interval periods, respectively. Blood flow, tissue oxygenation, metabolic, cardiorespiratory, and perceptual responses were measured during the cycling protocol. Maximal knee extensor voluntary isometric torque (MVIC) was assessed before and 1, 5, and 10 min after exercise. Knee extensor MVIC torque-time profile **(B)**. Voluntary activation was assessed using the interpolated twitch technique and calculated as voluntary activation = 100 × (1 – $T_{interpolated}/T_{control}$), where $T_{interpolated}$ was the size of the interpolated twitch and $T_{control}$ was the amplitude of the control twitch produced by stimulation of the muscle in a relaxed but potentiated state.

around the right thigh, at the same position as exercise. The ultrasound probe was positioned distal to the cuff over the superficial femoral artery. Limb occlusion pressure was identified by inflating the cuff to 75 mmHg, and slowly increasing the pressure until blood velocity reached zero based on the absence of the Doppler spectrum. The minimum pressure required to do this was recorded as the limb occlusion pressure. The measurement of limb occlusion pressure using this method in our laboratory was reliable across exercise sessions (ICC = 0.89; 95% CI 0.80–0.94).

Tissue Oxygenation

A continuous-wave near-infrared spectroscopy device (PortaLite; Artinis Medical Systems BV, Elst, Netherlands) was utilized to detect changes in the concentrations of oxygenated hemoglobin and deoxygenated hemoglobin. Wavelengths (760 and 850 nm) were emitted from LEDs with an inter-optode distance of 3.5 cm. A differential path-length factor of 4.0 was used to correct for photon scattering within the tissue. Data were collected at 10 Hz (Oxysoft; ArtinisMedical Systems BV, Elst, Netherlands). The sensor was placed midway between the anterior superior iliac spine and the proximal patella parallel to the muscle fibers. The sensor was attached with double-sided tape and wrapped in an opaque bandage to prevent ambient light from reaching the sensor.

$$\text{Tissue Saturation Index} = \frac{\text{oxyhemoglobin}}{\text{deoxyhemoglobin} + \text{oxyhemoglobin}}$$

was calculated using integrated software (Oxysoft; ArtinisMedical Systems BV, Elst, Netherlands). The average tissue saturation index over the last 10 s of each time period was recorded. Changes in deoxyhemoglobin were assessed by calculating the difference between the average value of the last 10 s of each time period and the last 10 s of data recorded prior to inflating the cuff. This near-infrared spectroscopy system is reliable for measurement of tissue saturation index during leg exercise (Lucero et al., 2018).

Metabolic, Cardiorespiratory, and Perceptual Responses

Oxygen consumption, ventilation, and heart rate were recorded using the metabolic measurement system described above. These data were averaged over the last 30 s of the exercise and recovery time periods. Perceptual responses (rating of perceived exertion and pain) were recorded during the last 30 s of each exercise and recovery period. Whole body rating of perceived exertion was assessed using a Borg 6–20 scale (Borg, 1982). Pain was assessed using an 11-point numeric rating scale (DeLoach et al., 1998). A blood sample was collected from the fingertip (5 μl) during baseline and 1 min after the final exercise interval from which blood lactate concentration was determined (Lactate Plus; Nova Biomedical, Waltham, MA, United States). This device provides a valid and reliable measure of blood lactate concentration (Hart et al., 2013).

Neuromuscular Function

Participants were positioned on an isokinetic dynamometer (Biodex 4, Biodex Medical Systems, NY, United States) at a hip angle of 85° and a knee angle of 90°. A seat belt and ankle strap were used to minimize hip and ankle movement. To measure knee extension maximal voluntary isometric contraction (MVIC) torque, participants were instructed to "push as hard and as fast as possible" against an immoveable pad. Standardized verbal encouragement was provided to the participant. Evoked torque was elicited by transcutaneous electrical stimulation over the knee extensors using a computer-controlled stimulator (D185; Digitimer, Welwyn Garden City, United Kingdom). The stimulating cathode was placed over the quadriceps femoris 10 cm distal to the anterior superior iliac spine and the anode was placed 2 cm proximal to the proximal border of the patella (Pietrosimone et al., 2011). An electrical pulse (singlet, square wave, and 100 μs duration) was used to elicit a superimposed twitch at the peak torque level during the MVIC, and an additional potentiated resting twitch was triggered upon relaxation (~2 s) following the MVIC. Stimulation intensity was determined based off no increase in twitch force despite increasing the stimulation current. A further increase of 20% was added to ensure that the stimulation was supramaximal. Voluntary activation was assessed using the interpolated twitch technique and calculated as $\text{Voluntary activation} = 100 \times \left(1 - \frac{T_{\text{interpolated}}}{T_{\text{control}}}\right)$ where $T_{\text{interpolated}}$ was the size of the interpolated twitch and T_{control} was the amplitude of the control twitch produced by stimulation of the muscle in a relaxed but potentiated state (Gandevia, 2001). Rate of torque development, time to peak torque, as well as the time to half-relaxation were calculated using a customized routine (Spike 2; Cambridge Electronics Design, Cambridge, United Kingdom) described by Yoon et al. (2007). At the start of the MVIC, rate of torque development was calculated as the peak tangential torque using a moving mean method of the torque-time curve over the first 400 ms from the onset of contraction. Time to peak torque was defined as the slope of the force-time curve from baseline to peak T_{control} torque. Half-relaxation time is defined as the slope of the line from peak T_{control} torque to half its value. These measurements were obtained three times at baseline with 2 min rest between contractions the highest of which was used for analysis. Post-exercise measurements were then recorded from a single contraction at 1, 5, and 10 min after the exercise. The measurement of MVIC torque using this equipment in our laboratory was reliable across exercise sessions (ICC = 0.91; 95% CI 0.76–0.98).

Statistical Analysis

Separate two-way repeated measures analysis of variance (ANOVA) procedures were used to evaluate the effect of cycling condition and time (baseline, cuff inflate, and recovery interval number) on changes in blood flow. If a significant main effect of cycling condition was found, then subsequent *post-hoc* tests (Fisher's least significant difference) were used to determine where the differences occurred. If a significant effect of time was found, blood flow values over the recovery intervals were pooled together and additional paired samples *t*-tests were performed to analyze simple main effects.

Separate two-way repeated measures ANOVA procedures were used to evaluate the effect of cycling condition and time (baseline, cuff inflate, exercise interval number, and recovery interval number) on changes in tissue saturation index, deoxyhemoglobin, VO_2, heart rate, ventilation, RPE, and pain. If a significant main effect of cycling condition was found, then subsequent *post-hoc* tests (Fisher's least significant difference) were used to determine where the differences occurred. Additionally, if a significant main effect of time or condition was found for tissue saturation index or deoxyhemoglobin, data for exercise intervals and also recovery intervals were pooled and additional paired samples *t*-tests were used to evaluate simple main effects.

A repeated measures ANOVA was used to evaluate the interaction of cycling condition and time (baseline to post-exercise) on whole blood lactate. If a significant interaction was identified, then a series of 2 × 2 repeated measures ANOVAs comparing each cycling condition at baseline and post-exercise were used to determine where the interactions occurred.

Finally, two-way repeated measures ANOVAs were used to evaluate the effect of cycling condition and time (baseline, post-1 min, post-5 min, and post-10 min), on changes in MVIC, T_{control}, voluntary activation, rate of torque development, time to peak torque, and half-relaxation time. If a significant main effect of cycling condition was found, then subsequent *post-hoc* tests (Fisher's least significant difference) were used to determine where the differences occurred. If a significant main effect of time was found paired samples *t*-tests were used to evaluate simple effects of time. If a significant interaction of cycling condition and time was found, a series of 2 × 2 repeated measures ANOVAs comparing each cycling condition at baseline and 1 min post-exercise were used to determine where the interactions occurred. Partial eta squared (η_p^2) was calculated as a measure of effect sizes with $\eta_p^2 \geq 0.01$ indicating small, ≥0.059 medium, and ≥0.138 large effects, respectively (Cohen, 1988). Statistical procedures were performed using SPSS 22 (Armonk, NY, United States). Data are reported as mean ± SD and alpha was set to 0.05.

RESULTS

Cycling Trials

Cuff pressures for the BFR60 and BFR80 cycling conditions were 125 ± 12 and 164 ± 15 mmHg, respectively. Mean power outputs were 89 ± 18 W for the LL, BFR60, and BFR80 cycling conditions and 240 ± 36 W for the HL cycling condition. Blood flow at baseline did not differ between conditions ($p = 0.45$). Likewise, LOP did not differ between the BFR60 and BFR80 cycling conditions (207 ± 21 vs. 205 ± 19 mmHg, $p = 0.46$). Two participants were unable to complete the last cycling interval in the BFR80 condition due to lightheadedness and/or intense pain at the site of the cuff. The cuff pressure was therefore released, and these side-effects were greatly reduced. These participants still completed the post-exercise assessment of neuromuscular function 1 min following the release of the occlusion cuff. For these two participants, tissue oxygenation, metabolic, cardiorespiratory, and perceptual data during the final interval were substituted using mean substitution.

Blood Flow

The repeated measures ANOVA revealed significant main effects of cycling condition ($p < 0.01$, $\eta_p^2 = 0.887$) and time ($p < 0.01$, $\eta_p^2 = 0.933$) and cycling condition × time interaction ($p < 0.01$, $\eta_p^2 = 0.802$) on blood flow. In general, blood flow was reduced in the BFR cycling conditions compared to the non-BFR conditions (**Figure 2A**) and tended to decrease further in the BFR80 condition compared to BFR60 ($p = 0.07$). Within in each time period, blood flow did not differ between conditions at baseline, decreased with cuff inflation for BFR60 and BFR80 (both $p < 0.05$), and differed between all conditions during the recovery periods (HL > LL > BFR60 > BFR80; all $p < 0.05$, **Figure 2B**).

Tissue Oxygenation

Results from the repeated measures ANOVA procedures for tissue saturation index and deoxyhemoglobin revealed significant main effects of cycling condition ($p < 0.01$, $\eta_p^2 = 0.741$; $p < 0.01$, $\eta_p^2 = 0.783$, respectively) and time ($p < 0.01$, $\eta_p^2 = 0.599$; $p < 0.01$, $\eta_p^2 = 0.687$, respectively) as well as a cycling condition × time interaction ($p < 0.01$, $\eta_p^2 = 0.511$; $p < 0.01$, $\eta_p^2 = 0.683$, respectively). Overall, tissue saturation index was higher in LL, and HL, than it was in the BFR conditions (all $p < 0.05$, **Figure 3A**). Tissue saturation index was reduced in the BFR80 condition compared to the BFR60 ($p < 0.01$). Changes in tissue saturation index within each time period are illustrated in **Figure 3C**. Compared to exercise, tissue saturation index increased during recovery for HL and LL cycling conditions (both $p < 0.05$). There was no difference in tissue saturation index during exercise and recovery within the BFR60 and BFR80 conditions. In general, concentrations of deoxyhemoglobin were higher in the BFR conditions (all $p < 0.05$) and increased with pressure ($p < 0.05$, **Figure 3B**). There was a trend for concentrations of deoxyhemoglobin to be lower in LL than HL ($p = 0.06$). Changes in concentrations of deoxyhemoglobin with in time period are illustrated in **Figure 3D**. Deoxyhemoglobin did not differ between exercise and recovery periods in the HL and LL conditions (both $p > 0.05$) but increased during the recovery period for the BFR60 and BFR80 conditions (both $p < 0.01$).

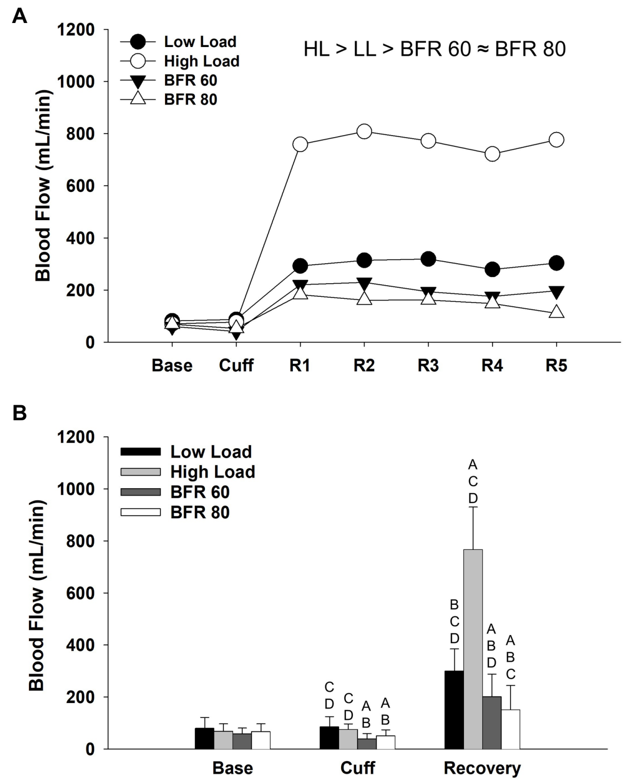

FIGURE 2 | Time course of alterations in superficial femoral artery blood flow across the different cycling conditions **(A)**. Significant main effect of condition is indicated above figure, ≈ ($p > 0.05$), < or > ($p < 0.05$). Base, Cuff, and R denote baseline, cuff inflate, and recovery interval periods, respectively. Data are reported as means and standard deviation bars were removed for clarity. Mean superficial femoral artery blood flow during baseline, cuff inflate, and recovery periods **(B)**. Blood flow different from LL, HL, BFR60, and BFR80 ($p < 0.05$) are indicated by ^{A}, ^{B}, ^{C}, and ^{D}, respectively. Data are reported as mean ± SD.

Metabolic, Cardiorespiratory, and Perceptual Responses

The repeated measures ANOVA procedures revealed main effects of cycling condition (all $p < 0.01$, all $\eta_p^2 > 0.678$) and time (all $p < 0.01$, all $\eta_p^2 > 0.818$) as well as a cycling condition × time interaction (all $p < 0.01$, all $\eta_p^2 > 0.511$) for all variables (VO_2, heart rate, ventilation, RPE, pain, and lactate). Due to the intermittent nature of the cycling protocol, VO_2 displayed a general "sawtooth" pattern for all conditions and overall was highest for HL (all $p > 0.05$, **Figure 4**). Heart rate was elevated in the BFR conditions compared to LL (both $p < 0.05$) but heart rate in the BFR80 condition did not significantly differ from HL ($p = 0.30$). Ventilation was highest in the HL condition followed by BFR80, BFR60, and LL, respectively (all $p < 0.05$). Cycling with BFR caused an increase in RPE compared to LL (both $p < 0.05$), but RPE in the BFR80 condition was not significantly different from HL ($p = 0.30$). Pain was generally low during LL and HL but increased with BFR and increased pressure (all $p < 0.05$). Most

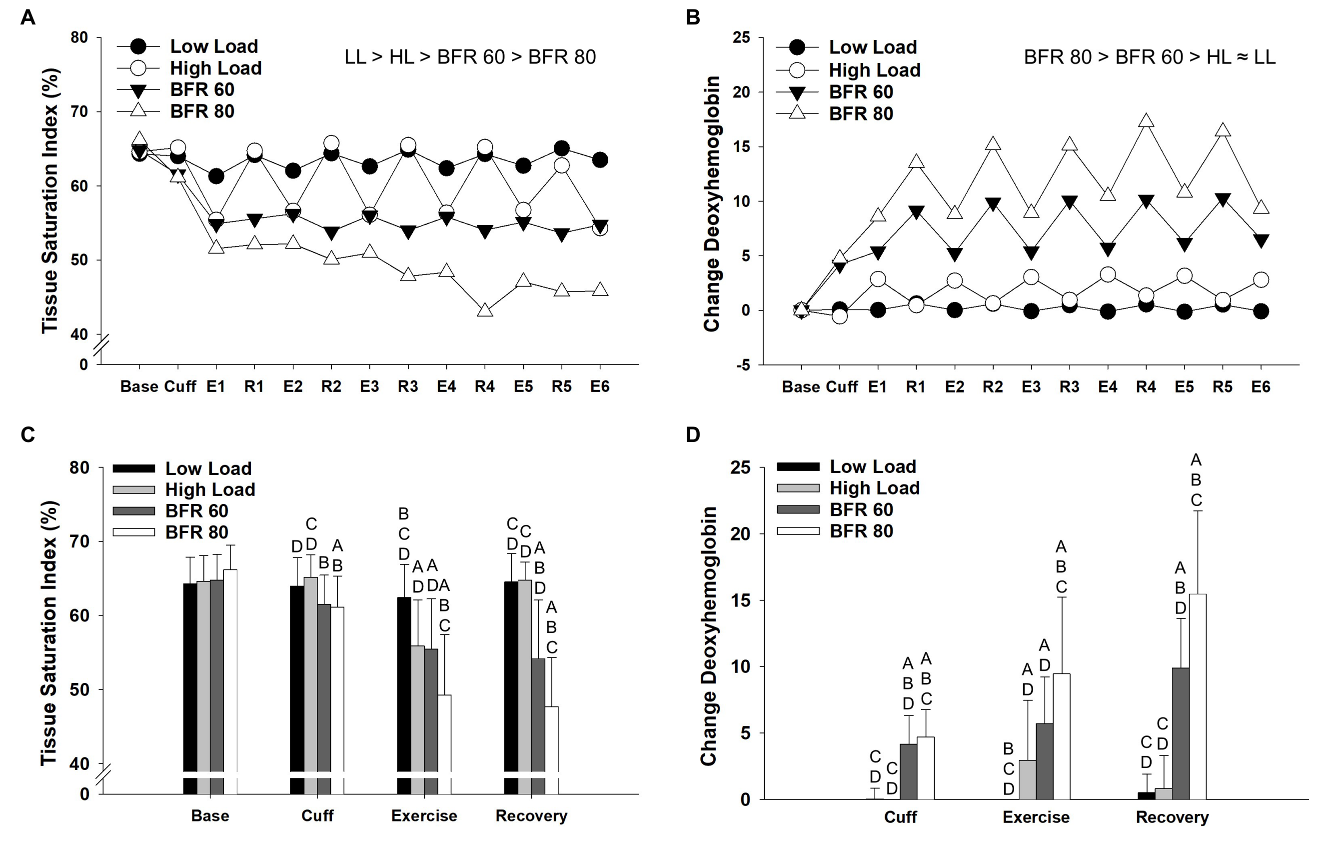

FIGURE 3 | Time course of alterations in tissue saturation index **(A)** and concentrations of deoxyhemoglobin **(B)** across the different cycling conditions. Significant main effects of condition are indicated above individual figures, ≈ ($p > 0.05$), < or > ($p < 0.05$). Base, Cuff, E, and R denote baseline, cuff inflate, exercise interval, and recovery interval periods, respectively. Data reported as means and standard deviation bars were removed for clarity. Mean values for tissue saturation index **(C)** and concentrations of deoxyemoglobin **(D)** during baseline, cuff inflate, exercise, and recovery periods. Tissue saturation index and concentrations of deoxyhemoglobin different from LL, HL, BFR60, and BFR80 ($p < 0.05$) are indicated by ^{A}, ^{B}, ^{C}, and ^{D}, respectively. Data are reported as mean ± SD.

notably, pain during BFR80 increased steadily and approached maximum values at the end of the final interval. Compared to baseline, end exercise whole blood lactate increased in the HL, BFR60, and BFR80 conditions (all $p < 0.05$). The increase in blood lactate for HL and BFR80 was greater than that for BFR60 but did not significantly differ between HL and BFR80 conditions ($p = 0.86$).

Neuromuscular Function

The repeated measure ANOVA procedures indicated significant main effects of cycling condition for MVIC torque, $T_{control}$, rate of torque development, and time to peak torque (all $p < 0.01$, all $\eta_p^2 > 0.348$; **Figure 5**). Significant main effects of time were found for MVIC, voluntary activation, $T_{control}$, Time to peak torque, and half-relaxation time (all $p < 0.01$, all $\eta_p^2 > 0.525$). Significant cycling condition × time interactions were found for MVIC, voluntary activation, $T_{control}$, time to peak torque, and rate of torque development ($p < 0.01$, all $\eta_p^2 > 0.258$). In general, MVIC torque produced in the BFR conditions was lower than the non-BFR conditions and was further reduced with increased pressure. Reductions in MVIC torque from baseline to 1 min post-exercise for the BFR60 condition were greater than those for LL and HL (both $p < 0.05$) but less than those for BFR80 ($p = 0.02$). Compared to baseline, MVIC torque was reduced at 10 min post-exercise for all conditions and was lowest for the BFR80 condition (all $p < 0.05$). Reductions in voluntary activation from baseline to 1 min post-exercise were greater in BFR80 compared to all other conditions (all $p < 0.05$). Voluntary activation did not differ from baseline at 10 min post in any condition (all $p > 0.05$). For $T_{control}$, BFR80 was lower than LL and BFR60 (both $p < 0.05$), but not different than HL ($p = 0.10$). The baseline to 1 min post-exercise reduction in $T_{control}$ was greater in BFR80 than all other conditions (all $p < 0.05$). The $T_{control}$ for all of the conditions were reduced 10 min post-exercise compared to baseline (all $p < 0.05$). BFR80 was generally lower than all other conditions for rate of torque development and time to peak torque (all $p < 0.05$). Similarly, the baseline to 1 min change in rate of torque development and time to peak torque for BFR80 was greater than all other conditions (all $p < 0.05$). The rate of torque development for both BFR conditions was reduced 10 min post-exercise (both $p < 0.05$). Compared to baseline, time to peak torque was reduced for all conditions 10 min post-exercise (all

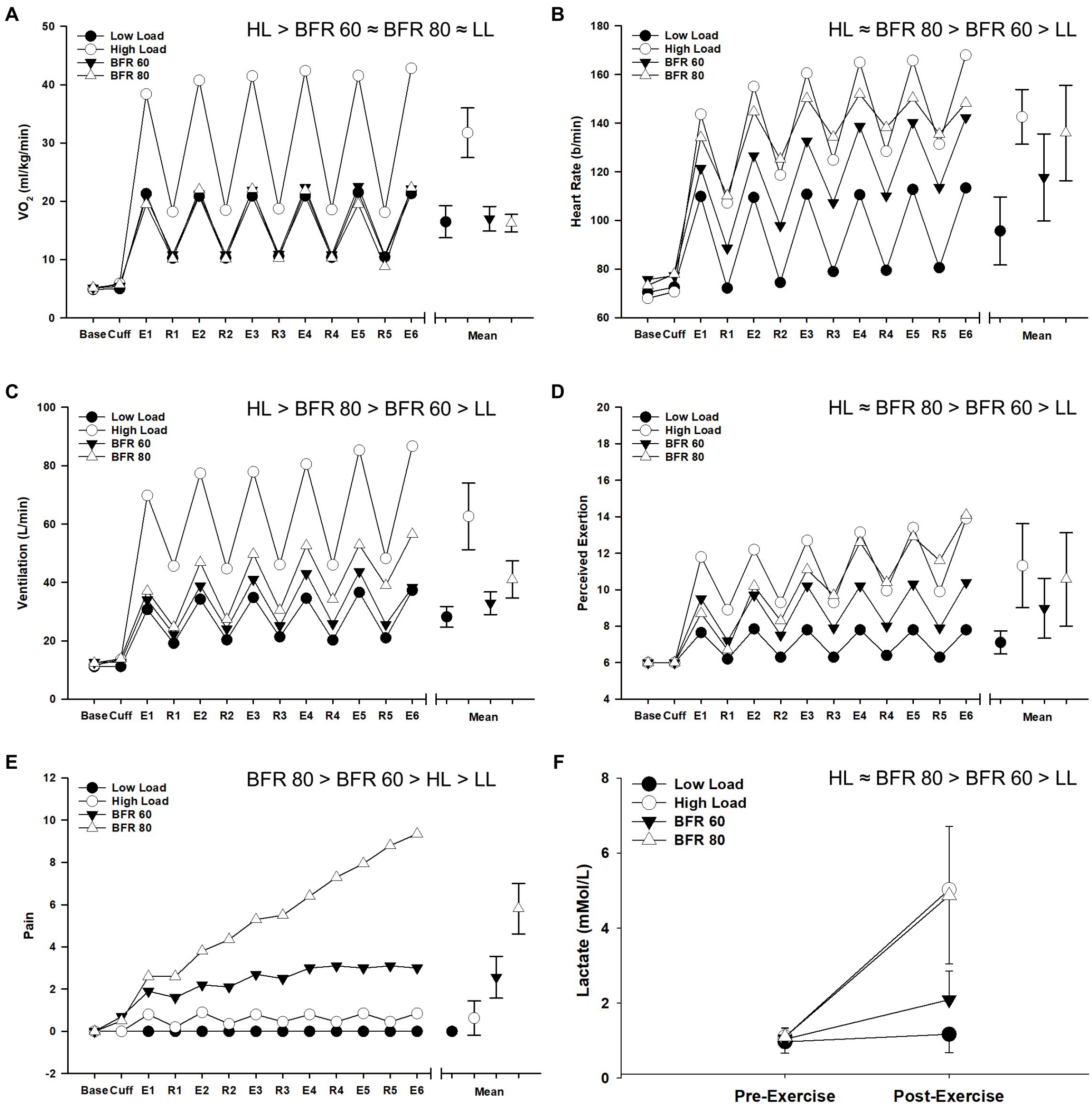

FIGURE 4 | Time course of alterations in VO_2 **(A)**, heart rate **(B)**, ventilation **(C)**, RPE **(D)**, pain **(E)**, and blood lactate **(F)** across the different cycling conditions. Significant main effects of condition are indicated above individual figures, ≈ ($p > 0.05$), < or > ($p < 0.05$). Base, Cuff, E, and R denote baseline, cuff inflate, exercise interval, and recovery interval periods, respectively. Data are reported as means and standard deviation bars were removed for clarity. Note that, for Panels **(A–E)**, a collapsed mean for the exercise interval and recovery periods is illustrated to the right (mean ± SD).

$p < 0.05$). Finally, half-relaxation time was not significantly different than baseline 10 min post-exercise in the LL condition ($p = 0.13$) but was increased in all other conditions (all $p < 0.05$).

DISCUSSION

In this investigation, we integrated measurements of blood flow, tissue oxygenation, and neuromuscular function to better characterize the acute effects of BFR during aerobic exercise. Our main findings were that cycling with BFR (1) caused a reduction in blood flow and tissue oxygenation an augmented metabolite accumulation compared to LL cycling, (2) resulted in lower cardiorespiratory responses compared to HL cycling, and (3) compromised knee extensor torque primarily through peripheral mechanisms. Collectively, these results indicate that both BFR60 and BFR80 provided considerable metabolic stress and resulted in neuromuscular fatigue. While increasing the cuff pressure increased metabolic

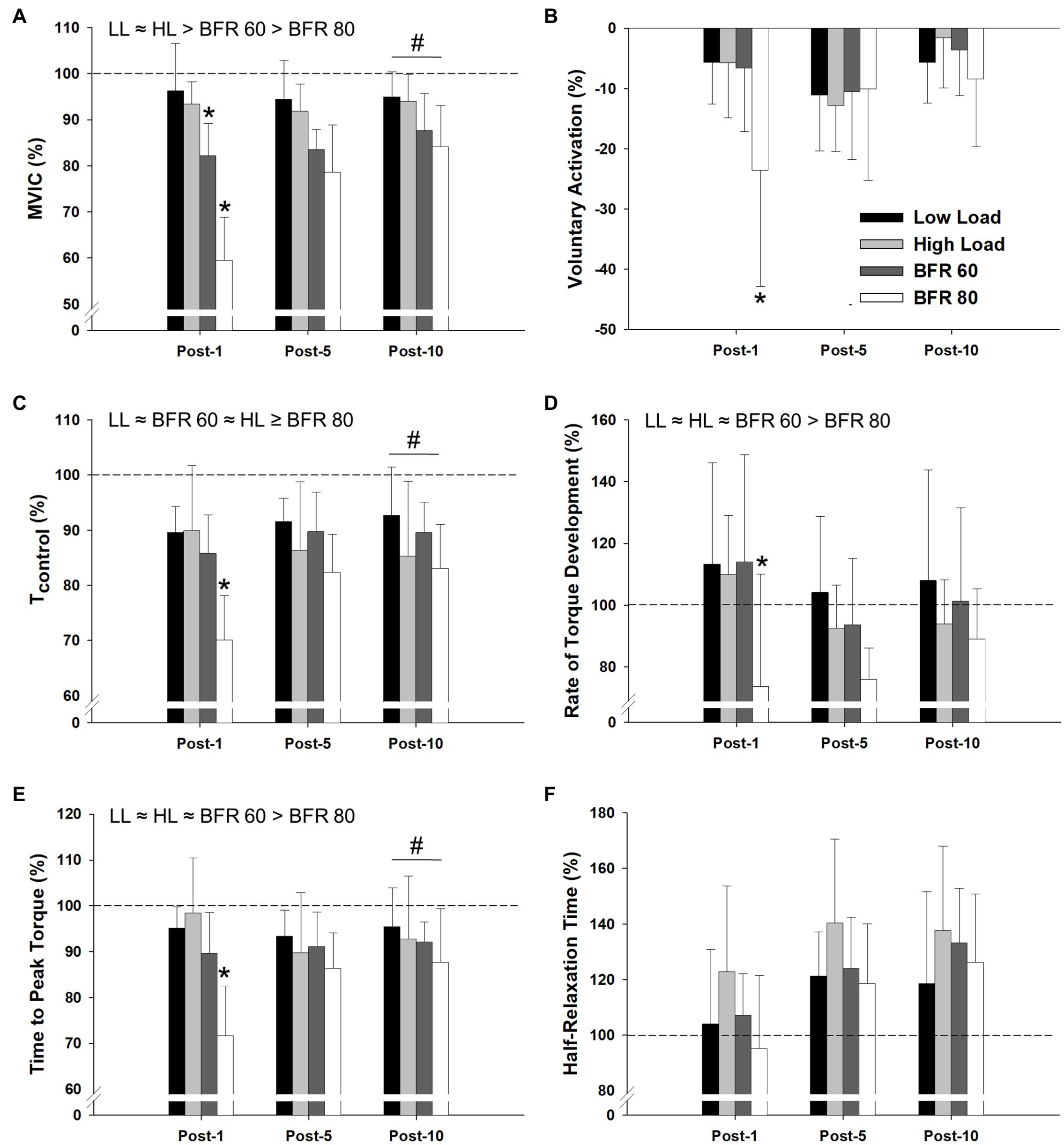

FIGURE 5 | Relative changes in maximal voluntary isometric contraction torque (MVIC), voluntary activation, evoked twitch torque ($T_{control}$), rate of torque development, time to peak torque, and half-relaxation time, as assessed at 1, 5, and 10 min post-exercise, are illustrated in panel **(A–F)**, respectively. Dashed line indicates baseline pre-exercise value. Significant main effects of condition are indicated above individual figures, ≈ (denotes $p > 0.05$), < or > (denotes $p < 0.05$). Note that, $T_{control}$ ≥ indicated BFR80 is different than LL and BFR60, but not different than HL. Condition × time interaction (baseline to 1 min post-exercise) different than all other conditions (*$p < 0.05$). All conditions different from baseline at post-10 min (#$p < 0.05$). Data are reported as mean ± SD.

stress and neuromuscular fatigue, it also increased pain and thus high pressures may not be feasible.

Blood Flow and Tissue Oxygenation

To the best of our knowledge, we are the first group to report changes in blood flow (as assessed in the superficial femoral artery) following aerobic exercise with BFR. Specifically, compared to the LL condition, blood flow during the intermittent recovery period was reduced by ~33% and ~50% in the BFR60 and BFR80 conditions, respectively. These results from aerobic exercise with BFR generally agree with previous literature analyzing reductions in blood flow following resistance exercise with BFR (~30–40%; Takano et al., 2005; Downs et al., 2014; Kilgas et al., 2019; Singer et al., 2020). This reduction in blood flow to the muscle was generally supported by our tissue oxygenation data. Specifically, tissue saturation index was reduced by ~5% and ~15% in the BFR60 and BFR80 conditions. These reductions support previous reports on muscle oxygenation during cycling with BFR. Specifically, Corvino et al. (2017) reported ~6% reduction in tissue saturation index during intermittent cycling with BFR with a cuff pressure of 20 mmHg above occlusion pressure. Additionally, Willis and coworkers (Willis et al., 2018) reported that tissue saturation index was lower than control at 60% of occlusion pressure, but not 45% of occlusion pressure following repeated cycling sprints until exhaustion. Previous authors have hypothesized that lower oxygen availability and venous occlusion induces training adaptions through a combination of cell swelling (Loenneke et al., 2012a), metabolite accumulation (Scott et al., 2014; Cayot et al., 2016), and type two muscle fiber recruitment (Yasuda et al., 2009). Understanding the acute changes in blood flow and tissue saturation during cycling with BFR is key to optimizing the training stimulus. Our data suggest that both BFR60 and BFR80 may serve as appropriate training pressure during cycling with BFR.

Metabolic, Cardiorespiratory, and Perceptual Responses

Oxygen consumption did not change with the addition of BFR. Previous researchers (Abe et al., 2006; Loenneke et al., 2011) reported an increase in VO_2 during aerobic exercise with BFR likely due to the metabolic cost of increased heart rate and ventilation. Discrepancies in these findings may be due to the duration of the cycling intervals. Because the intervals in the present study were limited to 2 min, steady-state VO_2 was not achieved. Heart rate, ventilation, RPE, pain, and lactate all increased with BFR and further increased with higher cuff pressure, which is consistent with previous research (Mendonca et al., 2014; Mattocks et al., 2017). Notably, heart rate and RPE increased in the BFR80 to a level that was not different from HL, additionally muscle pain during the last cycling interval was near maximum values. Therefore, BFR80 may not be tolerable for everyone.

Neuromuscular Function

Cycling exercise with BFR reduced MVIC torque by ~18% and ~40% in the BFR60 and BFR80 conditions, respectively. These results generally agree with previous reports documenting changes in neuromuscular function following resistance exercise with BFR (Cook et al., 2007; Karabulut et al., 2010; Husmann et al., 2018); however, prior studies examining neuromuscular function following aerobic exercise with BFR have varied (Ogawa et al., 2012; Kim et al., 2015; Willis et al., 2018). These reductions in muscular torque in the current study were likely influenced by peripheral mechanisms as indicated by the reduction in T_{control} for both the BFR60 and BFR80 conditions. Exercise with BFR may have caused peripheral fatigue by the reduction in blood flow to the working muscles reducing their energy supply and/or by the accumulation of metabolites inhibiting cross-bridge formation (Husmann et al., 2018).

In addition to peripheral fatigue, central fatigue was also present in the BFR80 condition. Specifically, voluntary activation was 23% lower in the BFR80 condition 1 min after exercise. Willis et al. (2018) reported a 6 and 16% reduction in voluntary activation following a repeated cycling sprint test with BFR at 45 and 60% occlusion pressure to exhaustion. The reduction in voluntary activation in the BFR80 condition could be due to several factors related to exercise with BFR. One explanation includes venous distension, and the accumulation of metabolites, both of which increase the firing rate of nociceptive group IV muscle afferents (Haouzi et al., 1999; Jankowski et al., 2013). As stated above, the BFR80 condition resulted in significant muscle pain, which increased throughout the protocol. Graven-Nielsen et al. (2002) previously reported muscle pain, *via* infusion of hypertonic saline, reduced MVIC torque through a centrally mediated mechanism. Greater neuromuscular fatigue has been associated with increased growth hormone concentrations (Hakkinen and Pakarinen, 1993; Pierce et al., 2006) which may play a role in training adaptations following aerobic and resistance training with BFR. Results from the current study provide evidence of neuromuscular fatigue following aerobic exercise with BFR.

Cuff Pressure

Proper selection of cuff pressure (e.g., 40–80% of limb occlusion pressure) is important for the safety and effectiveness of exercise with BFR. At rest, application of pressure would initially occlude venous blood flow while maintaining some arterial blood flow until the arterial to venous pressure gradient is eliminated at which arterial blood flow would stop. During exercise, blood flow would increase only if the intramuscular pressure generated during the muscle contraction exceeds the cuff pressure (Kilgas et al., 2019; Singer et al., 2020). By reducing blood flow, this causes a reduction in tissue oxygenation and a build-up of metabolites and fluid within the limb. Previous authors have proposed these as possible mechanisms responsible for the training adaptations following exercise with BFR (Loenneke et al., 2014; Scott et al., 2015). Higher cuff pressures likely result in greater venous occlusion which augments cell swelling by causing blood to pool within the limb, which is supported by data in the present study. Loenneke et al. (2012b) suggested that the ideal cuff pressure necessary for training adaptation is less than previously used in the literature. This could be due to very high cuff pressures further occluding arterial blood flow and thus attenuating the cell swelling response. Increasing cuff pressure also likely increases metabolite accumulation within the limb, which activate the exercise pressor reflex. The activation of the exercise pressor reflex and increased metabolite concentrations may explain the increased heart rate, ventilation, pain, and fatigue seen in the present study. These results may decrease BFR exercise training volume by early termination of the exercise. It should be noted that while BFR80 resulted in a greater increase in metabolite accumulation, it also resulted in substantial pain by the end of the final cycling interval (two participants could not complete the protocol). While both BFR60 and BFR80 reduced tissue oxygenation, increased metabolite accumulation, and caused neuromuscular fatigue, BFR60 was more tolerable.

Implications

Researchers, clinicians, and practitioners should take great care in selecting cuff pressures as pressure effects acute and likely chronic responses to exercise. In this investigation, cuff pressures of 60 and 80% limb occlusion pressure resulted in reduced blood flow, decreased muscle oxygenation, increased metabolite accumulation, and reduced neuromuscular function, yet only BFR60 resulted in lower metabolic, cardiorespiratory, and perceptual responses than HL cycling. It is important to note that limb occlusion pressures vary by individual, cuff type, cuff width, and body position used (Hughes et al., 2018a; Sieljacks et al., 2018). Therefore, cuff pressures should be based on individual limb occlusion pressure if possible. Using an absolute pressure may result in inconsistent training adaptations or adverse side-effects (Rolnick et al., 2021). Finally, this study highlights cuff pressures that elicit specific stresses to the cardiovascular and neuromuscular systems that may be advantageous for cycling exercise with BFR, which may aid researchers in the development of robust cycling exercise with BFR guidelines (exercise protocols and cuff pressures) for healthy, clinical, and athletic populations.

Limitations

There are some limitations to our study that must be addressed. First, blood flow measurements using Doppler ultrasound during cycling could not be performed; therefore, we measured blood flow in the superficial femoral artery immediately (within 10 s) after each cycling interval. Although not directly measured, we can speculate that blood flow during exercise was higher than during recovery in the BFR conditions based on the tissue oxygenation data. Additionally, although careful control was taken to minimize day to day variation in blood flow and no differences in baseline blood flow were found, this variation may affect our findings. Second, limb occlusion pressure was measured in the superficial femoral artery at rest while seated on the ergometer. Because limb occlusion pressure is dependent on body position (Hughes et al., 2018a) and deeper arteries will require higher pressures to fully occlude, absolute cuff pressures from the current study may not be applied when limb occlusion pressure is measured in different body position or different arteries. Third, our measurements of tissue oxygenation using near inferred spectroscopy may be affected by adipose tissue, higher skin perfusion during exercise, melanin in the skin, and heterogeneity of blood flow within the muscle (Jones et al., 2016). Finally, our measurements of neuromuscular function were performed 1 min after the conclusion of exercise. This minute was used for the participant to transfer from the cycling ergometer to the isokinetic dynamometer. This time may have masked some of the changes to neuromuscular function following exercise. Moreover, changes in neuromuscular function are task-specific (Bigland-Ritchie et al., 1995), and therefore, caution must be taken when extrapolating these findings to other modes of aerobic exercise with BFR, exercise protocols, and/or other populations including women and older adults.

SUMMARY

In summary, cycling with BFR decreased blood flow and tissue oxygenation and increased metabolite accumulation when compared to LL cycling without BFR. Moreover, cycling with BFR generally resulted in lower metabolic and cardiorespiratory responses than traditional HL cycling and reduced neuromuscular function primarily by peripheral mechanisms. Additionally, higher cuff pressure not only increased metabolic stress and fatigue but also increased pain. We conclude that intermittent cycling with a cuff pressure of 60% limb occlusion pressure has the potential to strike a balance between reducing blood flow and increasing metabolite stress, which is needed for training adaptations, without causing excessive cardiorespiratory strain and severe pain. Therefore, cycling with this pressure could offer an alternative when high-intensity aerobic exercise is not suitable.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board at Michigan Technological University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

FUNDING

Funding to support this investigation was received from the Michigan Space Grant Consortium.

ACKNOWLEDGMENTS

The authors would like to sincerely thank the participants who took part in this study for their enthusiastic efforts throughout the cycling protocols.

REFERENCES

Abe, T., Fujita, S., Nakajima, T., Sakamaki, M., Ozaki, H., Ogasawara, R., et al. (2010). Effects of low-intensity cycle training with restricted leg blood flow on thigh muscle volume and VO_{2max} in young men. *J. Sports Sci. Med.* 9, 452–458.

Abe, T., Kearns, C. F., and Sato, Y. (2006). Muscle size and strength are increased following walk training with restricted venous blood flow from the leg muscle, Kaatsu-walk training. *J. Appl. Physiol.* 100, 1460–1466. doi: 10.1152/japplphysiol.01267.2005

Bigland-Ritchie, B., Rice, C., Garland, S., and Walsh, M. (1995). "Task-dependent factors in fatigue of human voluntary contractions," in *Fatigue*. (New York: Springer), 361–380.

Bigland-Ritchie, B., and Woods, J. (1984). Changes in muscle contractile properties and neural control during human muscular fatigue. *Muscle Nerve* 7, 691–699. doi: 10.1002/mus.880070902

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Med. Sci. Sports Exerc.* 14, 377–381. doi: 10.1249/00005768-198205000-00012

Cayot, T. E., Lauver, J. D., Silette, C. R., and Scheuermann, B. W. (2016). Effects of blood flow restriction duration on muscle activation and microvascular oxygenation during low-volume isometric exercise. *Clin. Physiol. Funct. Imaging* 36, 298–305. doi: 10.1111/cpf.12228

Christiansen, D., Eibye, K., Hostrup, M., and Bangsbo, J. (2020). Training with blood flow restriction increases femoral artery diameter and thigh oxygen delivery during knee-extensor exercise in recreationally trained men. *J. Physiol.* 598, 2337–2353. doi: 10.1113/JP279554

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences. 2nd Edn*. Hillsdale, NJ: Erlbaum.

Conceicao, M. S., Junior, E. M. M., Telles, G. D., Libardi, C. A., Castro, A., Andrade, A. L. L., et al. (2019). Augmented nabolic responses after 8-wk cycling with blood flow restriction. *Med. Sci. Sports Exerc.* 51, 84–93. doi: 10.1249/MSS.0000000000001755

Cook, S. B., Clark, B. C., and Ploutz-Snyder, L. L. (2007). Effects of exercise load and blood-flow restriction on skeletal muscle function. *Med. Sci. Sports Exerc.* 39, 1708–1713. doi: 10.1249/mss.0b013e31812383d6

Cook, S. B., Murphy, B. G., and Labarbera, K. E. (2013). Neuromuscular function after a bout of low-load blood flow-restricted exercise. *Med. Sci. Sports Exerc.* 45, 67–74. doi: 10.1249/MSS.0b013e31826c6fa8

Corvino, R. B., Fernandes, M., Mendes de Oliveira, M. F., Penteado, R., Denadai, B., and Caputo, F. (2014). Four weeks of blood flow restricted training increases time to exhaustion at severe intensity cycling exercise. *Rev. Bras. Cineantropom. Desempenho Hum.* 16, 570–578. doi: 10.5007/1980-0037.2014v16n5p570

Corvino, R. B., Rossiter, H. B., Loch, T., Martins, J. C., and Caputo, F. (2017). Physiological responses to interval endurance exercise at different levels of blood flow restriction. *Eur. J. Appl. Physiol.* 117, 39–52. doi: 10.1007/s00421-016-3497-5

De Oliveira, M. F., Caputo, F., Corvino, R. B., and Denadai, B. S. (2016). Short-term low-intensity blood flow restricted interval training improves both aerobic fitness and muscle strength. *Scand. J. Med. Sci. Sports* 26, 1017–1025. doi: 10.1111/sms.12540

DeLoach, L. J., Higgins, M. S., Caplan, A. B., and Stiff, J. L. (1998). The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. *Anesth. Analg.* 86, 102–106.

Downs, M. E., Hackney, K. J., Martin, D., Caine, T. L., Cunningham, D., O'Connor, D. P., et al. (2014). Acute vascular and cardiovascular responses to blood flow-restricted exercise. *Med. Sci. Sports Exerc.* 46, 1489–1497. doi: 10.1249/MSS.0000000000000253

Gandevia, S. C. (2001). Spinal and supraspinal factors in human muscle fatigue. *Physiol. Rev.* 81, 1725–1789. doi: 10.1152/physrev.2001.81.4.1725

Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I.-M., et al. (2011). Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med. Sci. Sports Exerc.* 43, 1334–1359. doi: 10.1249/MSS.0b013e318213fefb

Graven-Nielsen, T., Lund, H., Arendt-Nielsen, L., Danneskiold-Samsøe, B., and Bliddal, H. (2002). Inhibition of maximal voluntary contraction force by experimental muscle pain: a centrally mediated mechanism. *Muscle Nerve* 26, 708–712. doi: 10.1002/mus.10225

Hakkinen, K., and Pakarinen, A. (1993). Acute hormonal responses to two different fatiguing heavy-resistance protocols in male athletes. *J. Appl. Physiol.* 74, 882–887. doi: 10.1152/jappl.1993.74.2.882

Haouzi, P., Hill, J. M., Lewis, B. K., and Kaufman, M. P. (1999). Responses of group III and IV muscle afferents to distension of the peripheral vascular bed. *J. Appl. Physiol.* 87, 545–553. doi: 10.1152/jappl.1999.87.2.545

Hart, S., Drevets, K., Alford, M., Salacinski, A., and Hunt, B. (2013). A method-comparison study regarding the validity and reliability of the lactate plus analyzer. *BMJ Open* 3:e001899. doi: 10.1136/bmjopen-2012-001899

Hughes, L., Jeffries, O., Waldron, M., Rosenblatt, B., Gissane, C., Paton, B., et al. (2018a). Influence and reliability of lower-limb arterial occlusion pressure at different body positions. *PeerJ.* 6:e4697. doi: 10.7717/peerj.4697

Hughes, L., Rosenblatt, B., Gissane, C., Paton, B., and Patterson, S. D. (2018b). Interface pressure, perceptual, and mean arterial pressure responses to different blood flow restriction systems. *Scand. J. Med. Sci. Sports* 28, 1757–1765. doi: 10.1111/sms.13092

Husmann, F., Mittlmeier, T., Bruhn, S., Zschorlich, V., and Behrens, M. (2018). Impact of blood flow restriction exercise on muscle fatigue development and recovery. *Med. Sci. Sports Exerc.* 50, 436–446. doi: 10.1249/MSS.0000000000001475

Jankowski, M. P., Rau, K. K., Ekmann, K. M., Anderson, C. E., and Koerber, H. R. (2013). Comprehensive phenotyping of group III and IV muscle afferents in mouse. *J. Neurophysiol.* 109, 2374–2381. doi: 10.1152/jn.01067.2012

Jones, S., Chiesa, S. T., Chaturvedi, N., and Hughes, A. D. (2016). Recent developments in near-infrared spectroscopy (NIRS) for the assessment of local skeletal muscle microvascular function and capacity to utilise oxygen. *Artery Res.* 16, 25–33. doi: 10.1016/j.artres.2016.09.001

Karabulut, M., Cramer, J. T., Abe, T., Sato, Y., and Bemben, M. G. (2010). Neuromuscular fatigue following low-intensity dynamic exercise with externally applied vascular restriction. *J. Electromyogr. Kinesiol.* 20, 440–447. doi: 10.1016/j.jelekin.2009.06.005

Kilgas, M. A., Mcdaniel, J., Stavres, J., Pollock, B. S., Singer, T. J., and Elmer, S. J. (2019). Limb blood flow and tissue perfusion during exercise with blood flow restriction. *Eur. J. Appl. Physiol.* 119, 377–387. doi: 10.1007/s00421-018-4029-2

Kim, D., Loenneke, J. P., Thiebaud, R. S., Abe, T., and Bemben, M. G. (2015). The acute muscular effects of cycling with and without different degrees of blood flow restriction. *Acta Physiol. Hung.* 102, 428–441. doi: 10.1556/036.102.2015.4.10

Loenneke, J. P., Fahs, C. A., Rossow, L. M., Abe, T., and Bemben, M. G. (2012a). The anabolic benefits of venous blood flow restriction training may be induced by muscle cell swelling. *Med. Hypotheses* 78, 151–154. doi: 10.1016/j.mehy.2011.10.014

Loenneke, J., Thiebaud, R., Abe, T., and Bemben, M. (2014). Blood flow restriction pressure recommendations: the hormesis hypothesis. *Med. Hypotheses* 82, 623–626. doi: 10.1016/j.mehy.2014.02.023

Loenneke, J. P., Thrower, A. D., Balapur, A., Barnes, J. T., and Pujol, T. J. (2011). The energy requirement of walking with restricted blood flow. *Sport Sci.* 4, 7–11.

Loenneke, J. P., Wilson, J. M., Marin, P. J., Zourdos, M. C., and Bemben, M. G. (2012b). Low intensity blood flow restriction training: a meta-analysis. *Eur. J. Appl. Physiol.* 112, 1849–1859. doi: 10.1007/s00421-011-2167-x

Lucero, A. A., Addae, G., Lawrence, W., Neway, B., Credeur, D. P., Faulkner, J., et al. (2018). Reliability of muscle blood flow and oxygen consumption response from exercise using near-infrared spectroscopy. *Exp. Physiol.* 103, 90–100. doi: 10.1113/EP086537

Lucia, A., Sanchez, O., Carvajal, A., and Chicharro, J. L. (1999). Analysis of the aerobic-anaerobic transition in elite cyclists during incremental exercise with the use of electromyography. *Br. J. Sports Med.* 33, 178–185. doi: 10.1136/bjsm.33.3.178

Mattocks, K. T., Jessee, M. B., Counts, B. R., Buckner, S. L., Mouser, J. G., Dankel, S. J., et al. (2017). The effects of upper body exercise across different levels of blood flow restriction on arterial occlusion pressure and perceptual responses. *Physiol. Behav.* 171, 181–186. doi: 10.1016/j.physbeh.2017.01.015

Mendonca, G. V., Vaz, J. R., Teixeira, M. S., Grácio, T., and Pezarat-Correia, P. (2014). Metabolic cost of locomotion during treadmill walking with blood flow restriction. *Clin. Physiol. Funct. Imaging* 34, 308–316. doi: 10.1111/cpf.12098

Nakajima, T., Kurano, M., Iida, H., Takano, H., Oonuma, H., Morita, T., et al. (2006). Use and safety of KAATSU training: results of a national survey. *Int. J. KAATSU Train. Res.* 2, 5–13. doi: 10.3806/ijktr.2.5

Nyberg, S. K., Berg, O. K., Helgerud, J., and Wang, E. (2018). Reliability of forearm oxygen uptake during handgrip exercise: assessment by ultrasonography and venous blood gas. *Physiol. Rep.* 6:e13696. doi: 10.14814/phy2.13696

Ogawa, M., Loenneke, J. P., Yasuda, T., Fahs, C. A., Rossow, L. M., Thiebaud, R. S., et al. (2012). Time course changes in muscle size and fatigue during walking with restricted leg blood flow in young men. *J. Phys. Educ. Sports Manag.* 3, 14–19.

Patterson, S. D., and Brandner, C. R. (2017). The role of blood flow restriction training for applied practitioners: a questionnaire-based survey. *J. Sports Sci.* 36, 1–8.

Patterson, S. D., Hughes, L., Warmington, S., Burr, J., Scott, B. R., Owens, J., et al. (2019). Blood flow restriction exercise: considerations of methodology, application, and safety. *Front. Physiol.* 10:533. doi: 10.3389/fphys.2019.00533

Pierce, J. R., Clark, B. C., Ploutz-Snyder, L. L., and Kanaley, J. A. (2006). Growth hormone and muscle function responses to skeletal muscle ischemia. *J. Appl. Physiol.* 101, 1588–1595. doi: 10.1152/japplphysiol.00585.2006

Pietrosimone, B. G., Selkow, N. M., Ingersoll, C. D., Hart, J. M., and Saliba, S. A. (2011). Electrode type and placement configuration for quadriceps activation evaluation. *J. Athl. Train.* 46, 621–628. doi: 10.4085/1062-6050-46.6.621

Rolnick, N., Kimbrell, K., Cerqueira, M. S., Weatherford, B., and Brandner, C. (2021). Perceived barriers to blood flow restriction training. *Front. Rehabilit. Sci.* 2:697082. doi: 10.3389/fresc.2021.697082

Scott, B. R., Loenneke, J. P., Slattery, K. M., and Dascombe, B. J. (2015). Exercise with blood flow restriction: an updated evidence-based approach for enhanced muscular development. *Sports Med.* 45, 313–325. doi: 10.1007/s40279-014-0288-1

Scott, B. R., Slattery, K. M., Sculley, D. V., and Dascombe, B. J. (2014). Hypoxia and resistance exercise: a comparison of localized and systemic methods. *Sports Med.* 44, 1037–1054. doi: 10.1007/s40279-014-0177-7

Sieljacks, P., Knudsen, L., Wernbom, M., and Vissing, K. (2018). Body position influences arterial occlusion pressure: implications for the standardization of pressure during blood flow restricted exercise. *Eur. J. Appl. Physiol.* 118, 303–312. doi: 10.1007/s00421-017-3770-2

Singer, T. J., Stavres, J., Elmer, S. J., Kilgas, M. A., Pollock, B. S., Kearney, S. G., et al. (2020). Knee extension with blood flow restriction: impact of cuff pressure on hemodynamics. *Eur. J. Appl. Physiol.* 120, 79–90. doi: 10.1007/s00421-019-04250-2

Takano, H., Morita, T., Iida, H., Asada, K.-I., Kato, M., Uno, K., et al. (2005). Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. *Eur. J. Appl. Physiol.* 95, 65–73. doi: 10.1007/s00421-005-1389-1

Willis, S. J., Alvarez, L., Borrani, F., and Millet, G. P. (2018). Oxygenation time course and neuromuscular fatigue during repeated cycling sprints with bilateral blood flow restriction. *Physiol. Rep.* 6:e13872. doi: 10.14814/phy2.13872

Wray, D. W., Witman, M. A., Ives, S. J., Mcdaniel, J., Fjeldstad, A. S., Trinity, J. D., et al. (2011). Progressive handgrip exercise: evidence of nitric oxide-dependent vasodilation and blood flow regulation in humans. *Am. J. Physiol. Heart Circ.* 300, H1101–H1107. doi: 10.1152/ajpheart.01115.2010

Yasuda, T., Brechue, W. F., Fujita, T., Shirakawa, J., Sato, Y., and Abe, T. (2009). Muscle activation during low-intensity muscle contractions with restricted blood flow. *J. Sports Sci.* 27, 479–489. doi: 10.1080/02640410802626567

Yoon, T., Schlinder Delap, B., Griffith, E. E., and Hunter, S. K. (2007). Mechanisms of fatigue differ after low-and high-force fatiguing contractions in men and women. *Muscle Nerve* 36, 515–524. doi: 10.1002/mus.20844

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Physiology

ORIGINAL RESEARCH
published: 17 March 2022
doi: 10.3389/fphys.2022.837631

Acute and Chronic Bone Marker and Endocrine Responses to Resistance Exercise With and Without Blood Flow Restriction in Young Men

Debra A. Bemben[1]*, *Vanessa D. Sherk*[2], *Samuel R. Buchanan*[3], *SoJung Kim*[4], *Kyle Sherk*[5] *and Michael G. Bemben*[1]

[1]Department of Health and Exercise Science, University of Oklahoma, Norman, OK, United States, [2]Department of Orthopedics, University of Colorado Anschutz Medical Campus, Aurora, CO, United States, [3]Department of Health and Human Performance, University of Texas Rio Grande Valley, Edinburg, TX, United States, [4]Department of Health and Exercise Science, Rowan University, Glassboro, NJ, United States, [5]Hanger Clinic, Denver, CO, United States

OPEN ACCESS

Edited by:
Adam Zajac,
University School of Physical Education in Wroclaw, Poland

Reviewed by:
Ashril Yusof,
University of Malaya, Malaysia
Danny Christiansen,
University of Copenhagen, Denmark

***Correspondence:**
Debra A. Bemben
dbemben@ou.edu

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: 16 December 2021
Accepted: 22 February 2022
Published: 17 March 2022

Citation:
Bemben DA, Sherk VD, Buchanan SR, Kim S, Sherk K and Bemben MG (2022) Acute and Chronic Bone Marker and Endocrine Responses to Resistance Exercise With and Without Blood Flow Restriction in Young Men. Front. Physiol. 13:837631. doi: 10.3389/fphys.2022.837631

In this study, we compared acute and chronic bone marker and hormone responses to 6 weeks of low intensity (20% 1RM) blood flow restriction (BFR20) resistance training to high intensity (70% 1RM) traditional resistance training (TR70) and moderate intensity (45% 1RM) traditional resistance training (TR45) in young men (18–35 years). Participants were randomized to one of the training groups or to a control group (CON). The following training programs were performed 3 days per week for 6 weeks for knee extension and knee flexion exercises: BFR20, 20%1RM, 4 sets (30, 15, 15, 15 reps) wearing blood flow restriction cuffs around the proximal thighs; TR70, 70% 1RM 3 sets 10 reps; and TR45, 45% 1RM 3 sets 15 reps. Muscle strength and thigh cross-sectional area were assessed at baseline, between week 3 and 6 of training. Acute bone marker (Bone ALP, CTX-I) and hormone (testosterone, IGF-1, IGFBP-3, cortisol) responses were assessed at weeks 1 and 6, with blood collection done in the morning after an overnight fast. The main findings were that the acute bone formation marker (Bone ALP) showed significant changes for TR70 and BFR20 but there was no difference between weeks 1 and 6. TR70 had acute increases in testosterone, IGF-1, and IGFBP-3 (weeks 1 and 6). BFR20 had significant acute increases in testosterone (weeks 1 and 6) and in IGF-1 at week 6, while TR45 had significant acute increases in testosterone (week 1), IGF-1 (week 6), and IGFBP-3 (week 6). Strength and muscle size gains were similar for the training groups. In conclusion, low intensity BFR resistance training was effective for stimulating acute bone formation marker and hormone responses, although TR70 showed the more consistent hormone responses than the other training groups.

Keywords: bone metabolism, hormones, muscle hypertrophy, strength, resistance training

INTRODUCTION

Low intensity resistance exercise combined with blood flow restriction (BFR) has been shown to improve muscle strength and mass (Abe et al., 2005; Laurentino et al., 2012; Bjørnsen et al., 2019); however, a meta-analysis by Lixandrão et al. (2018) suggests that BFR training stimulates similar gains in muscle hypertrophy but smaller increases in strength compared to traditional high intensity resistance training intensity (≥65% 1 repetition maximum, 1RM). This type of training program may be beneficial for individuals who have difficulty performing high intensity resistance exercise, such as those with chronic diseases such as multiple sclerosis, osteoporosis, and osteoarthritis (Freitas et al., 2021).

Possible mechanisms for the adaptations that occur with BFR exercise include enhanced metabolic stress resulting from the accumulation of metabolic by-products in the occluded limbs affecting fast-twitch motor unit recruitment and the secretion of hormones and factors that promote protein synthesis and angiogenesis (Takarada et al., 2000; Suga et al., 2012; Karabulut et al., 2014). Acute bouts of BFR resistance exercise stimulate increases in blood lactate and anabolic hormones (e.g., growth hormone, testosterone, insulin-like growth factor-1, IGF-1) with minimal changes in muscle damage markers (Takarada et al., 2000; Abe et al., 2005; Takano et al., 2005; Madarame et al., 2010; Manini et al., 2012; Yinghao et al., 2021). Another mechanism is the activation of localized chemoreceptors and exercise-induced muscle swelling, often observed following BFR exercise, that may play a role in shifting the protein balance toward anabolism. Wilson et al. (2013) reported that muscle activation increased by ~20 mV and swelling increased 0.5 cm, while muscle damage indices remained unchanged during acute bouts of practical BFR. It is well-documented that low intensity BFR resistance exercise increases muscle protein synthesis by altering signaling pathways, including the mammalian target of rapamycin complex 1 (mTORC1) and the inhibition of atrogenes like Muscle RING Finger1 (MuRF1) and atrogin-1 and the inhibition of the myostatin pathway (Fujita et al., 2007; Fry et al., 2010; Laurentino et al., 2012).

It is well established that mechanical loading induces positive effects on bone metabolism. For example, high intensity traditional resistance exercise has been shown to result in small (~1–3%) but significant increases in bone mineral density (BMD) at clinically relevant skeletal sites assessed by dual energy x-ray absorptiometry (DXA; see meta-analyses by Zhao et al., 2015; Shojaa et al., 2020). In addition to BMD, bone metabolism is frequently assessed by serum bone turnover markers; these biomarkers reflect the bone formation and bone resorption phases of the bone remodeling cycle (Szulc et al., 2019), and have several advantages as they respond more rapidly to treatments than DXA measurements and they may show greater responses than BMD (Bauer et al., 2012), making them very useful for evaluating bone responses to exercise interventions that are shorter in duration (e.g., <6 months) than the bone remodeling cycle. Previous studies have documented significant bone marker responses to both acute (Bemben et al., 2015) and chronic resistance training protocols (Pasqualini et al., 2019); however, the effects of low intensity BFR resistance exercise on bone marker responses has not been extensively examined. We previously reported that the bone resorption marker, N-terminal cross-linking telopeptide of type I collagen (NTX-I), decreased 30 min after a single bout of low intensity BFR resistance exercise in young men, thus reflecting a decrease in bone resorption rate in response to the exercise (Bemben et al., 2007). The results are mixed for bone responses to chronic BFR training programs. Kim et al. (2012) found no changes in bone markers in response to 3 weeks of BFR training in young men, in contrast to a significant increase in the bone formation marker, bone-specific alkaline phosphatase (Bone ALP) in the high intensity traditional resistance exercise group indicating an increase in bone formation only for the high intensity exercise stimulus. However, Bone ALP significantly increased after 6 weeks of BFR training in older men, and the increase was similar in magnitude to the high intensity resistance training group (Karabulut et al., 2011). Linero and Choi (2021) conducted a 12-week study comparing bone marker responses to low intensity (30% 1RM) BFR resistance exercise and moderate-high intensity (60–80% 1RM) traditional resistance exercise in postmenopausal women with osteoporosis or low bone mass. The bone resorption marker, C-terminal cross-linking telopeptide of type I collagen (CTX-I), significantly increased only in the moderate-high intensity training group. All groups, including the control group, had significant increases in the bone formation marker, procollagen type 1 N-terminal propeptide (P1NP), suggesting this bone formation marker response was a seasonal effect, rather than a training effect. At present, the underlying mechanisms responsible for these adaptations are unclear as low intensity BFR resistance exercise does not apply high magnitude external loads on bone. It could affect bone metabolism by increased intramedullary pressures and interstitial fluids through increased vascular restriction (Loenneke et al., 2012). Also, BFR results in a hypoxic condition that could activate hypoxia induced transcription factor (HIF) leading to increased expression of vascular endothelial growth factor (VEGF) and the formation of new blood vessels in the bone tissue (Araldi and Schipani, 2010). Bone formation (osteoblasts) and bone resorption (osteoclasts) cells are functionally linked to blood vessels, which transport osteoblast and osteoclast precursors to the local remodeling sites; this cross-talk between bone and vascular cells is recognized as critical for bone remodeling (Lafage-Proust and Roche, 2019).

Hormones play an important role in modulating intracellular signaling pathways, including signaling pathways that regulate muscle cell growth in response to resistance exercise (Kraemer et al., 2020; Gharahdaghi et al., 2021). Anabolic hormones, such as testosterone, growth hormone, and IGF-1, promote muscle hypertrophy *via* genomic (e.g., alter gene expression) and non-genomic (e.g., increase calcium release, mTOR pathway activation) signaling (Kraemer et al., 2020; Gharahdaghi et al., 2021). These hormones also regulate bone metabolism by promoting bone formation and/or inhibiting bone resorption (Hamdy and Appelman-Dijkstra, 2019; Shigehara et al., 2021).

Cortisol is a glucocorticoid hormone released in response to stress, such as high intensity/volume resistance exercise that exerts catabolic effects on muscle and bone tissue. Cortisol increases energy substrate availability through protein breakdown and counteracts muscle inflammation (Kraemer et al., 2020). Chronically elevated cortisol is associated with bone loss and increased bone fragility (Hamdy and Appelman-Dijkstra, 2019). Acute bouts of BFR resistance exercise have been shown to stimulate significant increases in testosterone (Madarame et al., 2010; Yinghao et al., 2021) and IGF-1 (Takano et al., 2005; Madarame et al., 2010; Yinghao et al., 2021) serum concentrations; however, the hormone adaptations to chronic BFR resistance training are not clear. Abe et al. (2005) reported a significant increase in resting serum IGF-1 concentrations after 2 weeks of BFR resistance training in young men, whereas Karabulut et al. (2013) found no significant changes in resting IGF-1, testosterone, or insulin-like growth factor binding protein-3 (IGFBP-3) serum concentrations in response to 6 weeks of either low intensity BFR or high intensity resistance training in older men. Also, the effects of BFR training programs on acute hormone responses to single bouts of resistance exercise have not been established.

While there is a growing body of literature related to BFR, there is a paucity of training studies that directly compare bone marker and hormone responses to low intensity BFR resistance exercise and traditional resistance exercise protocols. The purpose of this study was to compare acute and chronic effects of 6 weeks of low intensity (20% 1RM) blood flow restriction resistance training to high intensity (70% 1RM) and moderate intensity (45% 1RM) traditional resistance training programs on bone marker and endocrine responses in 18–35 year-old males. We hypothesized that acute bone marker and endocrine responses would be similar for the low intensity BFR and the high intensity resistance exercise groups, and that the responses for these two groups would be greater than the moderate intensity resistance exercise group and the control group. We expected that 6 weeks of low intensity BFR resistance training would elicit positive bone marker adaptations indicating increased bone formation (increased Bone ALP) and decreased bone resorption (decreased CTX-I) rates, however, these chronic responses would be greater in the high intensity resistance exercise group compared to the other training groups. We hypothesized that low intensity BFR training and high intensity resistance training would elicit similar hormone adaptations with an increase in anabolic hormones and a decrease in cortisol.

MATERIALS AND METHODS

Participants

Forty-three recreationally active healthy men aged from 18 to 35 years met the study inclusion criteria and gave their written informed consent to participate in the study. Two participants (1 from moderate intensity group, 1 from control group) dropped from the study prior to the pre-testing due to time constraints. Participants must not have been engaged in a resistance training program for the previous 4 months prior to the beginning of the study. Information regarding past and present health status was obtained through a health status questionnaire and a pre-participation questionnaire (Par-Q). Males with cardiovascular, pulmonary or metabolic disease, orthopedic problems, or smokers were excluded from the study. The university institutional review board approved this study, which was written in accordance with standards set by the Declaration of Helsinki.

Research Design

This study utilized a randomized control repeated measures design where participants were randomly assigned to one of four groups: high intensity traditional resistance training (70% 1RM: TR70, $n = 12$), moderate intensity traditional resistance training (45% 1RM: TR45, $n = 9$), low intensity resistance training with blood flow restriction (20% 1RM + Blood Flow Restriction: BFR20, $n = 12$) groups, or to a control group (CON, $n = 8$). Exercise groups trained 3 days Per week for 6 weeks while the control group maintained their normal daily activities and only participated in the pre, mid (week 3), and post training testing sessions.

During the pre, mid, and post testing sessions, participants were assessed for 1RM maximal strength for each of the six exercises used during training (lat pull down, biceps curl, triceps extension, shoulder press, knee flexion, and knee extension; **Figure 1**). Blood samples were obtained at the Pre and post exercise sessions at baseline and week six of training and were analyzed for hormones (total testosterone, IGF-1, IGFBP-3, cortisol) and bone turnover markers (Bone ALP, CTX-I). Body composition (total body scans) was assessed pre- and post-training and thigh muscle cross-sectional areas (femur scans) were assessed pre-, mid- (week 3), and post-training.

Training Protocols

Following baseline testing, participants were randomly assigned to the TR70, TR45, BFR20 training groups, or to a control group. Participants in the TR70 ($n = 12$), TR45 ($n = 9$), and BFR20 ($n = 12$) groups trained 3 days a week for about 1 h per session for 6 weeks. All sessions were monitored by trained lab staff. Participants began each training session with a 5 min standardized warm-up on cycle ergometer and 5 min stretching. Participants in the TR70 group performed four upper body exercises at 50% 1RM, 3 sets, 10 repetitions (lat pull down, shoulder press, biceps curl, and triceps extension) and two lower body exercises (knee flexion and knee extension) for 3 sets of 10 repetitions at 70% 1RM. Participants in the TR45 performed the same four upper body exercises at 50% 1RM, 3 sets, 10 repetitions and the knee flexion and knee extension exercises for 3 sets of 15 repetitions at 45% 1RM. Participants in the BFR20 group performed the same upper body exercises at the same intensity (50% 1RM), but performed the exercises for the lower body with specially designed restrictive cuffs (50 mm width, KAATSU Master, Sato Sports Plaza, Tokyo, Japan) placed at the upper most portion (1–2 cm distal to the inguinal folds) of both thighs. Participants completed 4 sets,

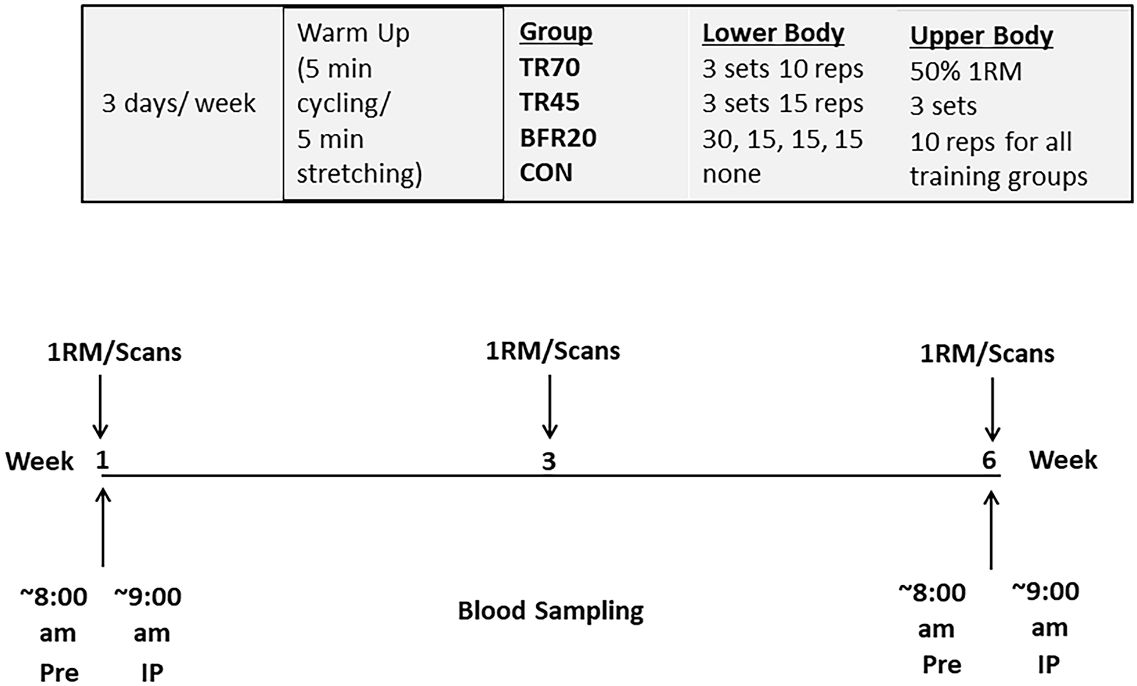

FIGURE 1 | Study protocol.

with the 30 repetitions in the first set and 15 reps for the remaining 3 sets at 20% 1RM. One minute rest separated each set of exercises for each training group. The initial restrictive cuff pressure was between 40 and 60 mmHg, and then the pressure was increased incrementally by 20 mmHg from 120 to 180 mmHg, inflated for 30 s and deflated for 10 s, until the training pressure of 160 mmHg was reached. One minute of rest separate each of the two BFR leg exercises and once both exercises were completed the cuffs were deflated and removed. Training loads were adjusted for strength gains after week 3 to maintain the required relative intensities. For the BFR20 group, cuff pressure was progressively increased every 2 weeks of training from 160 mmHg for weeks 1–2, 180 mmHg for weeks 3–4, and 200 mmHg for weeks 5–6. The control group ($n = 8$) participated in the pre, mid (week 3), and post testing sessions and were asked to maintain their normal daily activities over the course of the 6 week intervention.

Muscular Strength Testing

1RM tests were performed at baseline to determine the appropriate training workloads and maximum strength for each exercise (lat pull down, biceps curl, shoulder press, triceps extension, knee flexion, and knee extension). 1RM's were reassessed at the midpoint of training (week 3), and after completion of the training protocol (week 6). Resistance exercises were performed using Cybex machines (Cybex International Inc., Medway, MA, United States). All testing was completed by trained laboratory staff following standardized protocols and after participants were familiarized with each lift and had completed a warm-up on a stationary bicycle. Each test first estimated a load of about 50% of 1RM and subjects completed five repetitions. Then three repetitions were completed at about 80% of 1RM. The maximal load that could be successfully lifted was then determined within five attempts. One minute rest periods separated each attempt and 5 min of rest separated different muscle groups. Testing order was as follows: lat pull down, shoulder press, knee extension, bicep curl, triceps extension, and knee flexion.

Body Composition and Thigh Muscle Cross Sectional Area

Total and regional body composition was assessed Pre and post training by dual energy x-ray absorptiometry (DXA) (GE Lunar Prodigy, enCORE software version 6.70.021; GE Healthcare, Madison WI). First, height was measured with a wall stadiometer (cm) and body mass was measured using a standard electronic scale (kg). Participants then were positioned on the DXA table for the total body scan. Scan speeds were determined by the truncal thickness (thick >25 cm; standard 13–15 cm, and thin <13 cm). Percent body fat (%BF), fat mass (FM), fat free mass (FFM) and total and regional bone free lean body mass (BFLBM) variables were obtained from the total body scan analysis. The DXA was calibrated prior to each testing session by a single trained laboratory technician. In this laboratory, root-mean-square coefficients of variation (RMS CV%) for %BF, FM, BFLBM, and FFM are 1.9%, 1.6%, 1.3%, and 1.2%, respectively.

Mid-thigh muscle cross-sectional area (MCSA) was obtained by pQCT (XCT 3000, Stratec Medizintechnik GmbH, Pforzheim, Germany) by a trained technician at baseline, week 3, and post training. Scans were obtained on the non-dominant leg at 50% of femur length. Participants were seated in the scanning chair with the leg in the support straps, positioned in the center of the gantry, and participant was asked to remain still and to breathe normally during the scan acquisition. Scans were acquired with a voxel size of 0.4 mm, a slice thickness of 2.2 mm, and a scan speed of 20 mm/s. Obtaining MCSA values requires two "CalcBd" analyses to separate muscle, fat, and bone. Scan analyses for MCSA used a threshold driven contour detection (Mode 1) and Peel (Mode 2). The thresholds used in analysis 1 were −100 and 40, and the thresholds used in analysis 2 were 710 and 40. MCSA is derived by subtracting the "subcortical area" of analysis 2 from "subcortical area" of analysis 1. The same technician performed all scans. In our laboratory, the 50% femur site precision value (RMS CV%) is 1.6% for MCSA.

Blood Samples and Biochemical Assays

Venous blood collection occurred in the morning with the subjects in 8 h fasted state to minimize the diurnal variation effects on bone markers and hormones. One Pre (Pre) and one post exercise (IP) blood sample was obtained by a nurse on the first (WK 1) and last (WK 6) days of training. Bone markers also were measured 60 min post exercise (60P). The control group attended the blood draw sessions but remained in a rested seated position for the same time intervals. Blood samples were allowed to clot then centrifuged to obtain the serum, which as aliquoted into 0.5 ml microtubes, frozen at −80°C, and thawed only one time prior to each assay to reduce protein degradation.

Hematocrit (%) was measured at pre and IP in duplicate using capillary tubes centrifuged with a CritSpin Microhematocrit Centrifuge (StatSpin, Norwood, MA, United States), and read on a CritSpin Digital Reader (StatSpin, Norwood, MA, United States). Lactate was measured at Pre and IP using a Lactate Plus Portable Lactate Analyzer (Nova Biomedical, Waltham MA, United States). Percent change in plasma volume from pre to IP (%ΔPV) was determined with the following equation: $\%\Delta PV = \{100/(100 - \text{Hct Pre}) \times 100[(\text{Hct Pre} - \text{Hct Post})/\text{Hct Post}]\}$; Van Beaumont, 1972). Since plasma volume shifts occur during acute bouts of exercise, it is important to correct blood-borne substances (e.g., hormones, bone markers) for the effects of hemoconcentration to determine whether the response is a true metabolic response to the exercise protocol (Brahm et al., 1997). Bone marker and hormone serum concentrations were adjusted for plasma volume changes using the following formula: Corrected concentration = Uncorrected concentration × [(100 + ΔPV%)/100].

Serum concentrations of the bone formation marker, Bone-specific Alkaline Phosphatase (Bone ALP), was assessed in duplicate using a Metra BAP Enzyme ImmunoAssay (EIA) kit (Quidel Corporation, Mountain View, CA, United States). Inter assay coefficients of variation (CV%) for Bone ALP assays ranged from 5.2% to 6.8%, and intra assay CV% ranged from 4.5% to 13.1%. The bone resorption marker, C-terminal Telopeptide of Type I Collagen (CTX-I), was measured in duplicate using a commercial ELISA kit (Immunodiagnostics Systems, Inc.). Intra assay CV% ranged from 4.1% to 8.4% and inter assay CV% ranged from 1.4% to 5.1% for CTX-I.

Serum hormone concentrations (IGF-1, IGFBP-3, total testosterone, and cortisol) were assayed in duplicate using the following kits: IGF-I ELISA (Immunodiagnostic Systems Inc., Fountain Hills AZ); IGFBP-3 ELISA (ALPCO Diagnostics, Salem NH); Testosterone (Serum) EIA (ALPCO Diagnostics, Salem NH); and Cortisol ELISA (ALPCO Diagnostics, Salem NH). The intra assay CV% ranged from 4.2% to 9.2% and the inter assay CV% ranged from 6.4% to 15.9%.

Statistical Analyses

Statistical analyses were performed using IBM SPSS for Windows (v. 26). All data are represented as Mean ± SD unless otherwise stated. Sample sizes were adequate for 80% power based an effect size of 1.68 for acute bone marker responses (Bemben et al., 2007) and an expected moderate effect size of 0.8 for strength variables (Rhea, 2004). Normality of dependent variables was examined by the Shapiro-Wilks test, skewness and kurtosis, and Q-Q plots. Group differences in baseline dependent variables were analyzed using a one-way analysis of variance (ANOVA). Three-way mixed factorial repeated measures ANOVA [Group × Training (Week 1, Week 6) × Time (Pre, IP, 60P)] was used to determine acute and chronic bone marker and hormone serum concentration responses. If there were significant interaction effects, then the model was decomposed using two-way repeated measures ANOVA (training × time) with Bonferroni *post hoc* tests within each group. Percent changes in blood variables were analyzed by two-way repeated measures ANOVA Group × Training (Week 1, Week 6) with Bonferroni *post hoc* tests. Pearson correlation coefficients (r) were computed to determine relationships between absolutes changes in hormone variables and muscle strength/CSA variables. Effect sizes for the ANOVA results were calculated as partial eta squared (η_p^2), which were classified as small (0.0099), medium (0.0588), or large (0.1379) (Richardson, 2011). Statistical significance was set at a probability of $p \leq 0.05$.

RESULTS

Physical Characteristics and Body Composition

At baseline, the CON group was significantly older ($p = 0.002$) than the other three groups (**Table 1**). There was a significant group effect for height ($p = 0.039$), but *post hoc* analyses did not detect any group differences. There were no group differences for any of the body composition variables (total or regional; **Supplementary Table 1**) or for mid-thigh muscle CSA at baseline (**Table 2**).

There were significant training effects for both BFLBM ($p < 0.0002$, $n_p^2 = 0.335$) and FFM ($p < 0.0002$, $n_p^2 = 0.334$), which increased pre- to post-training; however, there were no significant group or group × training interaction effects. There were no significant group differences in percent changes pre- to post-training in body composition variables (**Figure 2**). Mid-thigh muscle CSA area significantly increased from pre- to mid- ($p = 0.028$), pre- to post- ($p < 0.001$), and mid- to post-training ($p = 0.026$), but there were no significant differences between groups for the gains in muscle CSA (**Table 2**). Although there were no significant group differences in muscle CSA percent changes, percent increases pre- to post-training for the training groups exceeded the pQCT precision error (1.9%), while the CON group percent changes were within the precision error. There were no significant correlations between absolute changes in hormone responses and body composition and muscle CSA absolute change variables.

Blood Lactate and Plasma Volume Changes

Blood lactate and plasma volume changes are presented in **Table 3**. There were missing hematocrit values for four participants (TR70 $n = 1$, BFR20 $n = 1$, CON $n = 2$) in week 1 blood testing, thus, $n = 37$ for plasma volume changes for that week. Plasma volume decreased for all training groups, and the percent changes pre to IP at week six were significantly different for training groups compared to CON (all $p \leq 0.03$). There were significant group ($p < 0.0001$), time ($p < 0.0001$) and group × time interaction effects for blood lactate, which significantly increased pre to IP for weeks 1 and 6 (all $p < 0.0002$) for the training groups but not for CON. Blood lactate at IP (both weeks 1 and 6) was significantly higher (all $p < 0.0001$) for the training groups vs. CON. Also, TR70 had higher blood lactate concentrations at IP than BFR20 (week 1 $p = 0.035$, week 6 $p < 0.0001$).

TABLE 1 | Baseline participant characteristics.

Variable	Group			
	TR70 (*n* = 12)	TR45 (*n* = 9)	BFR20 (*n* = 12)	CON (*n* = 8)
Age (years)[a]	20.9 ± 2.9**	20.6 ± 1.7**	21.3 ± 2.5**	25.6 ± 4
Height (cm)[a]	179.9 ± 7.5	176.7 ± 5.7	179.7 ± 4.4	172.9 ± 3.6
Weight (kg)	82.8 ± 24.4	71.0 ± 7.8	83.5 ± 17.8	84.8 ± 17.2
% Body fat	19.7 ± 10.4	16.3 ± 5.8	23.5 ± 8.1	24.4 ± 7.9
FM (kg)	18.32 ± 15.98	11.70 ± 5.32	20.58 ± 10.67	21.47 ± 9.82
BFLBM (kg)	60.57 ± 8.36	55.99 ± 5.70	59.23 ± 8.27	59.26 ± 7.84
FFM (kg)	64.01 ± 8.93	59.24 ± 6.06	62.64 ± 8.69	62.75 ± 8.33

Values are mean ± SD. TR70, high intensity 70% 1RM; TR45, moderate intensity 45% 1RM; BFR20, blood flow restriction 20% 1RM; CON, control; FM, fat mass; BFLBM, Bone-free lean body mass; and FFM, fat-free mass. [a]Significant group effect.
$^{**}p \leq 0.01$ vs. CON.

Bone Turnover Markers

Bone marker responses to the acute resistance exercise protocols at weeks 1 and 6 of training are shown in **Table 4**. Effect sizes for three way repeated measures ANOVA bone marker analyses are shown in **Supplementary Table 2**. Large effect sizes ($n_p^2 \geq 0.1379$) were observed for the significant effects for Bone ALP and CTX-I. Resting Bone ALP and CTX-I concentrations were not significantly different between groups nor different between weeks 1 and 6 of training. There were significant time ($p < 0.0001$, $n_p^2 = 0.357$) and group × time interaction effects ($p < 0.0002$, $n_p^2 = 0.295$) for Bone ALP. TR70 had significant Bone ALP increases from Pre to IP followed by decreases from IP to 60P (all $p < 0.007$), BFR20 had a significant decrease from IP to 60P ($p = 0.001$), but TR45 or CON did not exhibit any time point differences. Similar patterns of responses were observed for percent changes in Bone ALP with TR70 and BFR20 showing significant time effects (both $p \leq 0.001$) as percent increases at IP were followed by decreases at 60P (**Figure 3A**). CTX-I had a significant time effect ($p < 0.0001$, $n_p^2 = 0.558$) showing a continual decrease from Pre to 60P (all $p < 0.004$) for all groups. CTX-I percent changes had significant time ($p < 0.0001$) and group × training × time ($p = 0.047$) interaction effects as TR70, BFR20, and CON groups had significantly greater percent decreases at 60P compared to IP (all $p < 0.004$) that was not observed for TR45 (**Figure 3B**). TR70 also had a significant training × time interaction ($p = 0.027$) showing a greater percent decrease in CTX-I at 60P for week 1 compared to week 6. Bone marker concentrations corrected for plasma volume changes are shown in **Supplementary Table 3**. There were no significant effects for Bone ALP after correcting

TABLE 2 | Mid-thigh muscle cross-sectional areas as measured by pQCT at baseline (pre), week 3 (mid), and post-training (post).

Variable	Group			
	TR70 (*n* = 12)	TR45 (*n* = 9)	BFR20 (*n* = 12)	CON (*n* = 8)
MCSA (mm²)[b]				
Pre	17167.4 ± 2702.8	15505.4 ± 1746.5	16162.0 ± 2564.4	17250.8 ± 2673.7
Mid*	17379.3 ± 2670.2	15771.3 ± 1736.5	16372.7 ± 2443.9	17395.9 ± 2555.3
Post**†	17526.6 ± 2714.9	16129.5 ± 1818.6	16603.9 ± 2703.8	17334.9 ± 2474.7
Abs Δ (mm²)				
Mid	211.9 ± 404.5	265.8 ± 458.0	210.7 ± 586.5	145.2 ± 412.8
Post	359.2 ± 341.5	624.1 ± 492.7	441.8 ± 318.6	84.1 ± 513.7
% Δ[b]				
Mid	1.32 ± 2.55	1.78 ± 2.92	1.47 ± 3.51	0.96 ± 2.43
Post††	2.15 ± 1.99	4.09 ± 3.12	2.68 ± 2.01	0.68 ± 3.06

Values are mean ± SD. TR70, high intensity 70% 1RM; TR45, moderate intensity 45% 1RM; BFR20, blood flow restriction 20%1RM; CON, control; MCSA, mid-thigh muscle cross-sectional area; Abs Δ-absolute change vs. Pre; % Δ-percent change vs. Pre. [b]Significant training effect.
$^{*}p \leq 0.05$ vs. pre. $^{**}p \leq 0.01$ vs. pre. $^{\dagger}p \leq 0.05$ vs. mid. $^{\dagger\dagger}p \leq 0.01$ vs. mid.

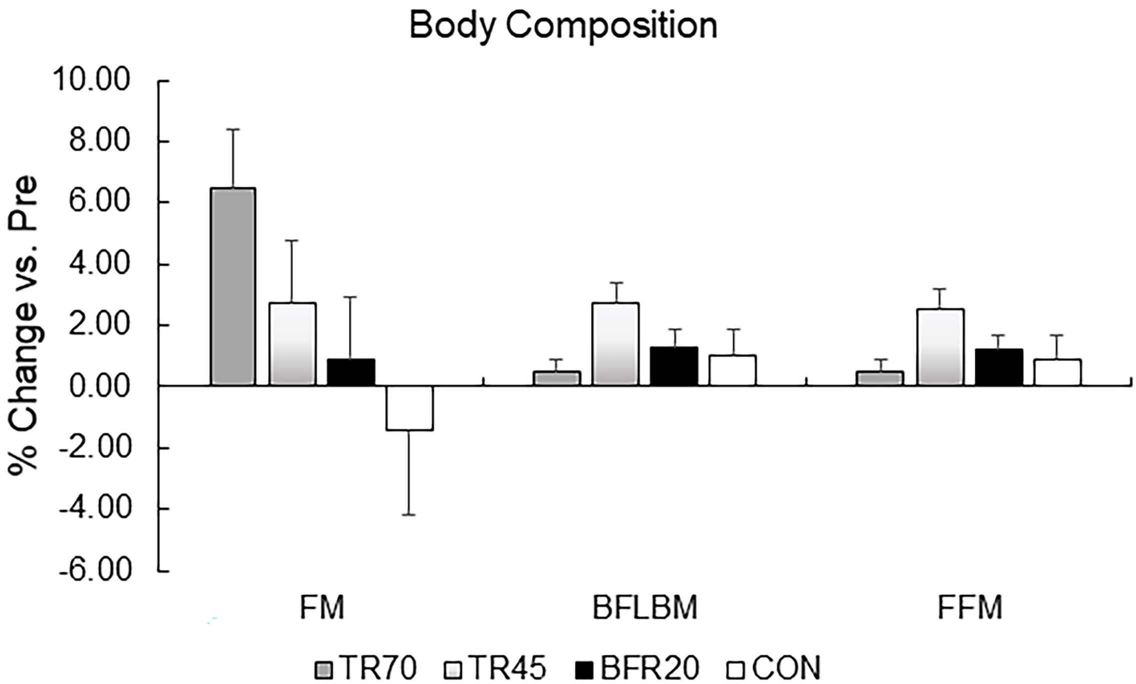

FIGURE 2 | Percent changes in body composition variables pre to post-training. TR70, high intensity 70% 1RM; TR45, moderate intensity 45% 1RM; BFR20, blood flow restriction 20% 1RM; CON, control; FM, fat mass; BFLBM, Bone-free lean body mass; and FFM, fat-free mass.

TABLE 3 | Plasma volume changes and blood lactate responses from pre-exercise (Pre) to immediately post-exercise (IP) at week 1 (WK1) and week 6 (WK6) of resistance training.

Variable	Group			
	TR70 (*n* = 12)	**TR45 (*n* = 9)**	**BFR20 (*n* = 12)**	**CON (*n* = 8)**
PVΔ WK1 (%)	−8.3 ± 1.7 (*n* = 11)	−8.2 ± 1.7	−5.2 ± 2.5 (*n* = 11)	0.8 ± 4.2 (*n* = 6)
PVΔ WK6 (%)	−7.9 ± 1.8*	−10.8 ± 2.1**	−8.9 ± 2.3*	1.5 ± 2.5
Lactate (mmol/L)^c				
WK1 Pre	0.88 ± 0.44	1.03 ± 0.75	1.55 ± 1.46	1.04 ± 0.59
WK1 IP	8.93 ± 2.56**†	8.23 ± 1.67**	6.33 ± 2.69**	0.88 ± 0.13
WK6 Pre	0.94 ± 0.88	0.81 ± 0.33	0.91 ± 0.52	0.99 ± 0.60
WK6 IP	10.05 ± 2.17**††	7.64 ± 2.56**	5.66 ± 3.01**	0.74 ± 0.29

Values are means ± SD. TR70, high intensity 70% 1RM; TR45, moderate intensity 45% 1RM; BFR20, blood flow restriction 20% 1RM; CON, control; PVΔ, plasma volume change. ^{c}Significant group × time interaction.
**p ≤ 0.05. **p ≤ 0.01 significant vs. CON. †p ≤ 0.05. ††p ≤ 0.01 significant vs. BFR20 group.*

for plasma volume changes; however, the significant time effects ($p < 0.0001$) remained for CTX-I.

Hormone Responses

Hormone responses to acute resistance exercise for weeks 1 and 6 of training are presented in **Table 5**, percent changes in hormone concentrations are shown in **Figure 3**, and hormone concentrations corrected for plasma volume shifts are shown in **Supplementary Table 4**. Effect sizes for three way repeated measures ANOVA hormone analyses are shown in **Supplementary Table 2**. Large effect sizes ($n_p^2 \geq 0.1379$) were observed for the significant effects from the three way repeated measures ANOVA for all hormones. There were no significant group differences or week differences in resting testosterone, and IGF-1 concentrations. Resting IGFBP-3 concentrations were significantly higher ($p = 0.025$) in the BFR20 group compared to TR70, and week 6 resting cortisol was significantly lower than week 1 ($p = 0.001$).

There were significant time ($p = 0.001$, $n_p^2 = 0.271$) and training × time interaction ($p = 0.019$, $n_p^2 = 0.140$) effects for testosterone. After decomposing the model, week 1 testosterone significantly increased from Pre to IP for week 1 ($p = 0.0004$), while week 6 testosterone had a significant group × time interaction ($p = 0.03$) as only the TR70 group showed a significant increase ($p = 0.005$) Pre to IP. Percent change in testosterone also showed a significant training effect ($p = 0.006$; **Figure 3C**) as significantly larger percent increases in testosterone occurred in week 1 compared to week 6. Correcting for plasma volume shifts eliminated the time effect, retained the training × time effect ($p = 0.011$), and added a significant group × time effect ($p = 0.019$) for testosterone responses. Both TR45 ($p = 0.023$) and BFR20 ($p = 0.049$) had significant decreases in corrected testosterone concentrations from Pre to IP.

Cortisol had a significant training effect ($p < 0.002$, $n_p^2 = 0.332$) as there was a significant decrease in serum cortisol concentrations from week 1 to 6. There were no significant group, training, or group × training interaction effects for percent changes in

TABLE 4 | Bone marker responses (uncorrected for plasma volume shifts) pre-exercise (Pre), immediately post-exercise (IP), and 60 min post-exercise (60P) at week 1 (WK1) and week 6 (WK6) of resistance training.

Variable	Group			
	TR70 (*n* = 12)	**TR45 (*n* = 9)**	**BFR20 (*n* = 12)**	**CON (*n* = 8)**
Bone ALP (U/L)[cd]				
WK1 Pre	40.54 ± 13.68	40.52 ± 10.58	36.17 ± 12.18	42.87 ± 15.99
WK1 IP	43.04 ± 13.61**	42.00 ± 8.60	37.48 ± 11.00	42.95 ± 15.97
WK1 60P	38.94 ± 13.41**††	40.65 ± 11.44	35.84 ± 11.49††	43.92 ± 17.51
WK6 Pre	41.93 ± 12.13	38.86 ± 10.97	36.15 ± 12.89	42.87 ± 13.81
WK6 IP	45.84 ± 12.99**	42.89 ± 10.52	39.15 ± 11.89	41.66 ± 13.33
WK6 60P	40.74 ± 11.56**††	38.64 ± 10.08	35.09 ± 10.24††	43.09 ± 15.74
Abs Δ (U/L)				
WK1 IP	2.50 ± 1.75	1.48 ± 2.71	1.30 ± 1.87	0.07 ± 1.72
WK1 60P	−1.60 ± 3.14	0.14 ± 2.51	−0.33 ± 3.00	1.05 ± 3.72
WK6 IP	3.91 ± 2.65	4.02 ± 6.06	2.99 ± 5.72	−1.22 ± 1.25
WK6 60P	−1.19 ± 1.89	−0.22 ± 3.38	−1.06 ± 5.63	0.21 ± 4.47
CTX-I (ng/ml)[d]				
WK1 Pre	1.29 ± 0.53	1.17 ± 0.45	1.02 ± 0.44	1.00 ± 0.28
WK1 IP**	1.21 ± 0.46	1.07 ± 0.51	0.96 ± 0.44	0.95 ± 0.26
WK1 60P**††	1.04 ± 0.41	1.03 ± 0.52	0.72 ± 0.31	0.71 ± 0.19
WK6 Pre	1.13 ± 0.53	1.18 ± 0.46	1.00 ± 0.41	1.03 ± 0.35
WK6 IP**	1.09 ± 0.43	1.07 ± 0.42	1.03 ± 0.42	0.97 ± 0.35
WK6 60P**††	1.02 ± 0.42	0.85 ± 0.34	0.81 ± 0.36	0.79 ± 0.17
Abs Δ (ng/ml)				
WK1 IP	−0.07 ± 0.09	−0.10 ± 0.24	−0.07 ± 0.18	−0.09 ± 0.12
WK1 60P	−0.25 ± 0.21	−0.14 ± 0.39	−0.29 ± 0.29	−0.29 ± 0.20
WK6 IP	−0.05 ± 0.10	−0.11 ± 0.14	0.03 ± 0.20	−0.05 ± 0.09
WK6 60P	−0.11 ± 0.17	−0.33 ± 0.23	−0.19 ± 0.25	−0.23 ± 0.23

Values are means ± SD. TR70, high intensity 70% 1RM; TR45, moderate intensity 45% 1RM; BFR20, blood flow restriction 20% 1RM; CON, control; Bone ALP, bone-specific alkaline phosphatase; CTX-I, C-terminal telopeptide of type I collagen; Abs Δ from Pre.
[c]$p \leq 0.001$ significant group × time interaction. [d]$p \leq 0.001$ significant time effect.
***$p \leq 0.01$ vs. Pre. ††$p \leq 0.001$ vs. IP.*

cortisol (**Figure 3D**). Adjusting IP cortisol concentrations for plasma volume shifts retained the training effect ($p < 0.0002$) and added a significant time effect ($p = 0.003$) with cortisol decreasing from Pre to IP.

IGF-1 had a significant time effect ($p < 0.0001$, $n_p^2 = 0.192$); overall, IGF-1 significantly increased from Pre to IP. There also was a trend for a significant group × training interaction ($p = 0.051$, $n_p^2 = 0.192$) as TR70 had significant IGF-1 increases pre to IP for both week 1 ($p = 0.005$) and week 6 ($p = 0.001$), and both BFR20 ($p = 0.002$) and TR45 ($p = 0.021$) had significant increases in IGF-1 for week 6 only. There were no significant effects for CON. There was a significant group effect ($p = 0.004$) for IGF-1 percent changes with TR70 showing greater percent increases ($p = 0.002$) in IGF-1 vs. CON (**Figure 3E**). There were no longer any significant effects for IGF-1 after correcting for plasma volume shifts.

There were significant group ($p = 0.048$, $n_p^2 = 0.190$), time ($p = 0.016$, $n_p^2 = 0.147$) and group × time interaction ($p < 0.0001$, $n_p^2 = 0.470$) effects for IGFBP-3. After decomposing the model, TR70 had significantly increased ($p = 0.001$) IGFBP-3 Pre to IP, TR45 had significantly increased ($p = 0.002$) IGFBP-3 only in week 6, CON had a significant decrease ($p = 0.029$) in IGFBP-3 Pre to IP, and BFR20 did not have any significant changes in IGFBP-3. There was a significant group effect ($p < 0.001$) for percent changes in IGFBP-3 as the training groups had greater percent changes than CON (all $p \leq 0.001$; **Figure 3F**). Correcting IGFBP-3 IP concentrations for plasma volume shifts eliminated the group × time interaction, but retained the significant group ($p = 0.007$) and time ($p < 0.0001$) effects. TR70 had significantly lower IGFBP-3 concentrations than BFR20, and there was a significant decrease in IGFBP-3 from Pre to IP time points.

Muscle Strength

Lower body strength results are shown in **Table 6** and percent changes in KE and KF strength variables are shown in **Figure 4**. There were no differences between the groups at baseline for any of the strength measures. There were significant training and group × training interaction effects for both KE and KF strength variables (all $p \leq 0.001$, $n_p^2 = 0.261$ to 0.576). The models were decomposed using one-way repeated measures ANOVAs with Bonferroni *post hoc* tests. All training groups showed significant increases from pre to mid for KE (all $p \leq 0.018$) and KF (all $p \leq 0.027$), and from pre to post training for KE ($p \leq 0.001$) and KF (all $p \leq 0.017$). There were no significant differences between mid and post for KE, however, KF strength significantly increased from mid to post for TR70 ($p = 0.008$) and BFR20 ($p = 0.05$). CON had no significant changes in KE or KF strength over the 6 week period. Group comparisons of percent changes in KE strength showed TR70 had greater strength gains than CON for mid ($p = 0.002$) and post ($p = 0.002$) time points (**Figure 4A**). BFR20 had greater percent increases in KF strength than CON for mid ($p = 0.027$) and post ($p = 0.002$) time points, and TR70 had greater percent increases in KF strength than CON for the post time point ($p = 0.002$; **Figure 4B**). There were few significant correlations between hormone and strength absolute change variables. The testosterone absolute change at week 1 was positively correlated with KE absolute change at week 3 ($r = 0.32$, $p = 0.044$). Absolute change in IGFBP-3 at week 1 was positively correlated with KF absolute changes at week 3 ($r = 0.51$, $p = 0.001$) and week 6 ($r = 0.37$, $p = 0.017$). Upper body strength measures are shown in **Supplementary Table 5**.

DISCUSSION

The unique findings of this study were that high intensity resistance exercise (TR70) and low intensity blood flow restriction resistance exercise (BFR20) elicited significant acute bone formation

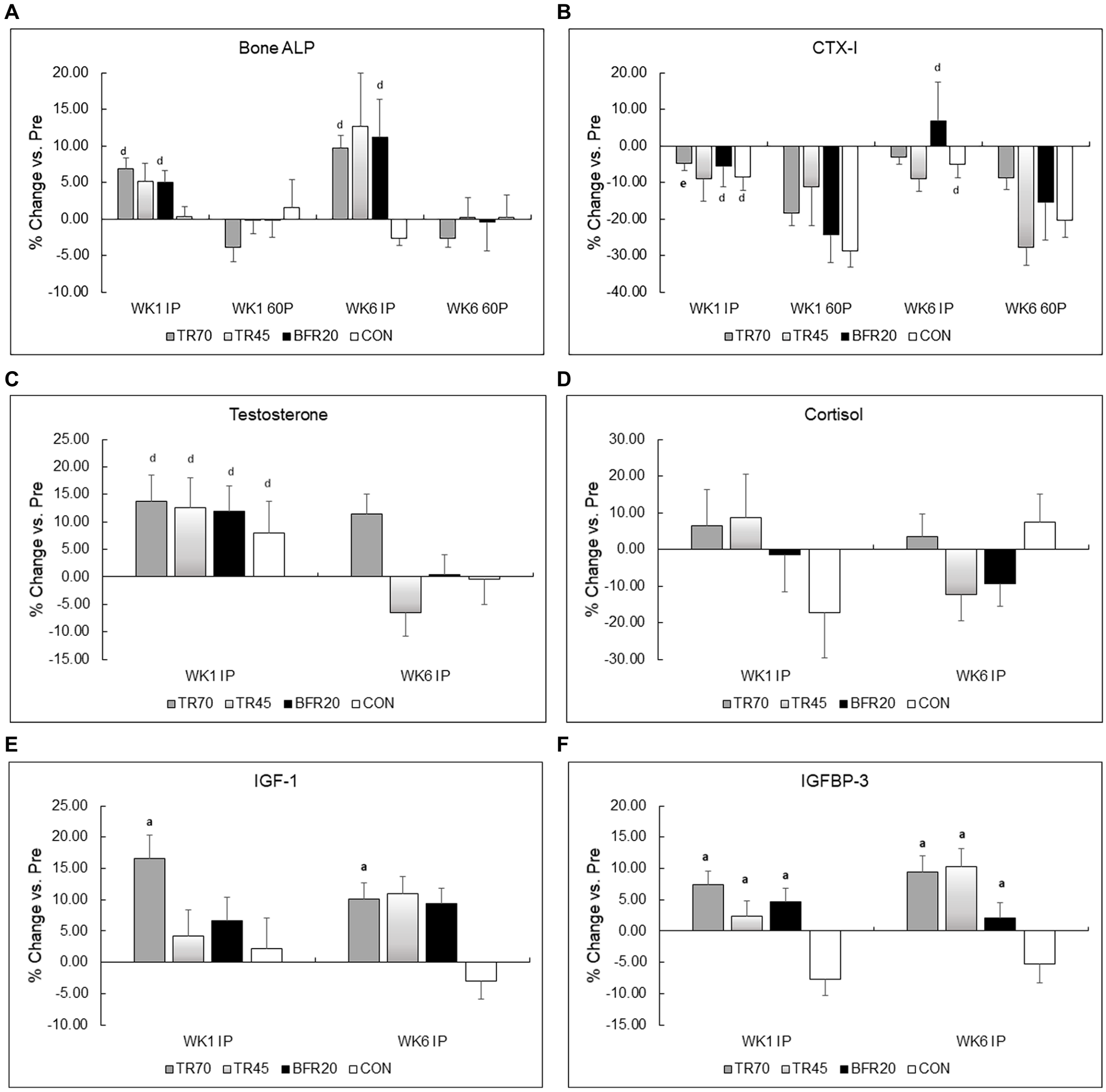

FIGURE 3 | Percent changes in bone markers (Panel **A** Bone ALP, Panel **B** CTX-I) and hormones (Panel **C** Testosterone, Panel **D** Cortisol, Panel **E** IGF-I, Panel **F** IGFBP-3) from pre-exercise (Pre) to immediately post-exercise (IP) for week 1 (WK1) and week 6 (WK6) of training. TR70, high intensity 70% 1RM; TR45, moderate intensity 45% 1RM; BFR20, blood flow restriction 20% 1RM; CON, control; Bone ALP, bone-specific alkaline phosphatase; CTX-I, C-terminal cross-linking telopeptide of type I collagen; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; $^{a}p \leq 0.002$ significant vs. CON; $^{d}p \leq 0.001$ significant time effect vs. 60P; $^{e}p = 0.027$ significant training × time interaction.

marker (Bone ALP) responses, but the bone resorption marker (CTX-I) was not affected by any of the acute exercise protocols. In addition, the 6 week training programs did not alter acute Bone ALP marker responses, however, the acute decrease in CTX-I was attenuated after training in the TR70 group suggesting a chronic adaptation. Acute and chronic hormone responses to the resistance exercise protocols differed based on training group. The TR70 group showed consistent acute increases in testosterone, IGF-1, and IGFBP-3 for both weeks 1 and 6 of training, and also had a greater percent increase in testosterone at week 6 compared to week 1. BFR20 had significant acute increases in testosterone at weeks 1 and 6 and in IGF-1 at week 6. TR45 had significant acute increases in testosterone at week 1 and in IGF-1 and IGFBP-3 at week 6. All groups had decreases in serum cortisol concentrations from week 1 to 6.

Bone Marker Responses

Significant changes in bone formation markers in response to acute bouts of BFR resistance exercise have not been reported previously. Our findings support our hypothesis that acute Bone ALP responses would be similar for TR70 and BFR20 groups. In our study, the primary mechanism for the increased serum Bone ALP concentrations was likely hemoconcentration as adjusting for plasma volume shifts eliminated the significant response. Circadian rhythm and

TABLE 5 | Hormone responses (uncorrected for plasma volume shifts) pre-exercise (Pre) to immediately post-exercise (IP) at week 1 (WK1) and week 6 (WK6) of resistance training.

Variable	Group			
	TR70 (*n* = 12)	**TR45 (*n* = 9)**	**BFR20 (*n* = 12)**	**CON (*n* = 8)**
Testosterone (ng/ml)[ce]				
WK1 Pre	4.62 ± 1.24	5.84 ± 2.85	4.57 ± 2.45	4.54 ± 1.42
WK1 IP**	5.21 ± 1.27	6.34 ± 2.53	4.99 ± 2.44	5.04 ± 2.48
WK6 Pre	4.82 ± 1.74	5.89 ± 2.08	5.10 ± 2.68	5.14 ± 2.20
WK6 IP	5.36 ± 1.95**	5.51 ± 2.37	5.13 ± 2.85	5.06 ± 2.09
Abs Δ (ng/m)				
WK1	0.59 ± 0.52	0.50 ± 0.84	0.41 ± 0.57	0.50 ± 1.31
WK6	0.55 ± 0.54	−0.38 ± 1.13	0.03 ± 0.51	−0.08 ± 0.46
Cortisol (μg/dL)[b]				
WK1 Pre	30.18 ± 9.99	30.29 ± 14.90	29.40 ± 11.14	23.01 ± 8.63
WK1 IP	31.12 ± 7.95	33.37 ± 22.79	28.06 ± 14.46	20.06 ± 11.78
WK6 Pre††	24.45 ± 8.68	28.71 ± 17.4	25.24 ± 8.27	19.01 ± 8.07
WK6 IP††	25.62 ± 11.77	24.13 ± 11.59	23.64 ± 11.16	19.29 ± 9.15
Abs Δ (μg/dL)				
WK1	0.94 ± 6.25	3.08 ± 11.18	−1.34 ± 10.33	−2.94 ± 4.06
WK6	1.17 ± 5.23	−4.59 ± 6.73	−1.60 ± 5.20	0.28 ± 5.80
IGF-1 (ng/ml)[d]				
WK1 Pre	137.32 ± 48.73	130.88 ± 44.06	131.76 ± 44.40	129.50 ± 73.32
WK1 IP	159.17 ± 55.68**	136.90 ± 49.69	139.12 ± 45.00	139.94 ± 105.19
WK6 Pre	137.26 ± 59.23	144.20 ± 44.64	145.32 ± 49.04	98.71 ± 33.94
WK6 IP	150.55 ± 63.39**	161.39 ± 57.31*	157.48 ± 50.23**	96.90 ± 39.00
Abs Δ (ng/ml)				
WK1	20.81 ± 17.86	6.02 ± 14.23	7.36 ± 9.48	10.44 ± 43.97
WK6	13.29 ± 9.14	17.19 ± 18.05	12.16 ± 10.24	−1.81 ± 11.65
IGFBP-3 (ng/ml)[acd]				
WK1 Pre	2160.98 ± 491.63	2442.78 ± 283.63	2609.21 ± 479.05	2387.45 ± 343.59
WK1 IP	2300.38 ± 420.17**	2497.93 ± 267.97	2717.69 ± 458.50	2199.03 ± 341.56*
WK6 Pre	2032.23 ± 306.47	2353.86 ± 274.93	2665.36 ± 659.23	2355.07 ± 692.00
WK6 IP	2242.02 ± 502.94**	2598.10 ± 372.74**	2697.48 ± 654.30	2204.61 ± 530.59*
Abs Δ (ng/ml)				
WK1	139.40 ± 170.50	55.15 ± 78.61	108.48 ± 200.96	−188.42 ± 252.75
WK6	209.79 ± 250.07	244.24 ± 161.0	32.11 ± 233.15	−150.46 ± 223.44

Values are mean ± SD. TR70, high intensity 70% 1RM; TR45, moderate intensity 45% 1RM; BFR20, blood flow restriction 20% 1RM; CON, control; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; Abs Δ-absolute change vs. Pre.
[a]*Significant group effect.*
[b]*Significant training effect.*
[c]*Significant group × time interaction.*
[d]*Significant time effect.*
[e]*Significant training × time interaction.*
**p ≤ 0.05. **p ≤ 0.01 vs. Pre. †p ≤ 0.05. ††p ≤ 0.01 vs. WK1.*

seasonal variations are sources of variability in serum bone marker concentrations (Szulc et al., 2019). For example, CTX-I shows large diurnal variation, peaking after midnight then decreasing throughout the day, and seasonal changes in vitamin D alter bone formation and resorption rates reflected by changes in bone markers (Szulc et al., 2019). Since we observed a significant decrease in CTX-I Pre to 60P in the control group as well as in all training groups, the underlying mechanism was likely a circadian rhythm effect rather than an exercise response. Previously, we reported the bone resorption marker (NTX-I) significantly decreased after an acute bout of low load BFR training in young men and correcting for plasma volume changes strengthened this response (Bemben et al., 2007). The explanation for the discrepant findings is not clear since the same BFR device and exercise protocol were used in both studies. BFR resistance exercise may affect bone cell activity by stimulating changes in pH and hypoxia (McCarthy, 2006), thereby activating factors [e.g., hypoxia induced transcription factor (HIF), vascular endothelial growth factor (VEGF)] important for formation of new blood vessels in bone tissue (Araldi and Schipani, 2010). In support of this mechanism, BFR training has been shown to increase serum VEGF concentrations (Takano et al., 2005; Patterson et al., 2013; Zhao et al., 2020). BFR also may alter vascular endothelial cell secretory functions (e.g., interleukin-6, endothelin-1, and nitric oxide) causing a disruption in the coupling process between bone resorption and formation. The evidence for this mechanism is mixed as studies have reported significant increases (Patterson et al., 2013) and no change in interleukin-6 (Bugera et al., 2018) to single bouts of BFR resistance exercise as well as increases (Zhao et al., 2020) and no change (Karabulut et al., 2013) in interleukin-6 to BFR resistance training programs.

In contrast to previous studies, Bone ALP responses did not show a training adaptation for any group; however, TR70 had an attenuated CTX-I decrease at week 6 compared to week 1. Karabulut et al. (2011) reported similar increases (~21%–23%) in resting Bone ALP serum concentrations after 6 weeks of BFR resistance training (20% 1RM) and high intensity (80% 1RM) resistance training in older men. Although we used the same BFR device and the same protocol, Karabulut et al. (2011) had their participants perform leg press instead of knee flexion. In a 12 week study comparing BFR (30% 1RM) resistance training to moderate-high intensity (60%–80% 1RM) resistance training in postmenopausal women, Linero and Choi (2021) found an increase in CTX-I only in the moderate-high intensity training group. Although significant increases in the bone formation maker, P1NP, occurred for both training groups, the control group also had a significant increase suggesting this response was not caused by the training programs, but rather the effect of sources of biological variability (e.g., seasonal changes in bone turnover).

TABLE 6 | Lower body 1RM strength (kg) for each group at baseline (pre), week 3 (mid), and post-training (post).

Variable	Group			
	TR70 (*n* = 12)	**TR45 (*n* = 9)**	**BFR20 (*n* = 12)**	**CON (*n* = 8)**
KE (kg)[bc]				
Pre	99.0 ± 16.9	88.1 ± 14.8	90.3 ± 17.7	101.6 ± 31.9
Mid	121.2 ± 24.9**	101.0 ± 17.3**	101.8 ± 19.3**	104.9 ± 35.3
Post	130.4 ± 32.2**†	106.0 ± 14.9**	109.6 ± 23.0**†	106.8 ± 35.0
Abs Δ (kg)				
Mid	22.2 ± 14.7	12.9 ± 10.5	11.5 ± 7.7	3.3 ± 8.5
Post	31.4 ± 17.4	17.9 ± 11.2	19.3 ± 13.2	5.1 ± 10.7
KF (kg)[bc]				
Pre	96.7 ± 16.7	85.6 ± 9.2	87.0 ± 20.3	97.0 ± 25.0
Mid	107.0 ± 22.2**	93.4 ± 11.0**	99.0 ± 15.3**	95.2 ± 23.5
Post	120.6 ± 25.4**††	97.0 ± 12.5*	105.3 ± 16.1**†	95.4 ± 26.0
Abs Δ (kg)				
Mid	10.3 ± 11.2	7.9 ± 6.3	11.9 ± 9.5	−1.8 ± 11.9
Post	23.9 ± 12.7	11.4 ± 11.1	18.3 ± 11.2	−1.6 ± 10.4

Values are mean ± SD. TR70, high intensity 70% 1RM; TR45, moderate intensity 45% 1RM; BFR20, blood flow restriction 20% 1RM; CON, control; KE, knee extension strength; KF, knee flexion strength; Abs Δ-absolute change vs. Pre.
[b]Significant training effect.
[c]Significant group × training interaction.
**p ≤ 0.05 vs. Pre. **p ≤ 0.01 vs. Pre. †p ≤ 0.05 vs. Mid. ††p ≤ 0.01 vs. Mid.*

Hormone Responses

Our findings did not support our hypothesis that TR70 and BFR20 groups would have similar acute hormone responses to the exercise protocols. Overall, the TR70 protocol was the most consistent stimulus for eliciting acute increases in testosterone, IGF-1, and IGFBP-3 both at week 1 and 6 of training. The BFR20 group had significant acute increases in testosterone (week 1 and 6) and IGF-1 (week 6), while TR45 had significant increases in testosterone at week 1 and in IGF-1 and IGFBP-3 at week 6. The acute hormone responses, with the exception of IGF-1, were not attributed to plasma volume shifts. Cortisol decreased from week 1 to week 6 in all groups, which also was not explained by plasma volume changes. Our findings agree with previous studies documenting increases in testosterone (Madarame et al., 2010; Yinghao et al., 2021) and IGF-1 (Takano et al., 2005; Madarame et al., 2010; Yinghao et al., 2021) and no change in cortisol (Patterson et al., 2013) in response to a single bout of BFR resistance exercise. Few studies have examined the endocrine adaptations to BFR resistance training programs. Karabulut et al. (2013) found no significant changes in resting serum testosterone, IGF-1, or IGFBP-3 concentrations after 6 weeks of BFR resistance training in older men.

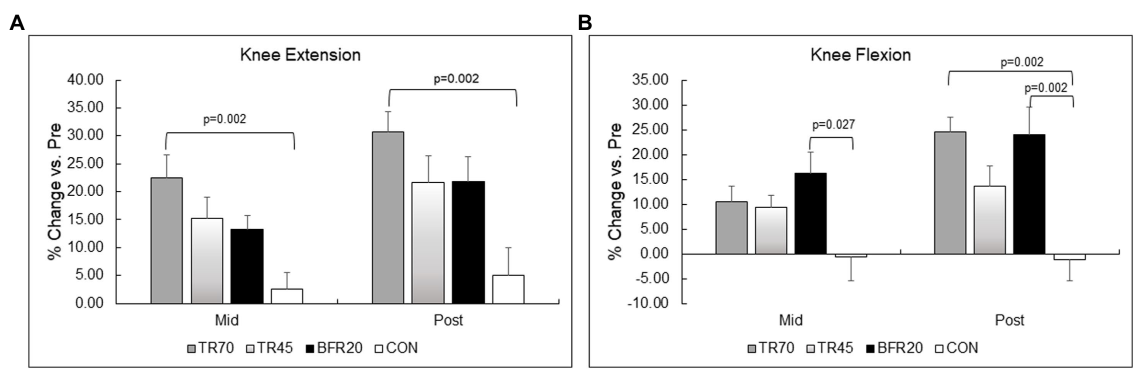

FIGURE 4 | Percent changes in lower body muscular strength for knee extension (Panel **A**) and knee flexion (Panel **B**). TR70, high intensity 70% 1RM; TR45, moderate intensity 45% 1RM; BFR20, blood flow restriction 20% 1RM; CON, control.

Endocrine responses to resistance exercise depend on the training protocol characteristics, such as exercise choice, intensity, volume, and rest periods; all are important determinants of increased metabolic demand resulting in changes in physiological conditions (e.g., increased lactate, hypoxia) that stimulate hormone secretion (Spiering et al., 2008). Recent muscle hypertrophy models recognize that protein synthesis is not regulated solely by hormone responses, but also by mechanical deformation and immune responses, and that all of these activate signaling pathways within skeletal muscle leading to increased translation and transcription, and ultimately, increased protein synthesis (Kraemer et al., 2020; Gharahdaghi et al., 2021). Testosterone and IGF-1 exert their anabolic effects through the mTOR pathway and satellite cell proliferation and differentiation, and testosterone regulates gene expression through binding to its androgen receptors on the cell nucleus (Kraemer et al., 2020; Gharahdaghi et al., 2021). The similar magnitude of the testosterone responses for the resistance exercise groups at week 1 suggests all groups were metabolically challenged enough at the onset of training to elicit increased testosterone release; however, only TR70 showed a training adaptation for testosterone. Cortisol, a catabolic hormone responsible for degrading protein and inhibition of protein synthesis, is typically upregulated following an acute bout of resistance exercise (Kraemer et al., 2020). In our study, the decreased resting cortisol levels, in conjunction with the acute increases in testosterone may provide a testosterone:cortisol ratio that would favor increased protein synthesis.

Muscle Strength and Size

In our study, BFR resistance training elicited similar knee flexion and extension strength gains as high intensity and moderate intensity traditional resistance exercise protocols. While the BFR20 group had ~9% lower knee extension strength gain than TR70 group, this difference was not statistically significant. A recent meta-analysis reported significantly lower strength gains (~7%) with BFR compared to high intensity resistance exercise (Lixandrão et al., 2018). As noted by Lixandrão et al. (2018), previous training studies may not have incorporated progression in the BFR protocols, whereas we increased cuff pressures every 2 weeks and increased training loads after week 3. There also is a possibility that strength gains with BFR protocols may be delayed as Bjørnsen et al. (2019) reported peak gains in muscle strength occurred 20 days after the training program.

Although all three training groups increased thigh muscle CSA, the underlying cellular mechanisms for hypertrophy may be different. Previous literature has identified activation of the mTOR pathway as being a potent stimulator of protein synthesis and subsequent muscle growth (Drummond et al., 2008; Dickinson et al., 2011), but BFR may follow a different response pattern than high intensity resistance exercise. Gundermann et al. (2014) documented a biphasic pattern for increased protein synthesis rates after an acute BFR resistance exercise protocol, in contrast to a continuous 24 h elevation in protein synthesis rates typically observed for high intensity resistance exercise protocols (Fry et al., 2013). However, the net balance in protein synthesis to breakdown rates improved by 24 h post BFR resistance exercise since there was minimal change in protein breakdown rates.

In this randomized control trial, we controlled for sources of biological error affecting bone marker and hormone responses, such as dietary intake and time of day for the acute testing sessions, and we also adjusted bone marker and hormone concentrations for plasma volume shifts. There are several limitations to our study. Our bone assessments were limited to bone markers as the short duration of the training programs did not allow sufficient time to assess bone mineral density changes by DXA. Another consideration is that bone marker and hormone concentrations may have been affected by seasonal changes since the study was conducted from early to late fall. A disadvantage of our standardized approach for setting cuff pressures was that it did not allow for individualized restrictive pressure settings that are currently recommended in the literature (Freitas et al., 2021).

In conclusion, low intensity BFR resistance training was effective for stimulating acute bone formation marker responses, although fewer acute hormone responses were observed for this protocol compared to high intensity traditional resistance exercise. BFR and moderate intensity resistance training groups had similar endocrine responses and muscular adaptations; however, the acute bone marker responses were different, suggesting that BFR training may be superior to moderate intensity resistance training for stimulating bone formation. There were no significant bone marker adaptations to chronic BFR resistance training, and cortisol decreased from week 1 to week 6 of BFR resistance training. The gains in lower body strength and muscle CSA were similar for the training groups. This study confirmed that low intensity BFR training can be performed safely in young men. The chronic effects of BFR resistance training on bone metabolism and bone mineral density remains to be determined, requiring longer duration interventions.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data used to support the findings of this study are restricted by the University of Oklahoma IRB in order to protect participant privacy. Data may be available in aggregate form from the corresponding author upon request. Requests to access the datasets should be directed to DB, dbemben@ou.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Oklahoma Norman campus. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DB revised the manuscript, contributed to the conception and design of the study and to the data analyses, and supervised the blood data collection and the bone marker and hormone assays. VS revised the manuscript, conducted data collection, and performed bone marker assays. SB wrote the first draft of the manuscript and contributed to the data analyses. SK assisted with data collection, performed bone marker assays, and revised the manuscript. KS assisted with data collection. MB revised the manuscript, developed the conception and design of the study, and supervised the training programs and the data collection. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded in part by a grant from the International Society for KAATSU Training Research awarded to MB (PI) and DB (Co-PI). Financial support was provided by the University of Oklahoma Libraries' Open Access Fund.

ACKNOWLEDGMENTS

The authors express our appreciation to the graduate students who assisted with supervising the training sessions for this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2022.837631/full#supplementary-material

REFERENCES

Abe, T., Yasuda, T., Midorikawa, T., Sato, Y., Inoue, K., Koizumi, K., et al. (2005). Skeletal muscle size and circulating IGF-1 are increased after two weeks of twice daily "KAATSU" resistance training. *Int. J. KAATSU Train. Res.* 1, 6–12. doi: 10.3806/ijktr.1.6

Araldi, E., and Schipani, E. (2010). Hypoxia, HIFs and bone development. *Bone* 47, 190–196. doi: 10.1016/j.bone.2010.04.606

Bauer, D., Krege, J., Lane, N., Leary, E., Libanati, C., Miller, P., et al. (2012). National bone health alliance bone turnover marker project: current practices and the need for US harmonization, standardization, and common reference ranges. *Osteoporos. Int.* 23, 2425–2433. doi: 10.1007/s00198-012-2049-z

Bemben, D. A., Palmer, I. J., Abe, T., Sato, Y., and Bemben, M. G. (2007). Effects of a single bout of low intensity KAATSU resistance training on markers of bone turnover in young men. *Int. J. KAATSU Train. Res.* 3, 21–26. doi: 10.3806/ijktr.3.21

Bemben, D. A., Sharma-Ghimire, P., Chen, Z., Kim, E., Kim, D., and Bemben, M. G. (2015). Effects of whole-body vibration on acute bone turnover marker responses to resistance exercise in young men. *J. Musculoskelet. Neuronal Interact.* 15, 23–31.

Bjørnsen, T., Wernbom, M., Løvstad, A., Paulsen, G., D'Souza, R. F., Cameron-Smith, D., et al. (2019). Delayed myonuclear addition, myofiber hypertrophy, and increases in strength with high-frequency low-load blood flow restricted training to volitional failure. *J. Appl. Physiol.* 126, 578–592. doi: 10.1152/japplphysiol.00397.2018

Brahm, H., Piehl-Aulin, K., and Ljunghall, S. (1997). Bone metabolism during exercise and recovery: the influence of plasma volume and physical fitness. *Calcif. Tissue Int.* 61, 192–198. doi: 10.1007/s002239900322

Bugera, E. M., Duhamel, T. A., Peeler, J. D., and Cornish, S. M. (2018). The systemic myokine response of decorin, interleukin-6 (IL-6) and interleukin-15 (IL-15) to an acute bout of blood flow restricted exercise. *Eur. J. Appl. Physiol.* 118, 2679–2686. doi: 10.1007/s00421-018-3995-8

Dickinson, J. M., Fry, C. S., Drummond, M. J., Gundermann, D. M., Walker, D. K., Glynn, E. L., et al. (2011). Mammalian target of rapamycin complex 1 activation is required for the stimulation of human skeletal muscle protein synthesis by essential amino acids. *J. Nutr.* 141, 856–862. doi: 10.3945/jn.111.139485

Drummond, M. J., Fujita, S., Takashi, A., Dreyer, H. C., Volpi, E., and Rasmussen, B. B. (2008). Human muscle gene expression following resistance exercise and blood flow restriction. *Med. Sci. Sports Exerc.* 40, 691–698. doi: 10.1249/MSS.0b013e318160ff84

Freitas, E. D. S., Karabulut, M., and Bemben, M. G. (2021). The evolution of blood flow restricted exercise. *Front. Physiol.* 12:747759. doi: 10.3389/fphys.2021.747759

Fry, C. S., Drummond, M. J., Glynn, E. L., Dickinson, J. M., Gundermann, D. M., Timmerman, K. L., et al. (2013). Skeletal muscle autophagy and protein breakdown following resistance exercise are similar in younger and older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* 68, 599–607. doi: 10.1093/gerona/gls209

Fry, C. S., Glynn, E. L., Drummond, M. J., Timmerman, K. L., Fujita, S., Abe, T., et al. (2010). Blood flow restriction exercise stimulates mTORC1 signaling and muscle protein synthesis in older men. *J. Appl. Physiol.* 108, 1199–1209. doi: 10.1152/japplphysiol.01266.2009

Fujita, S., Abe, T., Drummond, M. J., Cadenas, J. G., Dreyer, H. C., Sato, Y., et al. (2007). Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *J. Appl. Physiol.* 103, 903–910. doi: 10.1152/japplphysiol.00195.2007

Gharahdaghi, N., Phillips, B. E., Szewczyk, N. J., Smith, K., Wilkinson, D. J., and Atherton, P. J. (2021). Links between testosterone, oestrogen, and the growth hormone/insulin-like growth factor axis and resistance exercise muscle adaptations. *Front. Physiol.* 11:621226. doi: 10.3389/fphys.2020.621226

Gundermann, D. M., Walker, D. K., Reidy, P. T., Borack, M. S., Dickinson, J. M., Volpi, E., et al. (2014). Activation of mTORC1 signaling and protein synthesis in human muscle following blood flow restriction exercise is inhibited by rapamycin. *Am. J. Physiol. Endocrinol. Metab.* 306, E1198–E1204. doi: 10.1152/ajpendo.00600.2013

Hamdy, N. A. T., and Appelman-Dijkstra, N. M. (2019). "Other secondary causes of osteoporosis" in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. ed. J. P. Bileszkian. *9th* ed (Hoboken, NJ: John Wiley & Sons, Inc), 510–516.

Karabulut, M., Bemben, D. A., Sherk, V. D., Anderson, M. A., Abe, T., and Bemben, M. G. (2011). Effects of high-intensity resistance training and low-intensity resistance training with vascular restriction on bone markers in older men. *Eur. J. Appl. Physiol.* 111, 1659–1667. doi: 10.1007/s00421-010-1796-9

Karabulut, M., Leal, J. A., Garcia, S. D., Cavazos, C., and Bemben, M. (2014). Tissue oxygenation, strength and lactate response to different blood flow restrictive pressures. *Clin. Physiol. Funct. Imaging* 34, 263–269. doi: 10.1111/cpf.12090

Karabulut, M., Sherk, V. D., Bemben, D. A., and Bemben, M. G. (2013). Inflammation marker, damage marker and anabolic hormone responses to resistance training with vascular restriction in older males. *Clin. Physiol. Funct. Imaging* 33, 393–399. doi: 10.1111/cpf.12044

Kim, S., Sherk, V. D., Bemben, M., and Bemben, D. A. (2012). Effects of short term low intensity resistance training with blood flow restriction on bone markers and muscle cross-sectional area in young men. *Int. J. Exerc. Sci.* 5, 136–147.

Kraemer, W. J., Ratamess, N. A., Hymer, W. C., Nindl, B. C., and Fragala, M. S. (2020). Growth hormone(s), testosterone, insulin-like growth factors, and cortisol: roles and integration for cellular development and growth with exercise. *Front. Endocrinol.* 11:33. doi: 10.3389/fendo.2020.00033

Lafage-Proust, M. H., and Roche, B. (2019). "The vasculature and bone" in *Primer on the Metabolic Bone Diseases And Disorders of Mineral Metabolism*. ed. J. P. Bileszkian. *9th* ed (Hoboken, NJ: John Wiley & Sons, Inc), 981–991.

Laurentino, G. C., Ugrinowitsch, C., Roschel, H., Aoki, M. S., Soares, A. G., Neves, M., et al. (2012). Strength training with blood flow restriction diminishes myostatin gene expression. *Med. Sci. Sports Exerc.* 44, 406–412. doi: 10.1249/MSS.0b013e318233b4bc

Linero, C., and Choi, S. J. (2021). Effect of blood flow restriction during low-intensity resistance training on bone markers and physical functions in postmenopausal women. *J. Exerc. Sci. Fit.* 19, 57–65. doi: 10.1016/j.jesf.2020.09.001

Lixandrão, M. E., Ugrinowitsch, C., Berton, R., Vechin, F. C., Conceição, M. S., Damas, F., et al. (2018). Magnitude of muscle strength and mass adaptations between high-load resistance training versus low-load resistance training associated with blood-flow restriction: a systematic review and meta-analysis. *Sports Med.* 48, 361–378. doi: 10.1007/s40279-017-0795-y

Loenneke, J. P., Young, K. C., Fahs, C. A., Rossow, L. M., Bemben, D. A., and Bemben, M. G. (2012). Blood flow restriction: rationale for improving bone. *Med. Hypotheses* 78, 523–527. doi: 10.1016/j.mehy.2012.01.024

Madarame, H., Sasaki, K., and Ishii, N. (2010). Endocrine responses to upper- and lower-limb resistance exercises with blood flow restriction. *Acta Physiol. Hung.* 97, 192–200. doi: 10.1556/APhysiol.97.2010.2.5

Manini, T. M., Yarrow, J. F., Buford, T. W., Clark, B. C., Conover, C. F., and Borst, S. E. (2012). Growth hormone responses to acute resistance exercise with vascular restriction in young and old men. *Growth Hormon. IGF Res.* 22, 167–172. doi: 10.1016/j.ghir.2012.05.002

McCarthy, I. (2006). The physiology of bone blood flow: a review. *J. Bone Joint Surg. Am.* 88, 4–9. doi: 10.2106/JBJS.F.00890

Pasqualini, L., Ministrini, S., Lombardini, R., Bagaglia, F., Paltriccia, R., Pippi, R., et al. (2019). Effects of a 3-month weight-bearing and resistance exercise training on circulating osteogenic cells and bone formation markers in postmenopausal women with low bone mass. *Osteoporos. Int.* 30, 797–806. doi: 10.1007/s00198-019-04908-9

Patterson, S. D., Leggate, M., Nimmo, M. A., and Ferguson, R. A. (2013). Circulating hormone and cytokine response to low-load resistance training with blood flow restriction in older men. *Eur. J. Appl. Physiol.* 113, 713–719. doi: 10.1007/s00421-012-2479-5

Rhea, M. R. (2004). Determining the magnitude of treatment effects in strength training research through the use of the effect size. *J. Strength Cond. Res.* 18, 918–920. doi: 10.1519/14403.1

Richardson, J. T. E. (2011). Eta squared and partial eta squared as measures of effect size in educational research. *Educ. Res. Rev.* 6, 135–147. doi: 10.1016/j.edurev.2010.12.001

Shigehara, K., Izumi, K., Kadono, Y., and Mizokami, A. (2021). Testosterone and bone health in men: a narrative review. *J. Clin. Med.* 10, 530. doi: 10.3390/jcm10030530

Shojaa, M., von Stengel, S., Kohl, M., Schoene, D., and Kemmler, W. (2020). Effects of dynamic resistance exercise on bone mineral density in postmenopausal women: a systematic review and meta-analysis with special emphasis on exercise parameters. *Osteoporos. Int.* 31, 1427–1444. doi: 10.1007/s00198-020-05441-w

Spiering, B. A., Kraemer, W. J., Anderson, J. M., Armstrong, L. E., Nindl, B. C., Volek, J. S., et al. (2008). Resistance exercise biology: manipulation of resistance exercise programme variables determines the responses of cellular and molecular signalling pathways. *Sports Med.* 38, 527–540. doi: 10.2165/00007256-200838070-00001

Suga, T., Okita, K., Takada, S., Omokawa, M., Kadoguchi, T., Yokota, T., et al. (2012). Effect of multiple set on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *Eur. J. Appl. Physiol.* 112, 3915–3920. doi: 10.1007/s00421-012-2377-x

Szulc, P., Bauer, D. C., and Eastell, R. (2019). "Biochemical markers of bone turnover in osteoporosis" in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. ed. J. P. Bileszkian. *9th* ed (Hoboken, NJ: John Wiley & Sons, Inc), 293–301.

Takano, H., Morita, T., Iida, H., Asada, K., Kato, M., Uno, K., et al. (2005). Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. *Eur. J. Appl. Physiol.* 95, 65–73. doi: 10.1007/s00421-005-1389-1

Takarada, Y., Nakamura, Y., Aruga, S., Onda, T., Miyazaki, S., and Ishii, N. (2000). Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J. Appl. Physiol.* 88, 61–65. doi: 10.1152/jappl.2000.88.1.61

Van Beaumont, W. (1972). Evaluation of hemoconcentration from hematocrit measurements. *J. Appl. Physiol.* 32, 712–713. doi: 10.1152/jappl.1972.32.5.712

Wilson, J. M., Lowery, R. P., Joy, J. M., Loenneke, J. P., and Naimo, M. A. (2013). Practical blood flow restriction training increases acute determinants of hypertrophy without increasing indices of muscle damage. *J. Strength Cond. Res.* 27, 3068–3075. doi: 10.1519/JSC.0b013e31828a1ffa

Yinghao, L., Jing, Y., Yongqi, W., Jianming, Z., Zeng, G., Yiting, T., et al. (2021). Effects of a blood flow restriction exercise under different pressures on testosterone, growth hormone, and insulin-like growth factor levels. *J. Int. Med. Res.* 49:3000605211039564. doi: 10.1177/03000605211039564

Zhao, Y., Lin, A., and Jiao, L. (2020). Eight weeks of resistance training with blood flow restriction improve cardiac function and vascular endothelial function in healthy young Asian males. *Int. Health* 13, 471–479. doi: 10.1093/inthealth/ihaa089

Zhao, R., Zhao, M., and Xu, Z. (2015). The effects of differing resistance training modes on the preservation of bone mineral density in postmenopausal women: a meta-analysis. *Osteoporos. Int.* 26, 1605–1618. doi: 10.1007/s00198-015-3034-0

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Physiology

SYSTEMATIC REVIEW
published: 08 April 2022
doi: 10.3389/fphys.2022.838115

Is There a Minimum Effective Dose for Vascular Occlusion During Blood Flow Restriction Training?

Arpan Das and Bruce Patons**

Institute of Sports, Exercise and Health, Department of Medical Sciences, University College of London, London, United Kingdom

OPEN ACCESS

Edited by:
Adam Zajac,
University School of Physical Education in Wrocław, Poland

Reviewed by:
Albert Gollhofer,
University of Freiburg, Germany
Michal Wilk,
Jerzy Kukuczka Academy of Physical Education in Katowice, Poland

***Correspondence:**
Arpan Das
arpan.das.11@ucl.ac.uk
Bruce Patons
b.paton@ucl.ac.uk

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *17 December 2021*
Accepted: *22 February 2022*
Published: *08 April 2022*

Citation:
Das A and Paton B (2022) Is There a Minimum Effective Dose for Vascular Occlusion During Blood Flow Restriction Training? Front. Physiol. 13:838115. doi: 10.3389/fphys.2022.838115

Background: Blood flow restriction (BFR) training at lower exercise intensities has a range of applications, allowing subjects to achieve strength and hypertrophy gains matching those training at high intensity. However, there is no clear consensus on the percentage of limb occlusion pressure [%LOP, expressed as a % of the pressure required to occlude systolic blood pressure (SBP)] and percentage of one repetition max weight (%1RM) required to achieve these results. This review aims to explore what the optimal and minimal combination of LOP and 1RM is for significant results using BFR.

Method: A literature search using PubMed, Scopus, Wiley Online, Springer Link, and relevant citations from review papers was performed, and articles assessed for suitability. Original studies using BFR with a resistance training exercise intervention, who chose a set %LOP and %1RM and compared to a non-BFR control were included in this review.

Result: Twenty-one studies met the inclusion criteria. %LOP ranged from 40 to 150%. %1RM used ranged from 15 to 80%. Training at 1RM ≤20%, or ≥ 80% did not produce significant strength results compared to controls. Applying %LOP of ≤50% and ≥ 80% did not produce significant strength improvement compared to controls. This may be due to a mechanism mediated by lactate accumulation, which is facilitated by increased training volume and a moderate exercise intensity.

Conclusion: Training at a minimum of 30 %1RM with BFR is required for strength gains matching non-BFR high intensity training. Moderate intensity training (40–60%1RM) with BFR may produce results exceeding non-BFR high intensity however the literature is sparse. A %LOP of 50–80% is optimal for BFR training.

Keywords: BFR, strength training, bloodflow restriction training, rehabilitation, kaatsu, 1RM, one repetition maximum, dosage

INTRODUCTION

Blood flow restriction (BFR) training is a novel area of research within the strength and conditioning world. A pressurized cuff is applied proximally to the muscle trained and is inflated to partially occlude arterial blood flow but fully occlude venous return. This training method shows similar results to standard high intensity resistance training in both hypertrophy and strength at much lower exercise intensities. An increase in maximal voluntary contraction of 26% was reported in subjects training at 40% of one repetition max (1RM) with a 250 mmHg cuff applied to their thigh after 4 weeks, versus a control group undergoing the same intervention without limb occlusion who saw no significant change (Shinohara et al., 1998). An increase in thigh muscle cross sectional area (CSA) of 10.3% was found in subjects training with BFR at total limb occlusion pressure (LOP) at 10–20% 1RM for 8 weeks, whereas the control group on the same program without BFR had no significant hypertrophy (Takarada et al., 2004). This training method has broad applications - not only to strength athletes and bodybuilders but also to those who may find high intensity training difficult, such as people with osteoporosis, the elderly, or those going through exercise rehabilitation. These groups may benefit from heavy load training (Watson et al., 2015) but struggle to train at high intensities due to fracture risk, pain (Csapo and Alegre, 2016), or due to healing tissue which may be vulnerable to loading. Adverse side effects such as acute hypotension and reduction in vascular compliance have been observed with BFR training (Loenneke et al., 2013), however previously anticipated complications such as deep vein thrombosis and rhabdomyolysis (Vanwye et al., 2017; Minniti et al., 2020) are extremely rare indicating that BFR appears to be safe.

Exercise discomfort, post training soreness and reduced exercise volume appear to be associated with higher cuff pressures (Brandner and Warmington, 2017). Therefore, it would be advantageous to find a minimum effective pressure of vascular occlusion which would still grant significant strength adaptations that meet or even exceed those achievable with standard high intensity resistance training. While many papers have studied the effects of BFR at set applied pressures, less have explored the effects of BFR at a percentage of individual LOP. Individualizing the applied pressure based on LOP should theoretically produce a more effective and uniform physiological stress than a standardized set pressure. However, a recent review found that over 86% of studies of BFR training included no justification of the LOP chosen in their methodology (Clarkson et al., 2020).

This systematic review aims to determine a minimal and optimal applied vascular occlusion pressure during BFR training. It will also seek to determine a minimum exercise intensity (%1RM), volume load and total repetitions required to produce significant strength improvements. This will guide blood flow restricted exercise prescription for recreational strength training and exercise rehabilitation. Determining minimum effective pressure will allow us to avoid adverse effects and minimize exercise discomfort and delayed onset soreness.

METHOD

This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines (Moher et al., 2009).

Search Method

Online research databases PubMed, Scopus, Wiley Online Library and Springer Link were searched from May 2021. Search terms included "BFR training," "resistance training," and "1RM" as well as variations of these terms (see **Figure 1**). Relevant citations from reference lists of BFR reviews were also included. Where possible, filters were applied including "available in English," "research article," and "full text available." No set range of publication date was used.

Inclusion Criteria

Search results were saved into Zotero and duplicates removed. Single screening was performed by title, abstract and full text. Inclusion criteria were;

(1) Text available in English.
(2) Full text was available.
(3) Original research papers only. Systematic and narrative reviews, editorials, abstracts, and discussions of previous original work were excluded. Relevant citations from reference lists of these papers were included.
(4) BFR must have been included as part of an ongoing exercise intervention. Studies that investigated the acute effect of BFR were excluded. The intervention must have lasted at least 4 weeks.
(5) Exercise interventions were resistance training based. Aerobic, cardiovascular, and walking studies were excluded as we were investigating the effect of BFR on strength outcomes from resistance training.
(6) BFR method used had to be continuous - i.e., the BFR cuff remained on the participant throughout the exercise session with no breaks (as opposed to intermittent, where the participant removes the cuff during breaks).
(7) A non-BFR using control group was required who were also involved in an exercise intervention. Studies with non-exercising controls were excluded, as well as studies that only compared different %LOP without a non-BFR control.
(8) Initially, only studies using a control that were training using a standard "high intensity" strength training protocol as per the American College of Sports Medicine guidelines (Liguori, 2021) were included (70–80% 1RM, 3–4 sets of 8–12 repetitions). Studies that used a control group exercising at the same exercise intensity and volume as the BFR test group were included separately. As BFR studies tend to use lower exercise intensities (20–30%1RM), this would allow comparison of BFR as an independent variable against non-BFR groups training with the same protocol.
(9) Only papers that used a set percentage of individual LOP were included. Appropriate measurement of LOP should have therefore been demonstrated. Papers that used a standardized pressure of mmHg for all participants were

SEARCH TERMS
Blood flow restriction OR Vascular Occlusion OR Kaatsu training
AND
Resistance training OR Strength training OR Weight training
AND
One repetition maximum OR 1RM OR Maximum Voluntary Contraction

FIGURE 1 | Search terms with alternatives used for literature search.

excluded as actual dosage of BFR could vary considerably between participants.

(10) Chosen percentage of LOP and %1RM stayed constant throughout the intervention period.
(11) 1RM strength change was included as an outcome measure with pre and post values to calculate % change and effect size.
(12) Methodology included full description of exercise intervention for both the BFR testing and control groups.
(13) Participant group had no prior relevant medical history which could affect result i.e., people with cardiovascular/orthopedic/rheumatological conditions or undergoing exercise rehabilitation, in order to prevent their symptoms and range of severity from confounding the results from these studies.
(14) Participants could be of any age.
(15) Participants could be of any gender.
(16) Participants could have any duration prior training experience.

We did not control for age or gender, but recognize that these factors may affect response to bloodflow restriction due to vascular differences (see section "Limitations"). Ideally, we would have liked to analyze sub groups in populations based on gender, age, and training experience however the sparseness of the literature at this time would not have allowed for adequate total sample size to make meaningful conclusions.

Exclusions are identified in the PRISMA flowchart below (see **Figure 2**).

Study Quality

Study quality and study bias were evaluated. Quality and bias assessment was performed using an original tool created for BFR studies (Clarkson et al., 2020; see **Appendix Figure 3**). Criteria in this tool included experimental design reporting, participant choice and selection, as well as clarity and reproducibility of method. The maximum score in this tool is thirteen, with papers scoring below seven deemed to be of lesser quality or high bias risk. Lower score did not result in exclusion but enabled measurement of the overall quality of BFR literature. Level of evidence was evaluated using the Oxford Centre for Evidence Based Medicine tool (Centre for Evidence-Based Medicine [CEBM], 2009) which assesses studies on the quality of randomization, blinding, equality of intervention, and handling of participant dropout.

Data Extraction and Analysis

On completion of the initial screening, data from the original research were extracted including participant demographic, sample size, muscle group tested, type and length of exercise intervention (BFR and control groups), % of LOP applied (%LOP), and exercise intensity (%1RM). %1RM change from baseline to completion for BFR and control group was calculated from available data if %/Δ change was not included in study results. Effect size was calculated using Cohen's d (see **Appendix Figures 4, 5**).

RESULTS

Search Results

A total of 775 articles were identified in databases and reference lists up to May 2021 (Scopus $n = 84$, PubMed $n = 42$, Wiley Online Library $n = 187$, Science Direct $n = 157$, Springer Link $n = 253$, Reference lists $n = 52$). Seventeen duplicates were removed. Of the 758 remaining papers, 625 were single-screened and excluded from title or abstract. One hundred thirty-three papers were then evaluated using a *pro forma* based on my inclusion criteria. From that *pro forma* 112 were excluded leaving 21 (**Figure 2**).

Study Characteristics

Key characteristics of the included studies were sample size, %LOP, %1RM, exercise intervention design and length, and muscle group targeted (see **Appendix Figure 4**). Control group was categorized as a high intensity (70–80% 1RM) protocol or an intensity and volume matched protocol to the BFR group. The 21 studies included had a total sample size of 590. In the 21 studies chosen, 48 different protocols were tested with different combinations of %LOP, %1RM and target muscle group. **Table 1** shows the distribution of %LOP across the 48 protocols. **Table 2** shows the distribution of %1RM intensity chosen for the BFR groups. **Table 3** shows the distribution of muscle groups tested.

Ten protocols used control groups who trained at the same exercise intensity and volume as the BFR test group (Manimmanakorn et al., 2013; Fahs et al., 2015; May et al., 2018; Neto et al., 2019; Hill et al., 2020). The most common exercise load dosage was four sets of 30,15,15,15 repetitions (19 protocols), with most citing Loenneke et al.'s (2012) paper as their reasoning (Loenneke et al., 2012).

Most studies used participants who were not currently undertaking resistance training with only 5 studies using resistance trained participants. Almost half the studies (10/21) used solely male participants, with a third of studies (7/21) using untrained young men. The remaining studies used mixed participants or female only samples (7 and 4, respectively). Almost three quarters (15/21) of the studies used young (age 20–30) participants, the remaining using participants over 50 years old (5/21) or middle aged (40–50 years old) participants (1/21). Papers including participants with existing injuries or medical conditions were intentionally excluded, however this could be studied in a further review.

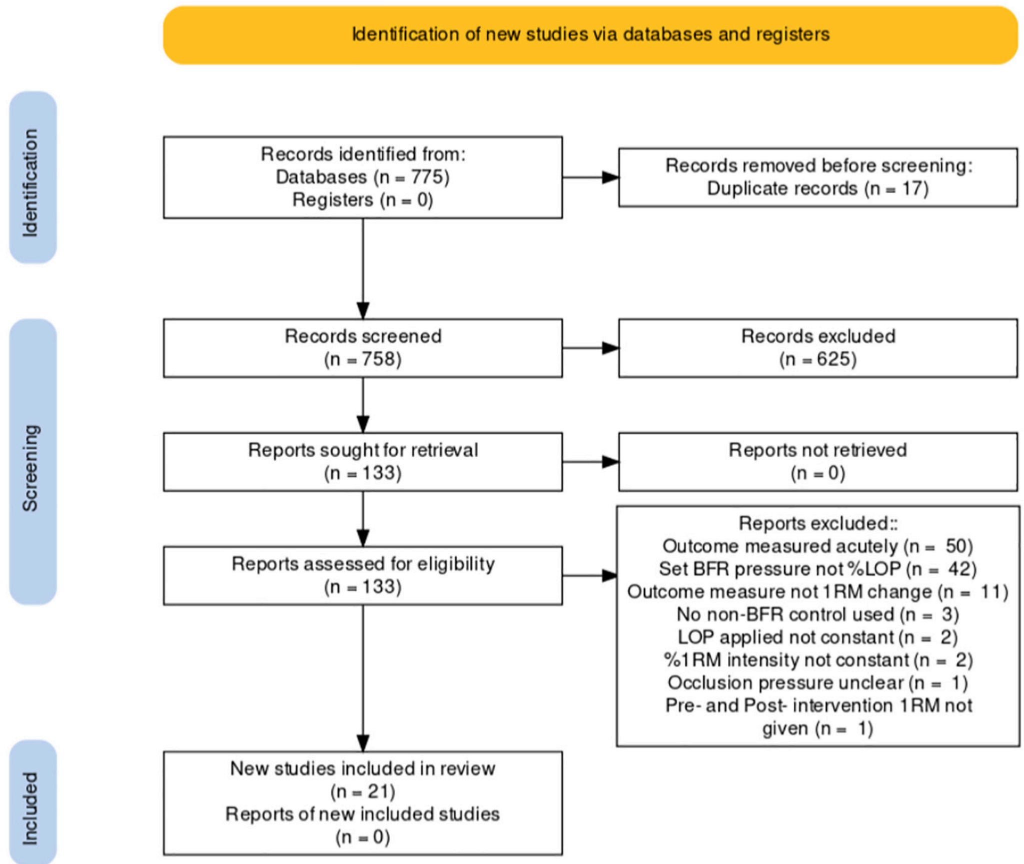

FIGURE 2 | PRISMA flowchart of exclusion process.

Study Findings

Limb Occlusion Pressure

At pressures at or exceeding total LOP (100–150%), high intensity training non-BFR groups (70–80%1RM) showed significantly greater strength improvements at all exercise intensities. At moderate to high intensities (60–80%) there was no statistically significant difference in strength gain found between BFR and non-BFR. BFR subjects in this study (Laurentino et al., 2008)however trained using a standard moderate repetition protocol rather than the higher repetition lower intensity protocol. At 80% LOP, BFR subjects who trained at very low intensities (15–20% 1RM) had statistically significantly lower strength gains compared to the high intensity control. One study however found that 20% 1RM was enough to produce strength improvements higher (but not statistically higher) than a high intensity non-BFR control. 30% 1RM at this BFR pressure produced similar strength improvements between the two groups. The study that tested 70% LOP found that strength (grip) was significantly higher in those training at 40% 1RM than non-BFR controls. At 60% LOP, non-BFR training produced better results for all exercises at 20% 1RM. This difference in strength gain between the groups was larger in exercises where the major contributing muscle group was too proximal to be occluded (bench press, seated row, and barbell squat) and less where the target muscle could be occluded (leg extension, bicep curl and calf raise). At 30% LOP, strength improvements were higher in the BFR group however there was not a statistical difference. At 50% LOP and 30% 1RM, interestingly Bemben (Bemben et al., 2019) found greater strength improvements in the BFR group in exercises where the target muscle could be occluded, such as bicep curl, knee extension and knee flexion, but

TABLE 1 | Distribution of applied LOP across the 48 protocols.

%LOP applied	Number of protocols
≥100 (Max 150)	9 (Laurentino et al., 2008; Manimmanakorn et al., 2013; Cook et al., 2017; Biazon et al., 2019; de Lemos Muller et al., 2019)
80	10 (Laurentino et al., 2012; Lixandrão et al., 2015; Jessee et al., 2018; de Lemos Muller et al., 2019; Neto et al., 2019)
70	1 (Ruaro et al., 2019)
60	11 (May et al., 2018; Brandner et al., 2019; Gavanda et al., 2020; Mendonca et al., 2021)
50	9 (Fahs et al., 2015; Vechin et al., 2015; Kim et al., 2017; Bemben et al., 2019; Centner et al., 2019)
40–45	7 (Lixandrão et al., 2015; Jessee et al., 2018; Letieri et al., 2018; Hill et al., 2020)

TABLE 2 | Distribution of %1RM intensity for BFR training across the 48 protocols.

%1RM intensity chosen	Number of protocols
80	3 (Laurentino et al., 2008; Lixandrão et al., 2015; Biazon et al., 2019)
50–60	3 (Laurentino et al., 2008; Cook et al., 2017; May et al., 2018)
40	2 (Cook et al., 2017; Ruaro et al., 2019)
30	20 (Fahs et al., 2015; Cook et al., 2017; Kim et al., 2017; Letieri et al., 2018; May et al., 2018; Bemben et al., 2019; de Lemos Muller et al., 2019; Gavanda et al., 2020; Hill et al., 2020)
15–20	20 (Laurentino et al., 2012; Manimmanakorn et al., 2013; Lixandrão et al., 2015; Jessee et al., 2018; Brandner et al., 2019; Neto et al., 2019; Clarkson et al., 2020; Mendonca et al., 2021)

TABLE 3 | Distribution of exercise choice/muscle group tested across the 48 protocols.

Exercise choice	Number of protocols
Leg extension/ quadricep extension	20 (Laurentino et al., 2008, 2012; Manimmanakorn et al., 2013; Fahs et al., 2015; Cook et al., 2017; Jessee et al., 2018; Letieri et al., 2018; May et al., 2018; Bemben et al., 2019; Biazon et al., 2019; Brandner et al., 2019; de Lemos Muller et al., 2019; Mendonca et al., 2021)
Elbow flexion/ bicep curl	7 (Kim et al., 2017; May et al., 2018; Bemben et al., 2019; Brandner et al., 2019; de Lemos Muller et al., 2019; Neto et al., 2019; Hill et al., 2020)
Leg flexion/ hamstring curl	5 (Cook et al., 2017; Letieri et al., 2018; May et al., 2018; Bemben et al., 2019)
Squat/leg press	4 (Vechin et al., 2015; Cook et al., 2017; Bemben et al., 2019; Brandner et al., 2019)
Bench press/chest press	3 (Bemben et al., 2019; Brandner et al., 2019; Neto et al., 2019)
Calf raise	3 (Brandner et al., 2019; Gavanda et al., 2020; Mendonca et al., 2021)
Lateral pulldown/ front Pulldown	2 (Bemben et al., 2019; Neto et al., 2019)
Elbow extension/ tricep extension	1 (Neto et al., 2019)
Seated row	1 (Brandner et al., 2019)
Wrist flexion/ grip strength	1 (Ruaro et al., 2019)

greater improvements in the non-BFR group in exercises where the primary muscle was too proximal such as lateral pulldown and bench press. At 20% however, the non-BFR group had significantly greater strength improvements. Finally at 40% LOP, Lixandrão et al. (2015), Jessee et al. (2018) and Letieri et al. (2018) found significantly lower strength improvements for the BFR group compared to non-BFR at all ranges of exercise intensities (80, 40, 30, 20, and 15%, respectively). Applied LOP does not appear to have the most significant effect on BFR strength adaptation, however extremes of pressures (<30%, >80%) appear to bring the worst results. Effect size varies wildly across amounts of applied LOP (see **Figure 3**), showing no true trend based on the studies chosen at this time.

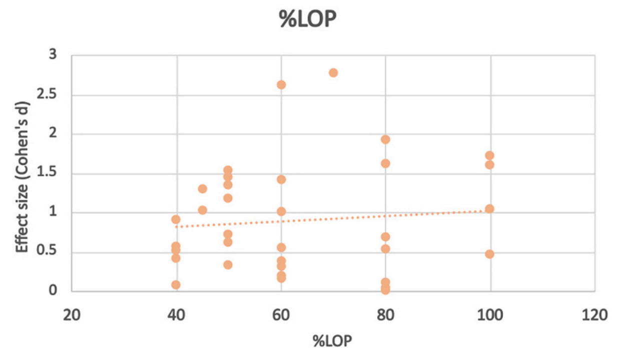

FIGURE 3 | Effect size observed at different%LOP applied during BFR exercise intervention with trendline.

Exercise Intensity

Training at 80% 1RM with low pressure BFR (40% LOP) produced significantly worse strength improvements than controls, although comparable results with high pressure BFR (100% LOP). Both studies looking at intensities of 50–60% 1RM with BFR found similar strength improvements to high intensity non-BFR but only at very high pressure (Laurentino et al., 2012; Cook et al., 2017) (100–150% LOP). Interestingly 40% 1RM with BFR produces significantly greater strength improvements when moderate pressure was applied (70% LOP), but significantly lower strength improvements at low-moderate pressure (40% LOP). 30% 1RM at BFR pressures exceeding total artery occlusion pressure produced significantly worse strength results than non-BFR controls. 30% 1RM at 80% LOP produced similar results between the BFR and non-BFR groups. At this exercise intensity and BFR pressure of 50–60% LOP, the BFR groups strength improvement exceeded the non-BFR group in exercises where the primary muscle group could be occluded. At 45% LOP, there was a significantly weaker effect than seen in the same study at 80% LOP. At very low intensities (15–20% 1RM), the non-BFR groups had significantly stronger strength improvements compared to the BFR groups at all pressures (100, 80, 60, 50, and 40%), the disparity seen most at the lower pressures applied (**Figure 4**).

In all studies where the control group trained at an exercise intensity and training volume matched to the low intensity BFR group, the BFR group had significantly greater strength improvements than the non-BFR group. In one study however, neither group made statistically significant strength improvements from baseline training at 20% 1RM.

Effect size appears to peak somewhere in the moderate intensity (50–60% 1RM) zone, however there is a significant skewness across distribution toward the lowest intensities due to very few studies using higher intensity protocols. Although there appears to be a trend, further work should be done in this area to verify whether this rings true.

Figure 5 shows the effect size plotted at each combination of %LOP and %1RM for the BFR test groups. Effect sizes were calculated for each combination of %LOP and %1RM from data presented in each study. Some studies were excluded as they did not present pre- and post-intervention, only presenting Δ

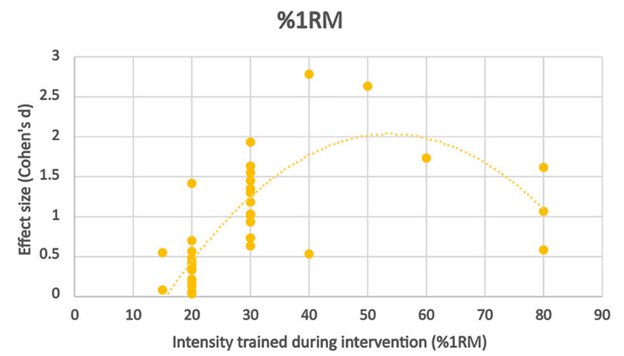

FIGURE 4 | Effect size observed at different%1RM trained during BFR exercise intervention with trendline.

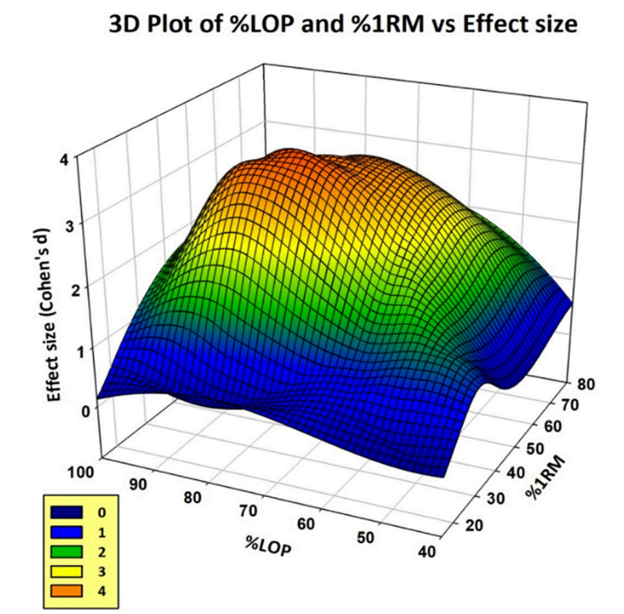

FIGURE 5 | 3D plot of %LOP (*x*-axis), %1RM (*y*-axis), and Effect Size (*z*-axis) for the 48 protocols.

strength improvement or percentage of strength increase, which prevented effect size from being calculated. As demonstrated, extremes of applied LOP and %1RM intensity respectively prove far less successful in generating significant improvements in strength gains using BFR training. However, combinations of moderate amounts of LOP and %1RM appear to show substantial effect. The "orange zone" of the graph shows the area of maximal effect. This appears to be between 60–80% LOP and 40–60% 1RM.

DISCUSSION

The purpose of this review was to determine the minimal and optimal amount of %LOP, exercise intensity and overall exercise dosage to elicit significant improvements in strength from BFR training. Results show that exercise intensity of 20% 1RM or below with BFR did not significantly increase strength compared to controls training at high intensity without BFR (70–80% 1RM). However, they did increase strength significantly against intensity matched controls. 30% 1RM with BFR appears to match high intensity non-BFR controls in strength gains, and 40%1RM appears to produce results that exceed high intensity controls.

Metabolic Stress

The above findings from clinical exercise-based studies may be explained by mechanism based BFR studies, with metabolic pathways in muscle affected differently by different dosages of LOP and exercise load/intensity. Suga et al. (2010) tested intramuscular levels of pH, phosphocreatine (PCr) and dihydrogen phosphate (H2PO4) in subjects training at 20, 30, and 40% 1RM with moderate BFR (130 mmHg), and 20% with high BFR (200 mmHg) against controls training at low and high intensities (20 and 80%, respectively). They found that 30% 1RM with moderate BFR caused drops in pH, PCr, and H2PO4 that matched the high intensity control, whereas 40% 1RM exceeded the change in these metabolic markers. Conversely, there was no significant difference in metabolite change between the 20%1RM group with moderate BFR and high BFR. This may explain why Lixandrao's study found that effect size favored 40% 1RM over 20%1RM at all LOPs, however there was no significant difference between 40 and 80% LOP at equal %1RM (Lixandrão et al., 2015). This reinforces the hypothesis that beyond a certain %LOP, there are no additional dose benefits to increased pressure and that exercise intensity becomes the primary variable for strength improvement.

The lower pH may be explained by increased levels of lactate during increasing exercise intensity. Goto et al. (2005) found that in two groups performing the same volume of exercise per session (3–5 sets of 10RM), the group who were given a 30 s break halfway through each set accumulated less lactate. They observed an increased growth hormone (GH) response and catecholamine release in the non-break group. The non-break group in this study consequently had a larger increase in lean mass, increased muscle CSA and increased leg extension at 12 weeks (Goto et al., 2005). Subjects training with BFR have been shown to have increased levels of GH, lactate, and noradrenaline post training than controls (Takarada et al., 2000). The increased lactate may be attributed to not only the impedance of venous return from the BFR cuff, but also reduced oxygen delivery due to partially occluded arterial flow, causing a hypoxic environment (Killinger et al., 2019). Lactate then accumulates in the muscle due to reduced aerobic respiration, at higher levels with increasing exercise intensity (Mazzeo et al., 1986). The increase in adrenaline seen in BFR training also contributes to lactate accumulation, as adrenaline reduces lactate uptake and metabolism in muscle *via* a β-adrenergic mechanism (Hamann et al., 2001).

Lactic Acid, pH, and Growth Hormone Stimulation

Kraemer's review found a strong association between muscle acidosis and GH release which he attributed to increased lactic acid (Kraemer and Ratamess, 2005). Increased GH was also associated with increased volume of exercise, as there was less time for lactate to be metabolised (Kraemer and Ratamess, 2005). In Reeves study, similar levels of lactate were observed between subjects training at 30%1RM with a BFR of 20 mmHg below SBP and controls training at 70%1RM without BFR. However, the GH response in the BFR group was fourfold of the non-BFR group (Reeves et al., 2006). The correlation between pH and GH was later confirmed by a study that found that subjects given an alkaline solution prior to a high intensity cycle trial had an attenuated GH response compared to controls given a neutral placebo (Gordon et al., 1994).

Growth Hormone

It is the increased stimulation of GH release by BFR training that likely causes desired strength outcomes. GH when released in pulses (such as after exercise) stimulates IGF-1 release. This increases muscle protein uptake, protein synthesis, and stimulates myoblast and satellite cell proliferation (Florini et al., 1996). Abe's study found that after even 2 weeks of BFR training at 20%1RM, circulating IGF-1 was 23.8% higher than baseline, whereas the non-BFR matched intensity group saw no significant change (Abe et al., 2005). IGF-1 activates mammalian target of Rapamycin (mTOR), resulting in a mechanism that causes cell division and tissue growth (Feng and Levine, 2010). In Fujita's study of BFR, subjects training at 20%1RM with a 200 mmHg cuff showed higher levels of lactate and GH than intensity matched non-BFR controls (Fujita et al., 2007). The BFR group had higher levels of Ribosome s6 Kinase phosphorylation (a target of mTOR signaling) and decreased levels of Eukaryotic Translation Elongation Factor 2 phosphorylation (Fujita et al., 2007). This resulted in a 46% increase in protein synthesis (Fujita et al., 2007). As seen above, the %1RM required during BFR to match the metabolic stress of high intensity exercise and elicit this mechanism, appears to be 30%, whereas to exceed high intensity exercise training at 40%1RM or above may be required (**Figure 6**).

Blood Flow and Hypoxia

As demonstrated in this review, extremely high BFR cuff pressure (≥100% LOP) resulted in far worse strength outcomes for the BFR group compared to high intensity controls. At the higher occlusion pressures earlier fatigability starts to impair training volume. 180 mmHg of cuff pressure was shown to reduce femoral blood flow by 52% compared to a non-BFR control during exercise (Christiansen et al., 2019). Sundberg et al. reported that higher external cuff pressure reduced blood oxygen delivery to skeletal muscle resulting in lower venous oxygen and higher lactate levels with increasing pressure (Sundberg, 1994). This impairs performance, as maximal voluntary contraction was shown to fall to similar levels between a normoxic training group and a hypoxic group from pre-exercise to exhaustion, however the time for the hypoxic group to reach exhaustion was 56% shorter (Fulco et al., 1996). Exercise studies at low oxygen levels shows significant drops in endurance, dynamic and static strength (Eiken and Tesch, 1984).

Hypoxia and Fatigue

Blood flow restriction effectiveness may then correlate directly with total volume of work done as this increases GH response and therefore greater strength improvements. Jessee et al. (2018) found that during their eight-week BFR study, subjects training to failure performed far less total volume load at every week at 80% LOP compared to 40% LOP. This might explain why both studies using pressures exceeding total LOP (Cook et al., 2017; de Lemos Muller et al., 2019) found significantly lower strength improvements in leg extension despite their participants training to failure, as early fatigability may have impaired the total repetition volume. Similarly, both studies who both had their BFR group train at high intensity, lower repetition protocols (60–80%1RM, 6–12 reps/set) did not see significantly different results compared to the control (Laurentino et al., 2008; Biazon et al., 2019). Higher loads typically result in greater improvements in 1RM than lower load programs (Schoenfeld et al., 2017). However, their BFR groups trained at much lower rep protocols which may not have been enough volume to produce significant lactic acid levels for GH stimulation. Also reduced muscle oxygenation likely impaired their subject's ability to train at their actual 80%1RM. Therefore, they did not elicit the metabolic stress required to achieve significant strength gains.

Confounding Factors

Cuff width between the 21 papers reviewed varied between 3 and 17 cm wide (see **Appendix Figure 13**). The pressure required to occlude blood flow reduces proportionally with increasing cuff width (Crenshaw et al., 1988; Loenneke et al., 2012). As the cuff width was not standardized between papers, the actual mmHg pressure applied to occlude blood flow would vary appreciably between studies even at the same %LOP. Wider cuffs may also contribute to higher loads being lifted, as the compressive force is spread over a larger area over the muscle. One study looking at compressive gear in powerlifting athletes found significantly higher maximal lifts in bench press, deadlift and squats in athletes using compressive support gear (Michal et al., 2020). It is suggested that the compressive gear such as knee wraps store elastic potential during the eccentric phase of the lift, then returning that energy as mechanical force during the concentric phase of the lift (Harman and Frykman, 1990). High BFR pressures (100–150% LOP) have been shown to significantly increase 1RM strength and repetitions to failure against controls not using external compression (Wilk et al., 2020). A wider cuff would distribute more of this energy across the target muscle, resulting in higher weights being lifted and potentially more strength adaptation stimulation (Michal et al., 2020). Narrow cuffs may cause more localized damage due to higher pressures being focused over a smaller area, as high applied pressures (230 mmHg) during BFR training have been shown to impair hypertrophy at the cuff site (Shaw and Murray, 1982). Other localized damage could be caused to tissues underneath a highly pressurized narrow cuff.

Also, thigh circumference strongly influences LOP and can influence the occlusive effect of a given pressure (Shaw and Murray, 1982). This may be due to the buffering effect

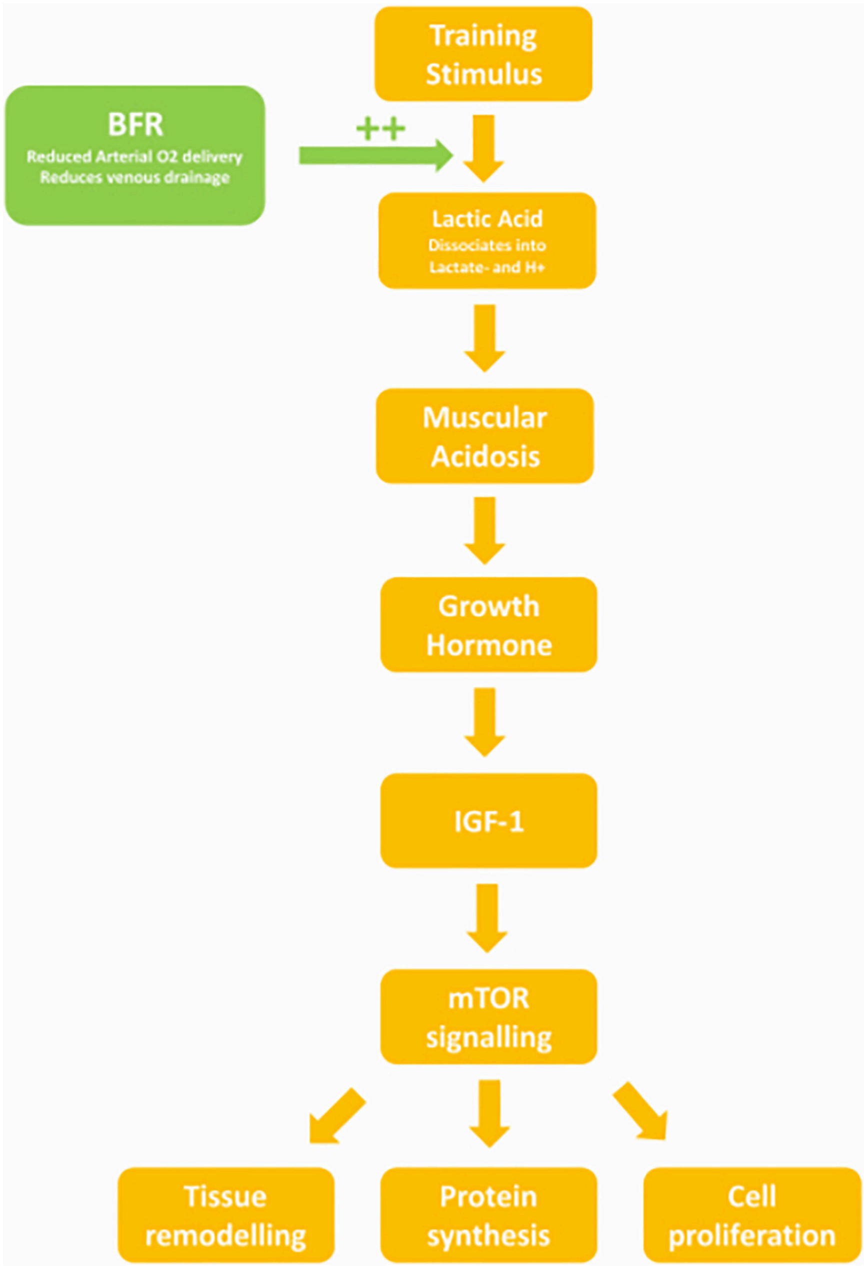

FIGURE 6 | Flowchart demonstrating the physiological effect of BFR.

of additional tissue and muscle mass between the cuff and vasculature. Composition of the tissue between the cuff and vasculature is also important, as Loenneke demonstrated the different pressure buffering abilities of fat and muscle at different respective tissue thicknesses (Loenneke et al., 2015). Loenneke proposed a formula for calculating arterial occlusion pressure accounting for blood pressure (BP), fat thickness and muscle thickness (Loenneke et al., 2015). This illustrates that body mass, limb CSA and body composition all play a significant role in LOP. It also demonstrates the need for individualized LOP to be applied for BFR training rather than standardized, as actual pressure exerted on the vascular system may vary wildly with cuff width, limb thickness and body composition.

Finally in all the studies discussed, LOP was tested pre training. BP rises significantly during exercise but also with length of session and fatigue (MacDougall et al., 1992). Peak mean BP during exercise has been found to increase with exercise intensity when tested at 50, 70, and 87.5% 1RM (MacDougall et al., 1992). This is attributed to the increased blood flow necessary to complete heavy lifts and the effect of the Valsalva manouevre (MacDougall et al., 1992). Contraction of the core musculature is required to stabilize the spine during heavy lifts. This increases intrathoracic pressure which is transmitted immediately through the arterial tree to the exercising limb. This can cause SBP to far exceed applied LOP, impacting occlusion dose and therefore physiological effect. Future studies into the effect of BFR should attempt to calibrate LOP during rather than pre-exercise, so that the true applied levels of %LOP are recorded.

Limitations

Studies chosen were not separated by sex of participants, however it has been established in prior literature that there are sex differences in skeletal muscle vasculature (Coutinho et al., 2013), muscle arterial compliance (Coutinho et al., 2013), rate of muscle oxygen desaturation during exercise (Keller and Kennedy, 2021) and degree of muscular and vascular adaptation from a training stimulus (Barnes and Fu, 2018). There is also an observed increase in mean and diastolic BP seen in women during the ovulation and luteal phase of the menstrual cycle (Lutsenko and Kovalenko, 2017) which would affect their minimum LOP during this time, changing their dosage of LOP for a significant period of any intervention lasting over 4 weeks.

Similarly studies were not separated by participant age, however both arterial and venous compliance (Olsen and Länne, 1998) and muscular blood flow during exercise (Lawrenson et al., 2003) reduces significantly with age especially in less active older people. This paper includes studies using participants with and without prior experience of resistance training. There is yet to be studies into whether prior strength training experience may influence the amount of strength gain using BFR with a resistance training program. However, exercise adaptations such as mitochondrial density, muscle capillary density and oxygen uptake (Bassett and Howley, 2000) may also result in differences of physiological effect from BFR training, however this is yet to be studied. All these factors would significantly influence LOP and degree of physiological effect from BFR, as well as training adaptation. Only studies that used a "continuous" method of BFR were used as opposed to intermittent. There is yet to be conclusive proof of a difference in training adaptation and intramuscular physiology between continuous and intermittent BFR (Fitschen et al., 2014; Freitas et al., 2020; Davids et al., 2021), and mixed results on level of perceived exertion and discomfort using either method (Fitschen et al., 2014; Freitas et al., 2019, 2020).

Although we did not control for the above variables, results were consistent between the different demographics and therefore still have validity. However because of this, findings should be qualified by future research due to the heterogeneity of populations. We would have liked to investigate the response to BFR among different patient demographic groups, however the sparseness of literature in this area would now allowed for adequate sampling to make meaningful conclusions.

Due to the strict inclusion criteria the pool of relevant papers became limited (Gavanda et al., 2020). Although several studies into BFR are being conducted in Japan and Brazil, mistranslation of the original articles may have affected results, so were excluded. Papers including specific patient groups could have been considered (i.e., those with cardiovascular/orthopedic/rheumatological conditions). However, factors such as pain and weakness may have confounded results.

This paper reviews the effect of BFR on maximal strength but does not look at its effect on hypertrophy, which may be achieved at different LOP and %1RM combinations than suggested by this review. While most papers studied low intensity training (20–30%1RM) with BFR, few have looked at moderate intensity (40–60%) which is where this review suggests the maximal benefit from BFR may be derived.

CONCLUSION

This was the first review that looked at the influence of combinations of pressure dosages (%LOP) and exercise intensity (%1RM) on strength gains during BFR training. Training at a %1RM of 20% or below did not exert enough physiological stress to induce strength improvements. 30%1RM appears to produce results matching non-BFR high intensity training, whereas 40%1RM may produce results exceeding high intensity training. %1RM appears to be a larger contributing factor to strength increases than dosage of LOP. Effect size rose progressively with increasing exercise intensity, whereas intensity matched protocols at moderate and high levels of LOP had no significant difference in strength gain. Significant results for BFR training seem to appear between 50–80% LOP, with the effect dropping off either side of this range due to insufficient metabolic stress or earlier fatigue. More research is needed into the apparent "maximal effect zone" identified in this meta-analysis to get optimal strength improvements from BFR training. Future studies should consider cuff width and thigh circumference when calculating chosen %LOP and should make efforts to test LOP during exercise to ensure adequate vascular occlusion during protocols. Studies should also consider comparing male vs. female participant groups, groups split by age range and resistance training experienced vs. unexperienced groups to see if there is a difference in response between them.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

AD collected the data, interpreted the results, and wrote the manuscript. BP acted as research supervisor and proof reader. Both authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2022.838115/full#supplementary-material

REFERENCES

Abe, T., Yasuda, T., Midorikawa, T., Sato, Y., Kearns, C., Inoue, K., et al. (2005). Skeletal muscle size and circulating IGF-1 are increased after two weeks of twice daily "KAATSU" resistance training. *Int. J. KAATSU Train. Res.* 1, 6–12. doi: 10.3806/ijktr.1.6

Barnes, J. N., and Fu, Q. (2018). Sex-specific ventricular and vascular adaptations to exercise. *Adv. Exp. Med. Biol.* 1065, 329–346. doi: 10.1007/978-3-319-77932-4_21

Bassett, D. R. Jr., and Howley, E. T. (2000). Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med. Sci. Sports Exerc.* 32, 70–84. doi: 10.1097/00005768-200001000-00012

Bemben, M. G., Mitcheltree, K. M., Larson, R. D., Ross, D., Cavazos, C., Friedlander, B., et al. (2019). Can blood flow restricted exercise improve ham:quad ratios better than traditional training? *Int. J. Exerc. Sci.* 12, 1080–1093.

Biazon, T. M. P. C., Ugrinowitsch, C., Soligon, S. D., Oliveira, R. M., Bergamasco, J. G., Borghi-Silva, A., et al. (2019). The association between muscle deoxygenation and muscle hypertrophy to blood flow restricted training performed at high and low loads. *Front. Physiol.* 10:446. doi: 10.3389/fphys.2019.00446

Brandner, C. R., and Warmington, S. A. (2017). Delayed onset muscle soreness and perceived exertion after blood flow restriction exercise. *J. Strength Cond. Res.* 31, 3101–3108. doi: 10.1519/JSC.0000000000001779

Brandner, C. R., Clarkson, M. J., Kidgell, D. J., and Warmington, S. A. (2019). Muscular adaptations to whole body blood flow restriction training and detraining. *Front. Physiol.* 10:1099. doi: 10.3389/fphys.2019.01099

Centner, C., Zdzieblik, D., Roberts, L., Gollhofer, A., and König, D. (2019). Effects of blood flow restriction training with protein supplementation on muscle mass and strength in older men. *J. Sports Sci. Med.* 18, 471–478.

Centre for Evidence-Based Medicine [CEBM] (2009). *Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009)*. Oxford: Centre for Evidence-Based Medicine.

Christiansen, D., Eibye, K. H., Rasmussen, V., Voldbye, H. M., Thomassen, M., Nyberg, M., et al. (2019). Cycling with blood flow restriction improves performance and muscle K^+ regulation and alters the effect of anti-oxidant infusion in humans. *J. Physiol.* 597, 2421–2444. doi: 10.1113/JP277657

Clarkson, M. J., May, A. K., and Warmington, S. A. (2020). Is there rationale for the cuff pressures prescribed for blood flow restriction exercise? A systematic review. *Scand. J. Med. Sci. Sports* 30, 1318–1336. doi: 10.1111/sms.13676

Cook, S. B., LaRoche, D. P., Villa, M. R., Barile, H., and Manini, T. M. (2017). Blood flow restricted resistance training in older adults at risk of mobility limitations. *Exp. Gerontol.* 99, 138–145. doi: 10.1016/j.exger.2017.10.004

Coutinho, T., Borlaug, B. A., Pellikka, P. A., Turner, S. T., and Kullo, I. J. (2013). Sex differences in arterial stiffness and ventricular-arterial interactions. *J. Am. Coll. Cardiol.* 61, 96–103. Erratum in: J Am Coll Cardiol. 2013;61(25):2573-2574, doi: 10.1016/j.jacc.2012.08.997

Crenshaw, A. G., Hargens, A. R., Gershuni, D. H., and Rydevik, B. (1988). Wide tourniquet cuffs more effective at lower inflation pressures. *Acta Orthop. Scand.* 59, 447–451. doi: 10.3109/17453678809149401

Csapo, R., and Alegre, L. M. (2016). Effects of resistance training with moderate vs heavy loads on muscle mass and strength in the elderly: a meta-analysis. *Scand. J. Med. Sci. Sports* 26, 995–1006. doi: 10.1111/sms.12536

Davids, C. J., Raastad, T., James, L. P., Gajanand, T., Smith, E., Connick, M., et al. (2021). Similar morphological and functional training adaptations occur between continuous and intermittent blood flow restriction. *J. Strength Cond. Res.* 35, 1784–1793. doi: 10.1519/JSC.0000000000004034

de Lemos Muller, C. H., Ramis, T. R., and Ribeiro, J. L. (2019). Effects of low-load resistance training with blood flow restriction on the perceived exertion, muscular resistance and endurance in healthy young adults. *Sport Sci. Health* 15, 503–510.

Eiken, O., and Tesch, P. A. (1984). Effects of hyperoxia and hypoxia on dynamic and sustained static performance of the human quadriceps muscle. *Acta Physiol. Scand.* 122, 629–633. doi: 10.1111/j.1748-1716.1984.tb07553.x

Fahs, C. A., Loenneke, J. P., Thiebaud, R. S., Rossow, L. M., Kim, D., Abe, T., et al. (2015). Muscular adaptations to fatiguing exercise with and without blood flow restriction. *Clin. Physiol. Funct. Imaging* 35, 167–176. doi: 10.1111/cpf.12141

Feng, Z., and Levine, A. J. (2010). The regulation of energy metabolism and the IGF-1/mTOR pathways by the p53 protein. *Trends Cell Biol.* 20, 427–434. doi: 10.1016/j.tcb.2010.03.004

Fitschen, P. J., Kistler, B. M., Jeong, J. H., Chung, H. R., Wu, P. T., Walsh, M. J., et al. (2014). Perceptual effects and efficacy of intermittent or continuous blood flow restriction resistance training. *Clin. Physiol. Funct. Imaging* 34, 356–363. doi: 10.1111/cpf.12100

Florini, J. R., Ewton, D. Z., and Coolican, S. A. (1996). Growth hormone and the insulin-like growth factor system in myogenesis. *Endocr. Rev.* 17, 481–517. doi: 10.1210/edrv-17-5-481

Freitas, E. D. S., Miller, R. M., Heishman, A. D., Aniceto, R. R., Silva, J. G. C., and Bemben, M. G. (2019). Perceptual responses to continuous versus intermittent blood flow restriction exercise: a randomized controlled trial. *Physiol. Behav.* 212:112717. doi: 10.1016/j.physbeh.2019.112717

Freitas, E. D. S., Miller, R. M., Heishman, A. D., Ferreira-Júnior, J. B., Araújo, J. P., and Bemben, M. G. (2020). Acute physiological responses to resistance exercise with continuous versus intermittent blood flow restriction: a randomized controlled trial. *Front. Physiol.* 11:132. doi: 10.3389/fphys.2020.00132

Fujita, S., Abe, T., Drummond, M. J., Cadenas, J. G., Dreyer, H. C., Sato, Y., et al. (2007). Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *J. Appl. Physiol.* 103, 903–910. doi: 10.1152/japplphysiol.00195.2007

Fulco, C. S., Lewis, S. F., Frykman, P. N., Boushel, R., Smith, S., Harman, E. A., et al. (1996). Muscle fatigue and exhaustion during dynamic leg exercise in normoxia and hypobaric hypoxia. *J. Appl. Physiol.* 81, 1891–1900. doi: 10.1152/jappl.1996.81.5.1891

Gavanda, S., Isenmann, E., Schlöder, Y., Roth, R., Freiwald, J., Schiffer, T., et al. (2020). Low-intensity blood flow restriction calf muscle training leads to similar functional and structural adaptations than conventional low-load strength training: a randomized controlled trial. *PLoS One* 15:e0235377. doi: 10.1371/journal.pone.0235377

Gordon, S. E., Kraemer, W. J., Vos, N. H., Lynch, J. M., and Knuttgen, H. G. (1994). Effect of acid-base balance on the growth hormone response to acute high-intensity cycle exercise. *J. Appl. Physiol.* 76, 821–829. doi: 10.1152/jappl.1994.76.2.821

Goto, K., Ishii, N., Kizuka, T., and Takamatsu, K. (2005). The impact of metabolic stress on hormonal responses and muscular adaptations. *Med. Sci. Sports Exerc.* 37, 955–963. doi: 10.1249/01.mss.0000170470.98084.39

Hamann, J. J., Kelley, K. M., and Gladden, L. B. (2001). Effect of epinephrine on net lactate uptake by contracting skeletal muscle. *J. Appl. Physiol.* 91, 2635–2641. doi: 10.1152/jappl.2001.91.6.2635

Harman, E., and Frykman, P. (1990). The effects of knee wraps on weightlifting performance and injury. *J. Strength Cond. Res.* 12, 30–35.

Hill, E. C., Housh, T. J., Keller, J. L., Smith, C. M., Anders, J. V., Schmidt, R. J., et al. (2020). Low-load blood flow restriction elicits greater concentric strength than non-blood flow restriction resistance training but similar isometric strength and muscle size. *Eur. J. Appl. Physiol.* 120, 425–441. doi: 10.1007/s00421-019-04287-3

Jessee, M. B., Buckner, S. L., Mouser, J. G., Mattocks, K. T., Dankel, S. J., Abe, T., et al. (2018). Muscle adaptations to high-load training and very low-load training with and without blood flow restriction. *Front. Physiol.* 9:1448. doi: 10.3389/fphys.2018.01448

Keller, J. L., and Kennedy, K. G. (2021). Men exhibit faster skeletal muscle tissue desaturation than women before and after a fatiguing handgrip. *Eur. J. Appl. Physiol.* 121, 3473–3483. doi: 10.1007/s00421-021-04810-5

Killinger, B., Lauver, J. D., Donovan, L., and Goetschius, J. (2019). The effects of blood flow restriction on muscle activation and hypoxia in individuals with chronic ankle instability. *J. Sport Rehabil.* 29, 633–639. doi: 10.1123/jsr.2018-0416

Kim, D., Loenneke, J. P., Ye, X., Bemben, D. A., Beck, T. W., Larson, R. D., et al. (2017). Low-load resistance training with low relative pressure produces muscular changes similar to high-load resistance training. *Muscle Nerve* 56, E126–E133. doi: 10.1002/mus.25626

Kraemer, W. J., and Ratamess, N. A. (2005). Hormonal responses and adaptations to resistance exercise and training. *Sports Med.* 35, 339–361. doi: 10.2165/00007256-200535040-00004

Laurentino, G. C., Ugrinowitsch, C., Roschel, H., Aoki, M. S., Soares, A. G., Neves, M. Jr., et al. (2012). Strength training with blood flow restriction diminishes myostatin gene expression. *Med. Sci. Sports Exerc.* 44, 406–412. doi: 10.1249/MSS.0b013e318233b4bc

Laurentino, G., Ugrinowitsch, C., Aihara, A. Y., Fernandes, A. R., Parcell, A. C., Ricard, M., et al. (2008). Effects of strength training and vascular occlusion. *Int. J. Sports Med.* 29, 664–667. doi: 10.1055/s-2007-989405

Lawrenson, L., Poole, J. G., Kim, J., Brown, C., Patel, P., and Richardson, R. S. (2003). Vascular and metabolic response to isolated small muscle mass exercise: effect of age. *Am. J. Physiol. Heart Circ. Physiol.* 285, H1023–H1031. doi: 10.1152/ajpheart.00135.2003

Letieri, R. V., Teixeira, A. M., Furtado, G. E., Lamboglia, C. G., Rees, J. L., and Gomes, B. B. (2018). Effect of 16 weeks of resistance exercise and detraining comparing two methods of blood flow restriction in muscle strength of healthy older women: a randomized controlled trial. *Exp. Gerontol.* 114, 78–86. doi: 10.1016/j.exger.2018.10.017

Liguori, G. (2021). *Guidelines for Exercise Testing and Prescription.* 11th ed. [ebook] Wolters Kluwer. Available online at: https://www.acsm.org/all-blog-posts/certification-blog/acsm-certified-blog/2018/07/27/featured-download-acsm-guidelines-for-exercise-testing-and-prescription-pdf (Accessed June 29, 2021)

Lixandrão, M. E., Ugrinowitsch, C., Laurentino, G., Libardi, C. A., Aihara, A. Y., Cardoso, F. N., et al. (2015). Effects of exercise intensity and occlusion pressure after 12 weeks of resistance training with blood-flow restriction. *Eur. J. Appl. Physiol.* 115, 2471–2480. doi: 10.1007/s00421-015-3253-2

Loenneke, J. P., Allen, K. M., Mouser, J. G., Thiebaud, R. S., Kim, D., Abe, T., et al. (2015). Blood flow restriction in the upper and lower limbs is predicted by limb circumference and systolic blood pressure. *Eur. J. Appl. Physiol.* 115, 397–405. doi: 10.1007/s00421-014-3030-7

Loenneke, J. P., Fahs, C. A., Rossow, L. M., Sherk, V. D., Thiebaud, R. S., Abe, T., et al. (2012). Effects of cuff width on arterial occlusion: implications for blood flow restricted exercise. *Eur. J. Appl. Physiol.* 112, 2903–2912. doi: 10.1007/s00421-011-2266-8

Loenneke, J. P., Fahs, C. A., Thiebaud, R. S., Rossow, L. M., Abe, T., Ye, X., et al. (2013). The acute hemodynamic effects of blood flow restriction in the absence of exercise. *Clin. Physiol. Funct. Imaging* 33, 79–82. doi: 10.1111/j.1475-097X.2012.01157.x

Lutsenko, O. I., and Kovalenko, S. O. (2017). Blood pressure and hemodynamics: mayer waves in different phases of ovarian and menstrual cycle in women. *Physiol. Res.* 66, 235–240. doi: 10.33549/physiolres.933313

MacDougall, J. D., McKelvie, R. S., Moroz, D. E., Sale, D. G., McCartney, N., and Buick, F. (1992). Factors affecting blood pressure during heavy weight lifting and static contractions. *J. Appl. Physiol.* 73, 1590–1597. doi: 10.1152/jappl.1992.73.4.1590

Manimmanakorn, A., Hamlin, M. J., Ross, J. J., Taylor, R., and Manimmanakorn, N. (2013). Effects of low-load resistance training combined with blood flow restriction or hypoxia on muscle function and performance in netball athletes. *J. Sci. Med. Sport* 16, 337–342. doi: 10.1016/j.jsams.2012.08.009

May, A. K., Russell, A. P., and Warmington, S. A. (2018). Lower body blood flow restriction training may induce remote muscle strength adaptations in an active unrestricted arm. *Eur. J. Appl. Physiol.* 118, 617–627. doi: 10.1007/s00421-018-3806-2

Mazzeo, R. S., Brooks, G. A., Schoeller, D. A., and Budinger, T. F. (1986). Disposal of blood [1-13C]lactate in humans during rest and exercise. *J. Appl. Physiol.* 60, 232–241. doi: 10.1152/jappl.1986.60.1.232

Mendonca, G. V., Vila-Chã, C., Teodósio, C., Goncalves, A. D., Freitas, S. R., Mil-Homens, P., et al. (2021). Contralateral training effects of low-intensity blood-flow restricted and high-intensity unilateral resistance training. *Eur. J. Appl. Physiol.* 121, 2305–2321. doi: 10.1007/s00421-021-04708-2

Michal, W., Michal, K., and Marcin, B. (2020). The influence of compressive gear on maximal load lifted in competitive powerlifting. *Biol. Sport* 37, 437–441. doi: 10.5114/biolsport.2021.100145

Minniti, M. C., Statkevich, A. P., Kelly, R. L., Rigsby, V. P., Exline, M. M., Rhon, D. I., et al. (2020). The safety of blood flow restriction training as a therapeutic intervention for patients with musculoskeletal disorders: a systematic review. *Am. J. Sports Med.* 48, 1773–1785. doi: 10.1177/0363546519882652

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., and Prisma Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 339:b2535. doi: 10.1136/bmj.b2535

Neto, G. R., da Silva, J. C. G., Freitas, L., da Silva, H. G., Caldas, D., Novaes, J. S., et al. (2019). Effects of strength training with continuous or intermittent blood flow restriction on the hypertrophy, muscular strength and endurance of men. *Acta Sci. Health Sci.* 41:42273.

Olsen, H., and Länne, T. (1998). Reduced venous compliance in lower limbs of aging humans and its importance for capacitance function. *Am. J. Physiol.* 275, H878–H886. doi: 10.1152/ajpheart.1998.275.3.H878

Reeves, G. V., Kraemer, R. R., Hollander, D. B., Clavier, J., Thomas, C., Francois, M., et al. (2006). Comparison of hormone responses following light resistance exercise with partial vascular occlusion and moderately difficult resistance exercise without occlusion. *J. Appl. Physiol.* 101, 1616–1622. doi: 10.1152/japplphysiol.00440.2006

Ruaro, M. F., Santana, J. O., Gusmão, N., De França, E., Carvalho, B. N., Farinazo, K. B., et al. (2019). Effects of strength training with and without blood flow restriction on quality of life in elderly women. *J. Phys. Educ. Sport* 19, 531–539.

Schoenfeld, B. J., Grgic, J., Ogborn, D., and Krieger, J. W. (2017). Strength and hypertrophy adaptations between low- vs. high-load resistance training: a systematic review and meta-analysis. *J. Strength Cond. Res.* 31, 3508–3523. doi: 10.1519/JSC.0000000000002200

Shaw, J. A., and Murray, D. G. (1982). The relationship between tourniquet pressure and underlying soft-tissue pressure in the thigh. *J. Bone Joint Surg. Am.* 64, 1148–1152.

Shinohara, M., Kouzaki, M., Yoshihisa, T., and Fukunaga, T. (1998). Efficacy of tourniquet ischemia for strength training with low resistance. *Eur. J. Appl. Physiol. Occup. Physiol.* 77, 189–191. doi: 10.1007/s004210050319

Suga, T., Okita, K., Morita, N., Yokota, T., Hirabayashi, K., Horiuchi, M., et al. (2010). Dose effect on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *J. Appl. Physiol.* 108, 1563–1567. doi: 10.1152/japplphysiol.00504.2009

Sundberg, C. J. (1994). Exercise and training during graded leg ischaemia in healthy man with special reference to effects on skeletal muscle. *Acta Physiol. Scand. Suppl.* 615, 1–50.

Takarada, Y., Nakamura, Y., Aruga, S., Onda, T., Miyazaki, S., and Ishii, N. (2000). Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J. Appl. Physiol.* 88, 61–65. doi: 10.1152/jappl.2000.88.1.61

Takarada, Y., Tsuruta, T., and Ishii, N. (2004). Cooperative effects of exercise and occlusive stimuli on muscular function in low-intensity resistance exercise with moderate vascular occlusion. *Japanese J. Physiol.* 54, 585–592. doi: 10.2170/jjphysiol.54.585

Vanwye, W. R., Weatherholt, A. M., and Mikesky, A. E. (2017). Blood flow restriction training: implementation into clinical practice. *Int. J. Exerc. Sci.* 10, 649–654.

Vechin, F. C., Libardi, C. A., Conceição, M. S., Damas, F. R., Lixandrão, M. E., Berton, R. P. B., et al. (2015). Comparisons between low-intensity resistance training with blood flow restriction and high-intensity resistance training on quadriceps muscle mass and strength in elderly. *J. Strength Cond. Res.* 29, 1071–1076. doi: 10.1519/JSC.0000000000000703

Watson, S. L., Weeks, B. K., Weis, L. J., Horan, S. A., and Beck, B. R. (2015). Heavy resistance training is safe and improves bone, function, and stature in postmenopausal women with low to very low bone mass: novel early findings from the LIFTMOR trial. *Osteoporos Int.* 26, 2889–2894. doi: 10.1007/s00198-015-3263-2

Wilk, M., Krzysztofik, M., Filip, A., Lockie, R. G., and Zajac, A. (2020). The acute effects of external compression with blood flow restriction on maximal strength and strength-endurance performance of the upper limbs. *Front. Physiol.* 11:567. doi: 10.3389/fphys.2020.00567

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

ORIGINAL RESEARCH
published: 13 June 2022
doi: 10.3389/fphys.2022.852693

Low-Load Blood Flow Restriction Squat as Conditioning Activity Within a Contrast Training Sequence in High-Level Preadolescent Trampoline Gymnasts

Shengtao Yang[1,2†], *Peng Zhang*[2†], *Marta Sevilla-Sanchez*[3], *Dong Zhou*[2], *Jie Cao*[2], *Jiajian He*[2], *Binghong Gao*[1]* and *Eduardo Carballeira*[3]*

[1]School of Physical Education and Training, Shanghai University of Sport, Shanghai, China, [2]Professional Sports Research Center, Shanghai Research Institute of Sports Science, Shanghai, China, [3]Department of Physical Education and Sport, Faculty of Sport Sciences and Physical Education, Campus Bastiagueiro, University of A Coruna, Oleiros, Spain

Edited by:
Adam Zajac,
University School of Physical Education in Wroclaw, Poland

Reviewed by:
Ashril Yusof,
University of Malaya, Malaysia
Erika Zemková,
Comenius University, Slovakia

***Correspondence:**
Binghong Gao
binghong.gao@hotmail.com
Eduardo Carballeira
eduardo.carballeira@udc.es

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: 11 January 2022
Accepted: 23 May 2022
Published: 13 June 2022

Citation:
Yang S, Zhang P, Sevilla-Sanchez M, Zhou D, Cao J, He J, Gao B and Carballeira E (2022) Low-Load Blood Flow Restriction Squat as Conditioning Activity Within a Contrast Training Sequence in High-Level Preadolescent Trampoline Gymnasts. Front. Physiol. 13:852693. doi: 10.3389/fphys.2022.852693

To investigate the effects of implementing low-load blood flow restriction exercises (LL-BFRE) instead of high-load exercises (HL-RE) in a contrast training program on strength and power performance of high-level young gymnasts. Fifteen high-level pre-pubescent trampoline gymnasts (national level, Tanner Stage II, intermediate experience in strength training) were divided into two groups to complete the same structure of a ten-week contrast strength training program differing only in the configuration of the first resistance exercise of the contrast sequence. The LL-BFRE group (n = 7, four girls, 13.9 ± 0.4 y) performed the first resistance exercise of the contrast with LL-BFRE (20%–30% 1RM, perceived pressure of 7 on a scale from 0 to 10). The HL-RE group (n = 8, four girls, 13.8 ± 0.5 y) trained the first resistance exercise of the contrast sequence with moderate-to-high load (60%–85% 1RM). Before and after the training period, isometric mid-thigh pull (IMTP), squat jump (SJ), counter movement jump (CMJ), and drop-jump (DJ) were performed to evaluate the effect of the intervention on strength and power capacities as primary outcomes. Changes in participants' anthropometric measures, muscle mass, left and right thigh girth, IMTP relative to bodyweight (IMTP-R), eccentric utilization ratio (EUR), and reactive strength index (RSI) were assessed as secondary outcomes. There was no significant interaction ($p > 0.05$) between group x time in any power and strength outcome, although SJ and EUR showed a trend to significant interaction ($p = 0.06$ and $p = 0.065$, respectively). There was an overall effect of time ($p < 0.05$) in all power and strength variables (CMJ, SJ, EUR, DJ, RSI, IMTP, and IMTP-R). There was a significant interaction in muscle mass (MM) [β = 0.57 kg, 95% CI = (0.15; 0.98), $t_{13} = 2.67$, $p = 0.019$], revealing that participants in LL-BFRE increased their muscle mass (6.6 ± 3.1%) compared to HL-RE (3.6 ± 2.0%). Anthropometric variables did not present any group or interaction effect. However, there was a time effect ($p < 0.05$). Implementing LL-BFRE in place of HL-RE as a conditioning activity in a contrast training sequence might be equally effective in improving lower-body strength and power in preadolescent trampoline gymnasts.

Keywords: blood flow restriction training, young athletes, contrast strength training, jump height, maximal isometric strength, high-load resistance exercise

1 INTRODUCTION

The trampoline gymnasts need high levels of power in their lower limbs to achieve an optimal height in the initial part of a routine and dispose of more aerial time for the functional part to encompass forwards and backward somersaults and twists (Jensen et al., 2013). Resistance training under close supervision and with correct guidance has been proven effective and beneficial in developing strength and power and enhancing athletic performance in young athletes (Behringer et al., 2010; Granacher et al., 2011; Harries et al., 2012; Granacher et al., 2016; Suchomel et al., 2016; McQuilliam et al., 2020). In general, it has been suggested that lifting high-load resistances (i.e., ≥80% of 1 repetition maximum, 1RM) increases strength and power in young athletes with advanced or intermediate experience (Faigenbaum et al., 2009; Lesinski, et al., 2016; Behm et al., 2017). Lifting high loads (HL) requires contractions at an unintentional slow velocity enabling more time for cross-bridge formation and thus producing higher forces than when lifting low loads (Fenwick et al., 2017). Training with HL is preferential to increase maximal (1RM) or near-maximal strength (Folland and Williams, 2007; Lopez et al., 2021), and it has the potential to maximize recruitment of the motor unit pool in fewer repetitions (Lopez et al., 2021) and with less fatigue in the central nervous system than low loads (LL) training when both strength trainings are performed to momentary failure (Farrow et al., 2021). On the other hand, training with moderate loads (that is, 60%–79%) to LL (that is, 30%–59%) inflicts less stress on the joints and tendons than HL (Bohm et al., 2015) and have demonstrated the ability to increase power in a broad load spectrum (McBride et al., 2002) and the ability to apply force at high velocity in the most resistance exercises, particularly in jumping exercises in young athletes (Behm et al., 2017). Lifting LL with maximal exertion enhances high-velocity strength (McBride et al., 2002) through an increment in motor unit firing rate (Van Cutsem et al., 1998) and refinement in neural modulation at high speed (Behm and Sale, 1993). However, since high levels of maximal strength underpin power output (McQuilliam et al., 2020), and HL have demonstrated more remarkable neural adaptations than low loads (Jenkins et al., 2017), some coaches and sports scientists have employed a combination of HL and LL or the so-called contrast training to increase lower-limb power output and jump performance (Duthie et al., 2002; Marshall et al., 2021). For all these reasons, contrast training can be a valuable tool for improving the jumping ability of trampoline gymnastics athletes.

In this regard, contrast training has been defined as a workout that involves using exercises with loads in a wide range of the force-velocity profile within a sequence, that is, alternating HL and LL exercises set for set (Marshall et al., 2021). Several works have found that contrast configurations improved strength and power in young athletes (Franco-Marquez et al., 2015; Bauer et al., 2019; Fathi et al., 2019). It is suggested that contrast configuration could bring a performance enhancement in submaximal or LL high-velocity exercises when those are preceded by a biomechanically similar HL (>80% of dynamic or isometric MVC) in the same circuit set by set (Duthie et al., 2002). The physiological mechanisms that explain the chronic adaptations produced after a contrast training period remain to be determined. The prescription of HL as a conditioning activity in a contrast training sequence is not always possible with young athletes, either due to a lack of strength in the trunk muscles that limits the correct execution of the exercises or because their sport modality already implies many impacts on joints and tendons. The trampoline practice entails a high volume of impacts on joints, tendons, and ligaments, especially in the spine and lower limbs (Grapton et al., 2013). Somersault is a commonly used skill in trampoline and one of the movements that most injury produces (Lindner and Caine, 1990; Grapton et al., 2013); consequently, the athletes sustain lower limb ligament damage frequently. Trampoline gymnasts would benefit from using effective training strategies to improve jumping performance, but on the other hand, they do not impose high stress on the joints and ligaments. The use of lower limb LL blood flow restriction exercises (LL-BFRE) has proven to be an efficacious alternative to high-load exercises (HL-RE) when used alternately within the same week or alternating weekly (Hansen et al., 2020). The employment of LL-BFRE can provide a less stressful stimulus on joints and tendons with a similar level of neuromuscular adaptations (Luebbers et al., 2019). Some studies have reported that low-load resistance exercises (i.e., ~30% 1 RM) with a high number of repetitions (12–30) (Pope et al., 2013) in combination with BFR (LL-BFRE) are effective at increasing muscle mass and strength across a wide range of populations (Loenneke et al., 2014; Loenneke et al., 2012b; Centner and Lauber, 2020; Pearson and Hussain, 2015). Interestingly, LL-BFRE and HL-RE resulted in similar levels of muscle water content (i.e., muscle swelling) (Freitas et al., 2017), mechanisms associated with post-activation performance enhancement (PAPE); however, LL-BFRE has been barely used in complex and contrast training sequences (Cleary and Cook, 2020; Doma et al., 2020). Cleary and Cook (2020) reported that in a complex strength session, both HL-RE and LL-BFRE failed to produce a PAP effect (Cleary and Cook, 2020). Nevertheless, they also pointed out that the absence of effect might be caused by an ineffective complex training protocol or other individual factors (Cleary and Cook, 2020).

Meanwhile, even though many studies have reported the effects of training with LL-BFRE on muscular strength and hypertrophy (Pearson and Hussain, 2015), the evidence of LL-BFRE's influence on power or jumping performance is unclear. Some authors have reported that LL-BFRE or jumping exercises with blood flow restriction in the legs did not affect the power or jumping performance (Abe et al., 2005; Horiuchi et al., 2018). Conversely, Cook et al. (2014) found that three weeks of BFR training with moderate-load (i.e., 70% 1 RM) induced significant increases in strength and countermovement jump performance in young adult rugby players (Cook et al., 2014). In addition, it was found that an increase in height, flight time, and power of drop jump when LL-BFRE, bodyweight lunges with occluded legs, are performed 6–16 min before the drop jumps (Doma et al., 2020). In brief, the LL-BFRE seems to be efficient to warm-up previous to power exercises or be part of a resistance training sequence, as contrast training, to enhance posteriorly executed jumping exercises. Nevertheless, to the best of our knowledge, the effect of LL-BFRE as a conditioning activity on a contrast training sequence has not been investigated with preadolescent or adolescent athletes.

Therefore, the present work aims to study the effects of LL-BFRE, as a conditioning activity, into a contrast training scheme, on strength and power outcomes in high-level preadolescent trampoline gymnasts.

2 MATERIALS AND METHODS

2.1 Participants

Fifteen preadolescent trampoline gymnasts (seven boys and eight girls) participated in the current study (age: 13.9 ± 0.4 y). All participants were high-level trampoline gymnasts, regional and national junior trampoline team members. Inclusion criteria were: 1) to play the national-level youth competitions finals; 2) to regularly train strength and conditioning, at least two sessions per week, for at least one year; and 3) to be in Tanner Stage II maturation level according to the evaluation of two certified and experienced doctors from Shanghai Sports Bureau. Legal guardians and participants provided informed consent and assent after a thorough explanation of the objectives and scope of the study, including procedures, risks, and benefits. All the procedures complied with ethical standards for research involving human participants set by the Declaration of Helsinki, and the study was approved by the Board of Research Committee of Shanghai Research Institute of Sports Science (no. 20J006, date: 30/09/2019).

2.2 Study Design

The present study used a matched pair design with two intervention groups and no control group. This procedure respected the "CONSORT" statement (http://www.consort-statement.org). Participants were ranked based on maximal isometric strength performance evaluated through the mid-thigh pull test (procedure detailed in testing procedures section) during the testing days pre-intervention and, once paired, were randomly allocated to one of the two experimental. One group, the HL-RE (n = 8, four female; age: 13.8 ± 0.5; height: 152.4 ± 7.9 cm; weight: 43.6 ± 7.2 kg; 3RM: 55.8 ± 8.4 kg), trained according to a traditional contrast sequence when the first exercise is performed with high-load resistance exercise (i.e., strength exercise), the second exercise is performed with a slow stretch-shortening cycle (SSC) exercise (i.e., power exercise) and the last one is a fast SSC exercise (i.e., plyometric exercise). The other group, the LL-BFRE (n = 7, four female; age: 13.9 ± 0.4 y, height: 156.7 ± 6.8 kg; weight: 43.1 ± 5.1 kg; 3RM: 56.3 ± 9.2 kg), performed identical contrast sequences and exact exercise only replacing the high-load employed by HL-RE group for low-loads with occlusive cuffs placed on the proximal area of the legs.

The participants completed a four-week familiarization period (8 sessions) before the ten-week intervention program (20 sessions of 90 min, 2 sessions per week). During familiarization sessions, participants spent one hour and a half practicing the strength, power, and plyometric exercises; meanwhile, researchers and coaches instructed the participants about the correct exercises' technique and safety issues. Additionally, all the participants practiced the testing protocol of strength and power tests and the utilization of the BFR wraps for half an hour every week. Participants recovered at least 48 h before each testing day, before (PRE) and after (POST) the intervention.

2.3 Blood Flow Restriction Set Up

According to previous recommendations, blood flow restriction was applied on the legs proximally on the femur near the inguinal crease through the individualized perceived pressure method (Wilson et al., 2013). In order to be ecologic and time-efficient during training sessions, researchers established the training cuff pressure with EDGE Restriction System BFR cuffs (size: 7.62 × 74.30 cm, The Edge Mobility System, United States) matching to the score provided for the participants in a pressure visual analogic scale (VAS). The VAS ranged from 0 to 10 points, where 0 was no pressure at all, 7 was moderate pressure with no pain, and 10 was intense pressure that causes pain (Wilson et al., 2013). The target pressure was set at 7 on the VAS scale for the entire intervention. Researchers calibrated the training cuff pressure to the target perceived pressure 24 h before the first training session of every week. During each training week, the LL-BFRE group trained with the cuffs on the legs, at the pressure set during calibration session, only in the first resistance exercise of the contrast sequence (i.e., back squat and front squat). They took off the cuffs for power and plyometric exercises. Researchers registered any sign of discomfort or possible adverse effects.

2.4 Training Program

We measured the three-repetition maximum (3RM) test on the back and front squat to prescribe the loads for the first resistance exercise of the contrast training in both groups (for more details see Testing procedures section). After 3RM measurement, the young trampoline gymnasts performed the contrast training shown in **Table 1** and the same specific trampoline and low-intensity aerobic training sessions. Both groups followed a linear periodization in the first conditioning resistance exercise (Harries et al., 2015). Recovery between exercises within the contrast sequence was one and a half minutes and 3 minutes between sets. LL-BFRE group performed the first conditioning resistance exercise with the proximal thighs occluded with the cuffs, a low-load (≤33% of 3 RM), and 3 or 4 sets of moderate effort (i.e., 10 to 12 repetitions). On the other hand, the HL-RE group performed the exact conditioning exercise but with a high load (87.5%–90% of 3RM) and 3 or 4 sets of moderate effort (4–5 repetitions). The training program aimed to improve strength and power capabilities; thus, the intensity effort of conditioning exercise was set at a moderate level (i.e., repetitions prescribed according to the 50–60% of the maximum repetitions that participants were able to lift with each conditioning during familiarization period) to avoid too much fatigue during the contrast sequence. The power and plyometric exercise were the same for both groups (**Table 1**).

TABLE 1 | Training program of HL-RE and LL-BFRE groups.

		Session 1						**Session 2**					
		Back squat		**Loaded squat jump**		**Drop jump from box**		**Front squat**		**CMJ with hex-barbell**		**Hurdle jump to box**	
		Intensity	set×reps	Intensity	set×reps	Intensity	set×reps	Intensity	set×reps	Intensity	set×reps	Intensity	set×reps
week1	HL-RE	67% 3RM	3 × 10	20% BW	3 × 4	BW	3 × 4	67% 3RM	3 × 10	20 kg	3 × 4	BW	3 × 4
	LL-BFRE	25% 3RM	3 × 10					25% 3RM	3 × 10				
week2	HL-RE	75% 3RM	3 × 10	20% BW	3 × 4	BW	3 × 4	75% 3RM	3 × 10	20 kg	3 × 4	BW	3 × 4
	LL-BFRE	30% 3RM	3 × 10					30% 3RM	3 × 10				
week3	HL-RE	85% 3RM	3 × 6	30% BW	3 × 5	BW	3 × 4	85% 3RM	3 × 6	20 kg	3 × 5	BW	3 × 4
	LL-BFRE	30% 3RM	3 × 12					30% 3RM	3 × 12				
week4	HL-RE	90% 3RM	3 × 5	30% BW	3 × 4	BW	3 × 4	90% 3RM	3 × 5	20 kg	3 × 4	BW	3 × 4
	LL-BFRE	35% 3RM	3 × 12					35% 3RM	3 × 12				
week5	HL-RE	90% 3RM	4 × 4	30% BW	3 × 4	BW	3 × 4	90% 3RM	4 × 4	20 kg	3 × 4	BW	3 × 4
	LL-BFRE	35% 3RM	3 × 10					35% 3RM	3 × 10				
week6	HL-RE	85% 3RM	4 × 4	30% BW	4 × 4	BW	4 × 3	85% 3RM	4 × 4	20 kg	4 × 4	BW	4 × 3
	LL-BFRE	30% 3RM	3 × 10					30% 3RM	3 × 10				
week7	HL-RE	85% 3RM	4 × 4	30% BW	4 × 4	BW	4 × 4	85% 3RM	4 × 4	20 kg	4 × 4	BW	4 × 4
	LL-BFRE	30% 3RM	3 × 12					30% 3RM	3 × 12				
week8	HL-RE	90% 3RM	3 × 5	30% BW	3 × 4	BW	3 × 4	90% 3RM	3 × 5	20 kg	3 × 4	BW	3 × 4
	LL-BFRE	35% 3RM	3 × 12					35% 3RM	3 × 12				
week9	HL-RE	85% 3RM	4 × 4	30% BW	4 × 4	BW	4 × 3	85% 3RM	4 × 4	20 kg	4 × 4	BW	4 × 3
	LL-BFRE	30% 3RM	3 × 10					30% 3RM	3 × 10				
week10	HL-RE	90% 3RM	3 × 5	30% BW	3 × 4	BW	3 × 4	90% 3RM	3 × 5	20 kg	3 × 4	BW	3 × 4
	LL-BFRE	35% 3RM	3 × 12					35% 3RM	3 × 12				

§Exact core exercises were employed for both HL-RE and LL-BFRE, it consisted of 3 sets of 3 exercises in each session.

2.5 Testing Procedures

Testing sessions before and after the intervention were conducted at the same time of the day (before breakfast), the same indoor gym with a similar temperature regulated by air-conditioning (~26°C). Evaluation sessions were under the supervision of the research team and qualified physicians and coaches. On the morning of the pre-test, two certified and experienced doctors established maturity through the Tanner scale (Marshall and Tanner, 1969; Marshall and Tanner, 1970). Then, the researchers measured the height (cm) and left and right mid-thigh girth (LTG and RTG, cm) using a measuring tape to the nearest 0.1 cm. The body mass (BM, kg) was measured by a bioimpedance scale (Inbody 270; InBody United States, Cerritos, CA, United States), and body composition was estimated from resistance obtained and through manufactured algorithms. Changes in muscle mass (MM, kg) and calculated body mass index (BMI, kg/m^2) were calculated pre- and post-intervention.

In the afternoon, participants performed a standardized 15 min warm-up (jogging, dynamic stretching, and muscle activation) before the power and strength tests. The lower body's power was assessed using the vertical squat jump test (SJ), the vertical countermovement jump test (CMJ), and the drop jump test from a 30 cm-height box (DJ). Furthermore, the eccentric utilization ratio (EUR) and the reactive strength index (RSI) were calculated from the jump tests (detailed below). Participants performed three maximal voluntary contractions in the isometric mid-thigh pull (IMTP). The exercise testing sequence and rest intervals between repetitions and sets for power and strength tests tried to minimize the accumulated fatigue through the evaluating session. The order within this protocol was constant: 1. SJ, 2. CMJ, 3. DJ, and 4. IMTP. The participants performed three successful repetitions, and they were blinded to the results of every repetition for ensuring the best effort in every repetition. If the last attempt was the highest, the participant performed one extra repetition to avoid possible deviations. The recovery between repetitions was 1 minute in jump tests and 2 minutes in the IMTP test. The power and strength evaluations were performed on a force platform (Kistler 9290AA, Instruments Inc., Amherst, NY, United States, sampling frequency of 1,000 Hz). The jumping height (cm) of SJ, CMJ, and DJ was automatically calculated by Mars (Version 5.0.0.0149, United States). The description of each test and the variable extracted are presented below.

2.5.1 Jump Tests

2.5.1.1 Squat Jump

The participants started from the static position with knees flexed to 90° and with hands on the hips (Petronijevic et al., 2018). After every repetition, researchers excluded any attempt if they detected any with countermovement by visual inspection. The repetition with the highest jumping height was used for further analysis.

2.5.2.2 Counter Movement Jump

The participant stood up-right and still on the force platform for at least one second. After hearing "go" the from tester, participants counter-moved (descend up to comfortable knee flexion, as close to 90° knee flexion as possible), and then vertically jumped with maximal effort (McMahon et al., 2018). The hands were required to remain on hips throughout the whole test. Repetitions with hip or knee flexion movement in the flight phase of the jump were excluded. The repetition with the highest jumping height was employed for further analysis.

2.5.2.3 Eccentric Utilization Ratio

The EUR was calculated by dividing the height (cm) reached in the CMJ by the height in the SJ. The EUR has been proposed to indicate SSC performance in various sports and during different training phases Mcguigan, 2006.

2.5.2.4 Drop-Jump

The participants stood upright and still on top of the 30 cm height box with their hands on hips. After the signal, they dropped from the box and, after the contact with the platform, jumped vertically with maximal effort (Bishop et al., 2019). The researchers encouraged the athletes to jump as high and quickly as possible with minimal ground contact time. The attempts were excluded if: 1) there was hip or knee flexion during the flight phase or the contact with the platform, 2) participants jumped from the box to the platform instead of dropping, or 3) the ground contact time was longer than 250 milliseconds. The jumping height of the repetition with the highest RSI was used for further analysis.

2.5.2.5 Reactive Strength Index

The RSI was calculated by dividing the height jumped by the time in contact with the ground prior to take-off during DJ (cm/seconds). This parameter has been suggested to quantify plyometric or fast SSC performance (Flanagan and Comyns, 2008).

2.5.2 Maximal Isometric Mid-thigh Pull Test

IMTP was conducted following the protocol recommended by previous studies (Chavda et al., 2019). In brief, participants were instructed to adjust the body posture mimicking a power position in the clean exercise. Athletes adjusted the bar height a knee angle of about 130° and a hip angle of about 145° and made three attempts pulling the bar at 50%, 70%, and 90% of maximal effort. After 1-min rest, participants were encouraged to pull the bar as fast and hard as possible to hold the pull action for at least 4 seconds. Researchers provided solid verbal encouragement during the maximal effort attempts. Criteria of nonvalid attempts were: 1) there was visible countermovement action in the force-time curve, and 2) the presence of the peak force at the end of the pull (Chavda et al., 2019). Participants performed three IMTP attempts, and the one with the highest peak force was employed for further analysis. Relative maximal strength (IMTP-R, $N*kg^{-1}$) was calculated as the force produced regarding the body mass.

2.5.3 Three-Repetition Maximum Test

After testing sessions and aimed to prescribe training loads for the conditioning activity within the contrast sequence, participants accomplished the 3RM test in the last session of the familiarization period. A qualified strength and conditioning coach supervised the test sessions and all the training sessions. A previously recommended protocol was followed (Faigenbaum et al., 2003). Briefly, after 15-min of a standardized warm-up, young athletes completed two approaching sets of 10 and 5 repetitions with 40% and 60% of the estimated time 1RM based on their performance during the familiarization. After two recovery minutes, the load was progressively increased by 10%–20% until the athletes could no longer complete the full range of movement for more than three repetitions. The 3RM load was determined as the last weight that the athletes successfully lifted for three repetitions (i.e., muscle or technical failure) through the entire range of motion.

2.6 Statistical Analyses

Test-retest reliability was reported using the intraclass correlation coefficient (ICC) with 95% confident interval a single-measurement, absolute-agreement, 2-way mixed-effects model. Based on the 95% confident interval (CI) of the ICC estimate, values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 were interpreted as poor, moderate, good, and excellent reliability, respectively (Koo and Li, 2016). Changes within and between groups for anthropometric measures, body composition, lower-body power, and strength were analyzed using linear mixed models for repeated measures designs. Normality of the residuals was analyzed with Shapiro-Wilk test in every variable and revealed no deviations from a normal distribution. Homoscedasticity was checked by plotting the residuals-predicted value (Santos Nobre and da Motta Singer, 2007), and we found the residuals were constant across the predicted values of every variable analyzed. We employed the module GAMLj, which uses the R formulation of random effects as implemented by the lme4 R package in jamovi software (https://www.jamovi.org/). GAMLj estimates variance components with restricted (residual) maximum likelihood, which, unlike earlier maximum likelihood estimation, produces unbiased estimates of variance and covariance parameters. The intersubject factor group (LL-BFRE and HL-RE), the intrasubject factor time (PRE and POST), and the interaction (Group × Time) were set as fixed effects and participants' intercepts were set as a random effect. F and t values and the corresponding degrees of freedom were computed. Within-subject changes were evaluated by the β coefficients and their corresponding 95% CI, representing a non-standardized effect size. Mean percentage changes (100 × [Post-Pre] × Pre^{-1}) and standard deviation were calculated for all parameters. Between-group changes were evaluated by the estimated parameter with the 95% CI of the interaction between the fixed effect of the model. The alpha level was set at $p < 0.05$.

3 RESULTS

3.1 Lower-Body Power and Strength Outcomes

The ICC with 95% CI of the variables were from "good" to "excellent" for CMJ (ICC = 0.99, 95% CI = 0.89–0.99) and DJ (ICC = 0.95, 95% CI = 0.89–0.98); and from "moderate" to "excellent" for SJ (ICC = 0.97, 95% CI = 0.65–0.99), RSI (ICC = 0.97, 95% CI = 0.67–0.99) and IMTP (ICC = 0.98, 95% CI = 0.63–0.99). There was no significant interaction ($p > 0.05$) between group x time in any power and strength outcome

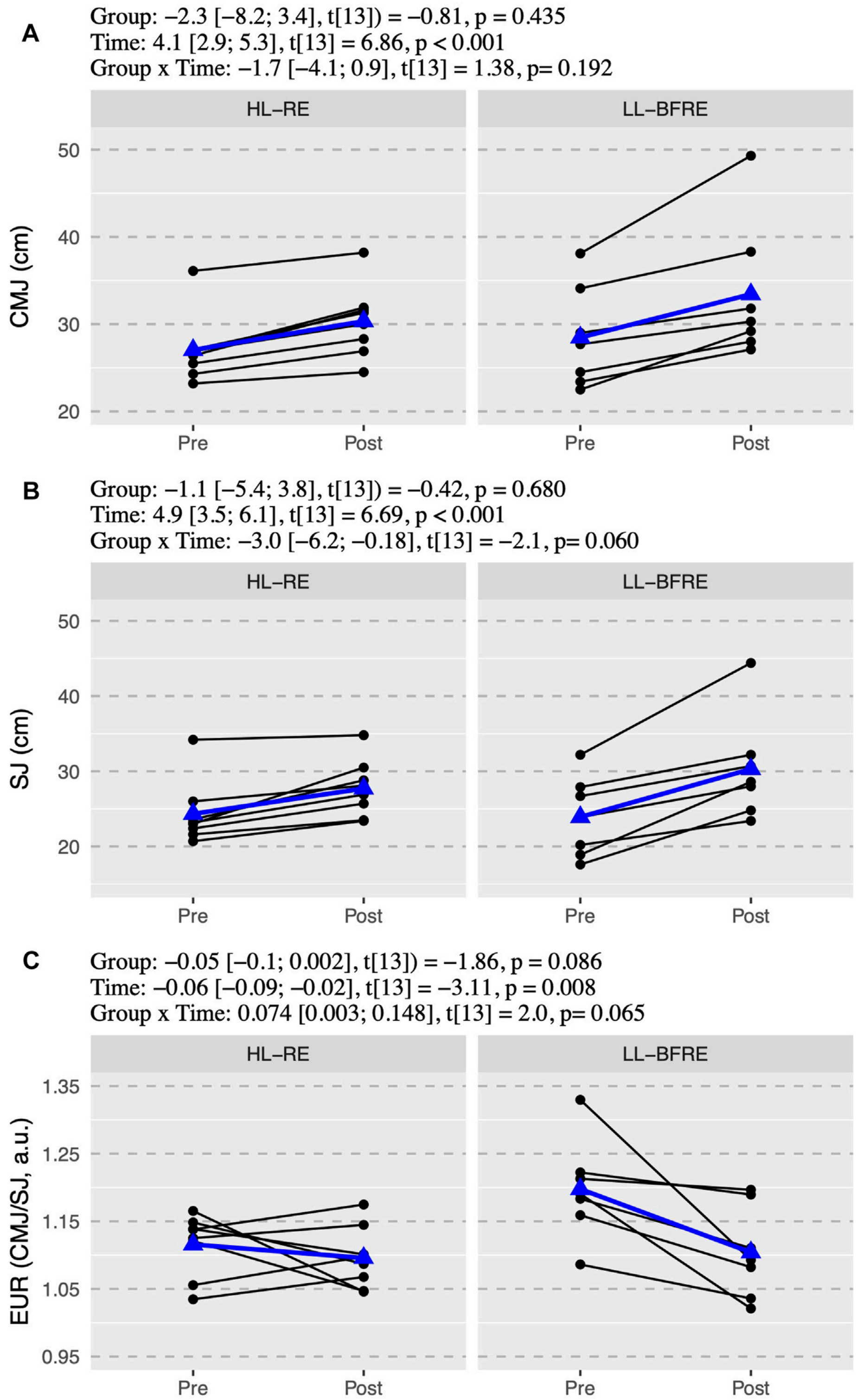

FIGURE 1 | The countermovement jump **(A)**, the squat jump test **(B)**, and the eccentric utilization ratio (EUR = CMJ/SJ) **(C)** values. Black points and lines represent individual responses. Blue triangles and regression line represent the mean response. Effects of the group (HL-RE vs. LL-BFRE), time (POST vs. PRE) and interaction (HL-RE vs. LLBFRE * POST vs. PRE) are presented through beta coefficient and 95% of the confidence interval, t-value and *p*-value obtained after mixed model analysis. HL-RE: high-load exercises group; LL-BFRE: low-load blood flow restriction exercise group; CMJ: countermovement jump, SJ: squat jump test, EUR: eccentric utilization ratio.

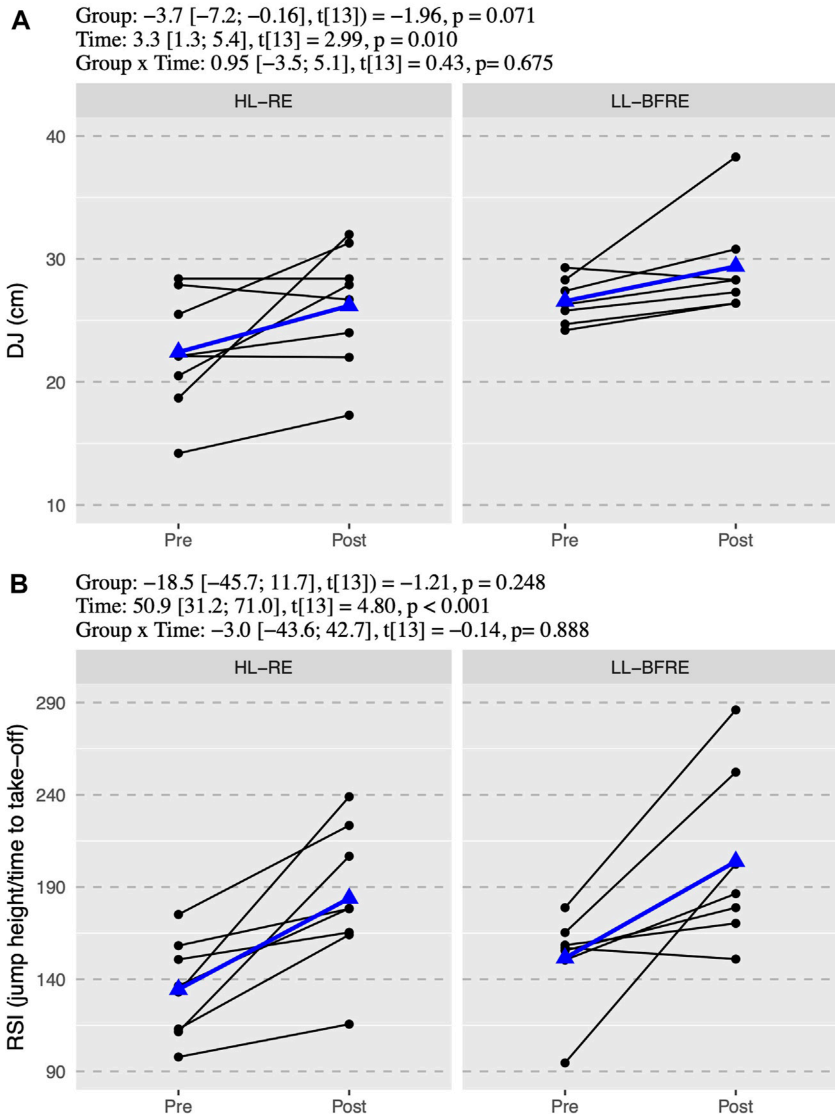

FIGURE 2 | The drop-jump values **(A)** and the reactive strength index **(B)**. Black points and lines represent individual responses. Blue triangles and regression line represent the mean response. Effects of the group (HL-RE vs. LL-BFRE), time (POST vs. PRE) and interaction (HL-RE vs. LLBFRE * POST vs. PRE) are presented through beta coefficient and 95% of the confidence interval, t-value and *p*-value obtained after mixed model analysis. HL-RE: high-load exercises group; LL-BFRE: low-load blood flow restriction exercise group; DJ: drop-jump, RSI: reactive strength index calculated as jump height (cm) and ground contact time before take-off (seconds).

(**Figures 1**–**3**). However, there was an overall effect of time ($p < 0.05$) in all power and strength variables (CMJ, SJ, EUR, DJ, RSI, IMTP, and IMTP-R).

CMJ increased 12.4 ± 5.4% and 17.2 ± 8.7% for HL-RE and LL-BFRE respectively, and simple effect analysis of time within each group revealed that LL-BFRE improved CMJ a mean of 5.0 cm (95% CI = [3.1; 6.9], $t_{13} = 5.64$, $p < 0.001$), and HL-RE improved 3.3 cm (95% CI = [1.5; 5.1], $t_{13} = 4.01$, $p = 0.001$) (**Figure 1**). On the other hand, SJ showed a trend to significant interaction effect ($p = 0.06$) and a significant time effect ($p < 0.001$). In fact, HL-RE increased 14.6 ± 9.4% (β = 3.4 cm, 95% CI = [1.2; 5.5], $t_{13} = 3.39$, $p = 0.005$) and LL-BFRE estimably more, 27.6 ± 15.3% (β = 6.4 cm, 95% CI = [4.1; 8.7], $t_{13} = 5.99$, $p < 0.001$) (**Figure 1**). Differentiated changes in SJ, not experimented in CMJ, affected EUR, thus there was a tendency ($p = 0.065$) to interaction in EUR. LL-BFRE significant decreased EUR (β = −0.09 a.u., 95% CI = [−0.15; −0.04], $t_{13} = -3.51$, $p = 0.004$), notwithstanding HL-RE did not change EUR (β = −0.02 a.u., 95% CI = [−0.07; 0.03], $t_{13} = -0.80$, $p = 0.437$) (**Figure 1**). The mean percentage change of EUR for HL-RE was −1.7 ± 5.4% and there was the same proportion (i.e., 50%) of participants who increased and decreased their values. However, the mean percentage change of EUR for LL-BFRE was −7.6 ± 6.1% and all the participants in that group decreased their EUR (**Figure 1**).

Outcomes in DJ showed a high variability of responses within groups (ICC random intercept = 0.482). DJ did not show

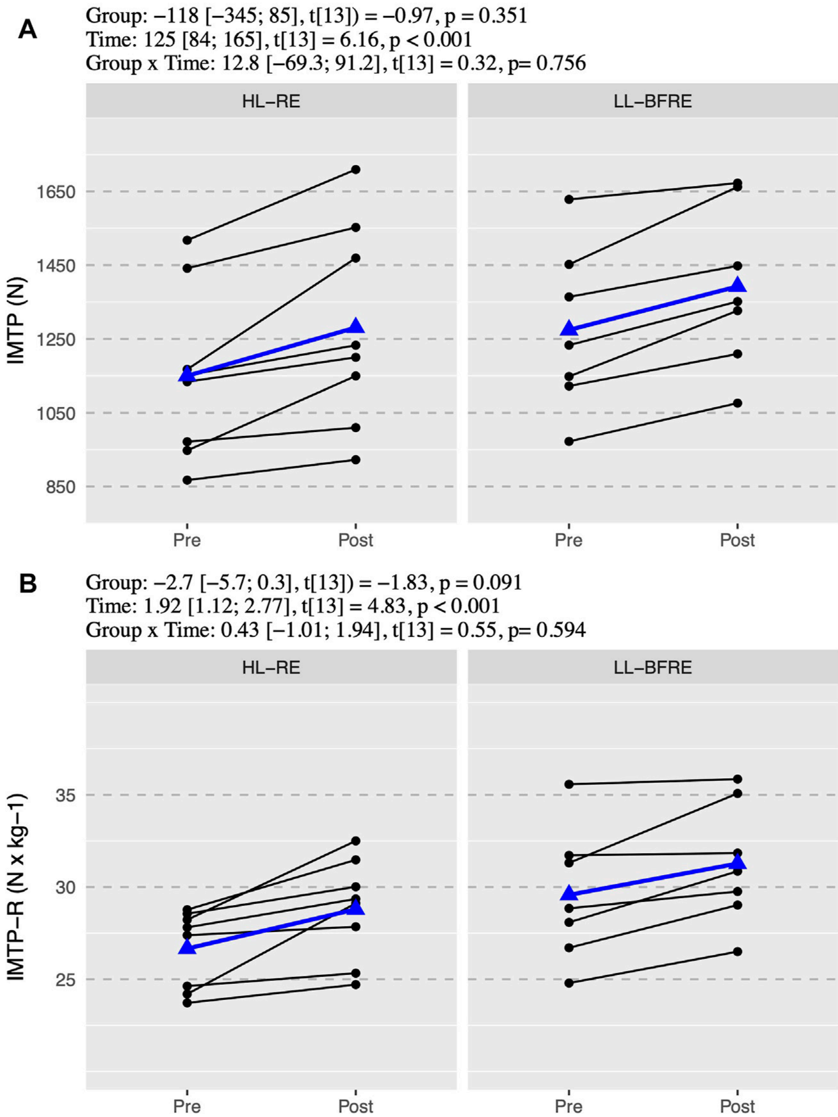

FIGURE 3 | Absolute **(A)** and relative isometric mid-thigh pull **(B)**. Black points and lines represent individual responses. Blue triangles and regression line represent the mean response. Effects of the group (HL-RE vs. LL-BFRE), time (POST vs. PRE) and interaction (HL-RE vs. LLBFRE * POST vs. PRE) are presented through beta coefficient and 95% of the confidence interval, t-value and *p*-value obtained after mixed model analysis. HL-RE: high-load exercises group; LL-BFRE: low-load blood flow restriction exercise group; IMTP: isometric mid-thigh pull; IMTP-R: isometric mid-thigh pull relative to bodyweight.

interaction effect (p = 0.675), but it showed a time effect that analyzed within each group revealed a 3.8 cm DJ improvement in HL-RE (95% CI = [0.5; 7.0], t_{13} = 2.50, p = 0.026), and not changes for LL-BFRE (β = 2.8 cm, 95% CI = [-0.7; 6.3], t_{13} = 1.76, p = 0.103) (**Figure 2**). Despite the different evolution in the DJ, the RSI improved in both groups 38.7 ± 29.3% (β = 49.4, 95% CI = [18.1; 80.7], t_{13} = 3.41, p = 0.005) in HL-RE and 38.4 ± 40.6% (β = 52.4, 95% CI = [18.9; 85.9], t_{13} = 3.38, p = 0.005) in LL-BFRE (**Figure 2**).

We observed a similar mean percentage improvement in IMTP for HL-RE (11.3 ± 8.0%) and LL-BFRE (9.6 ± 4.5%). Moreover, simple effects analysis showed that both groups improved IMTP (HL-RE: β = 131 N, 95% CI = [71; 191], t_{13} = 4.74, p < 0.001; and LL-BFRE: β = 118 N, 95% CI = [54; 182], t_{13} = 4.00, p = 0.002). The IMTP-R increased similarly in both groups (HL-RE: β = 2.1 N/kg, 95% CI = [0.9; 3.3], t_{13} = 3.93, p = 0.002; and LL-BFRE: β = 1.7 N/kg, 95% CI = [0.5; 2.9], t_{13} = 2.93, p = 0.012) (**Figure 3**).

3.2 Anthropometric Measures and Muscle Mass Changes

Changes in anthropometric measures and body composition are presented in **Table 2**. There was a significant interaction (group x time) in muscle mass (MM) (β = 0.57 kg, 95% CI = [0.15; 0.98], t_{13} = 2.67, p = 0.019), revealing that participants in LL-BFRE

TABLE 2 | Changes in body composition of low-load blood flow restriction exercise group (LL-BFRE) and high-load exercise group (HL-RE).

	LL-BFRE (n = 7)		POST vs. PRE		HL-RE (n = 8)		POST vs. PRE		LL-BFRE vs. HL-RE		Group×Time Interaction	
	PRE	POST	β [95% CI]	*p*-value	PRE	POST	β [95% CI]	*p*-value	β [95% CI]	*p*-value	β [95% CI]	*p*-value
Weight (kg)	43 ± 7	45 ± 7	1.4 (0.8; 2.1)	<0.001***	43 ± 7	44 ± 7	1.3 (0.7; 1.9)	<0.001***	0.04 (−6.6; 6.7)	0.990	0.14 (−0.7; 0.9)	0.730
Height (cm)	157 ± 7	158 ± 7	1.4 (1.0; 1.8)	<0.001***	152 ± 8	153 ± 8	1.1 (0.7; 1.5)	<0.001***	4.51 (−3.1; 12.1)	0.264	0.36 (−0.2; 0.9)	0.199
BMI (kg/m^2)	18 ± 1	18 ± 1	0.3 (0.0; 0.5)	0.049*	18 ± 1	19 ± 1	0.3 (0.1; 0.5)	0.022*	−0.96 (−2.2; 0.3)	0.164	−0.03 (−0.4; 0.3)	0.851
MM (kg)	20 ± 3	21 ± 3	1.2 (0.9; 1.6)	<0.001***	19 ± 3	20 ± 3	0.7 (0.4; 1.0)	<0.001***	0.57 (−2.8; 3.9)	0.742	0.57 (0.15; 0.98)	0.019*
LTG (cm)	43 ± 4	45 ± 4	2.0 (1.3; 2.7)	<0.001***	43 ± 4	45 ± 4	1.9 (1.2; 2.6)	<0.001***	−0.63 (−4.1; 2.9)	0.728	0.09 (−0.8; 1.0)	0.851
RTG (cm)	43 ± 8	45 ± 43	1.0 (0.3; 1.8)	0.011*	44 ± 4	45 ± 4	1.2 (0.5; 1.8)	0.003**	−0.65 (−4.4; 3.1)	0.737	−0.14 (−1.1; 0.8)	0.778

*Data are estimated marginal means ± standard deviation. PRE, vs. POST, is a simple effects analysis within each group. 95% CI: confidence interval at 95%; LL-BFRE: low-load blood flow restriction exercises group; HL-RE, high-load exercises group; PRE, preintervention assessment; POST, postintervention assessment; BMI, body mass index; MM, muscle mass; LTG, left mid-thigh girth; RTG, right mid-thigh girth. Significance: *p < 0.05, **p < 0.01, ***p < 0.001.*

increased their muscle mass (6.6 ± 3.1%) compared to HL-RE (3.6 ± 2.0%). The fixed effect omnibus test did not reveal any group or interaction effect in the anthropometric variables. However, there was a time effect on all the variables ($p < 0.05$). Group simple effects within PRE revealed no significant differences between groups, which ruled out group allocation or initial bias. The simple effects of time within each group are shown in **Table 2**.

4 DISCUSSION

We found that preadolescent trampoline gymnasts increased their jump height (CMJ, SJ) and strength capabilities (IMTP) regardless of employing HL or blood flow restricted LL as conditioning activity within a contrast training strength program performed two days per week for ten weeks. These results suggest the potential usefulness of BFR with low loads as a conditioning activity in a contrast training sequence in preadolescents athletes. However, our results must be interpreted with caution since we could not have a group that only trained specific trampoline sessions and thus compare the magnitude of change between the two interventions group with a control group. Participants' allocation was based on the rank obtained from the maximal isometric mid-thigh pull test in the pre-intervention to prevent participants' force level from influencing the present study's independent variable (i.e., the type of conditioning activity). Moreover, the groups did not significantly differ in any jump measures (i.e., CMJ, SJ, DJ) in the PRE, meaning that post-training differences could not be attributed to unequal group composition or pre-experimental biases.

The present work is the first investigation to study the effects of contrast-type resistance exercise training on the performance of high-level early adolescent trampoline gymnasts. The increments observed CMJ (HL-RE: 12.4 ± 5.4% and LL-BFRE: 17.2 ± 8.7%) and SJ (HL-RE: 14.6 ± 9.4% and LL-BFRE: 27.6 ± 15.3%) in both groups were much higher than those reported in the literature for pubertal volleyball players when trained with plyometrics (CMJ: 3.4% and SJ: 4.1%) or combining resistance and plyometric exercises (CMJ: 6.3% and SJ: 7.1%) (Fathi et al., 2019). In the last experiment, authors implemented a control group that continued their regular volleyball training, and they reported no changes in CMJ and SJ after 16-weeks of regular training (Fathi et al., 2019). A higher volume of jumps is performed during trampoline gymnastics sessions than in volleyball training, and likely a control group would show an improvement in those jumps. However, the magnitude of improvement reached in the present study after only ten weeks of two different contrast training configurations in pre-pubertal athletes warrants more studies that might highlight the contribution of that training strategy to increasing jump capabilities in young athletes. It has been signaled that jump trainability is mediated by biological maturation (Moran et al., 2017), that conclusion is derived from a meta-analysis of plyometric controlled trials in young individuals where authors indicated that adaptative responses were higher between the mean ages of 10 and 12.99, and between 16 and 18 years, than the mean ages of 13 and 15.99 despite greater exposure (Moran et al., 2017). Surprisingly, the athletes from our study were ~14 years old what becomes the results obtained in the present study even more relevant because we found significant improvements in athletes that were within a period of lowered response to maximize performance.

Trampoline athletes in LL-BFRE improved more SJ than CMJ (27.6 ± 15.3% vs. 17.2 ± 8.7%, respectively), contrasting to HL-RE that experimented a similar improvement in both exercises (14.6 ± 9.4% vs. 12.4 ± 5.4%, SJ and CMJ respectively). SJ and CMJ performance depends on common factors related to changes in muscle structure (Moran et al., 2017) and neural drive to muscles and on specific factors related to the ability to manage SSC (Kozinc et al., 2021). We believe that even the athletes in LL-BFRE reduced their EUR, more increment in CMJ in LL-BFRE might show that LL-BFRE did not weaken their capability to use the eccentric phase but simply increased more SJ. We also consider that one possible reason for this outcome might be the higher increment in muscle mass in the LL-BFRE group. The muscle mass increment could have contributed to the improvement of SJ and to a lesser extend in CMJ (Van Hooren and Zolotarjova, 2017; Radnor et al., 2018). Jumps with a previous countermovement require mastery stretching shortening cycle (SSC) characterized by an eccentric "stretching" action prior to a subsequent concentric "shortening" action (Nicol et al., 2006). Performance during an SSC is attributed to muscle pre-activation, the stretch reflex, and the release of stored passive-elastic energy in the muscle-tendinous tissue (Groeber et al., 2021). An augmentation in muscle mass is usually produced by an increment in contractile and no-contractile tissue. Differences in the proportion of contractile and no-contractile augmentation because of the type of conditioning activity within the contrast sequence might be the reason for the differences in the increment of performance between SJ and CMJ.

As aforementioned, trampoline athletes in LL-BFRE gained more muscle mass than those in HL-RE (6.6 ± 3.1% vs.3.6 ± 2.0%, respectively). The result of our study is consistent with the evidence from other previous studies employing BFR with young adult populations (Loenneke et al., 2012b). Furthermore, it has been observed that LL-BFR training stimulated physiological factors associated with skeletal muscle hypertrophy conversely to training without BFR with equal relative loads (20% 1RM) or even higher (50% 1RM) (Haddock et al., 2020). Since LL-BFRE performed more repetitions than HL-RE and athletes lifted at moderate effort intensity, we suggest that these circumstances might be responsible for the muscle mass changes. It has to be highlighted that the maturity process during the intervention period could have influenced the results. Food intake was not controlled during the study; however, athletes made their meals in the dining room inside the training center; thus, it is not expected that there have been considerable differences in the quality and quantity of the food intake.

On the other hand, the current study demonstrated that a contrast training program using low-loads with BFR as a conditioning activity might provide an effective and equivalent positive influence on maximal strength compared to using high-loads for preadolescents athletes. Our results agree with the evidence from other previous studies employing low load BFR with other populations (Loenneke et al., 2012b; Yamanaka et al., 2012; Luebbers et al., 2019; Hansen et al., 2020) and high school adolescent weightlifters (Mohamed et al., 2017; Luebbers et al., 2019). No side-effects (hazards or unbearable discomfort) were reported during the ten weeks of training, which implicates that LL-BFRE integrated into a contrast training sequence is effective and safe for young athletes' strength development. Potential mechanisms of LL-BFRE training for young athletes was not within the scope of the current study, but previous research has suggested that the increased hormone level (such as plasma concentration of growth hormone) (Manini and Clark, 2009), fast-twitch fibers recruitment, and muscle cell swelling (Loenneke et al., 2012a) might be the factors for improvement of maximal strength in LL-BFRE.

The contrast training sequence is characterized by high-load resistant strength exercises followed by lighter-loads with similar movement pattern power exercises and plyometric exercises (Marshall et al., 2021) that try to cause a PAPE effect within the sets and between them. Initially, some authors suggested that the acute physiological effects linked to post-activation potentiation (PAP) (e.g., improvement of the sensitivity of the Ca^{2+} released by the sarcoplasmic reticulum due to phosphorylation of the regulatory light chain of myosin) caused by a precedent conditioning activity is the cause of improved performance in high-speed strength or power exercises during a session (Sale, 2002). The repetition of contrast training configurations can achieve a long-term improvement in the performance of activities such as jumping, throwing, or all those that depend on high values of rate of force development (Sale, 2002; Tillin and Bishop, 2009). However, other authors have exposed their concerns about PAP causing an improvement in force production after conditioning activity because the specific physiological mechanism of PAP is based on the contractile response after a conditioning activity that could or not contribute to the posterior performance enhancement (Cuenca-Fernandez et al., 2017; Boullosa et al., 2020). Conversely, it has been indicated that highly probable that other physiological effects such as changes in muscle temperature, the water content of muscles and cells, and muscle activation may be responsible, at least in part, for the improvement in voluntary strength and power (Blazevich and Babault, 2019) after a conditioning activity, the so-called PAPE (Cuenca-Fernandez et al., 2017). These physiologic mechanisms related with PAPE may have been responsible to performance increases in HL-RE and LL-BFRE contrast training sequences in our study. Cleary and Cook (2020) studied the acute effects of HL-RE and LL-BFRE in a complex training sequence in college-aged men, and they did not find an increase in the subsequent vertical jumps' height. Conversely, our results support that HL-RE and LL-BFRE could provide a performance enhancement in jump and strength capabilities when employed chronically (i.e., ten weeks) within a contrast training sequence in pre-adolescents. If PAPE effects are responsible for improving the performance observed in contrast training with HL or LL-BFR as conditioning activity, it should be clarified in future studies. Furthermore, it has to be highlighted that LL-BFRE group trained their lower limb extension pattern at execution speeds closer to those sport-specific. As stated almost three decades ago, velocity specificity of resistance training has demonstrated that the greatest strength gains occur at or near the training velocity (Behm and Sale, 1993). Therefore, the LL-BFRE group was training at a higher velocity than HL-RE, trampoline-specific performance in longer training interventions. The results of our study should be contrasted with future designs that analyze structural and neural chronic adaptations of contrast training using LL-BFRE in young athletes' power performance.

Moreover, our study did not find an interaction effect on reactive, explosive strength (DJ), but simple effects showed an increment in the HL-RE and no changes in LL-BFRE. As shown in **Figure 2**, the responses to the DJ test in HL-RE presented high variability between participants. The reason that could explain high variability in the DJ responses of the HL-RE group may be that high loads training presented specific difficulties related to the capacity to place the load on the gymnasts' back and subsequent demands for their core strength and stability. Core weakness limits load progression and applying force efficiently when performing strength exercises like back or front squat. Nevertheless, high loads contribute to stiff muscle-tendon structures (Fenwick et al., 2017), which can explain the magnitude of response experimented by some athletes.

4.1 Limitations

Our study was not without limitations. Small sample size and the absence of a control group training only specific sessions must be addressed in future investigations. Furthermore, a study design with bigger samples with higher representation by sex is warranted to understand better sex differences in adaptations to LL-BFRE in power and strength training. Lastly, electrophysiologic measures to analyze motor unit recruitment and firing rate and changes in tendon-muscle architecture can give valuable information about the origin of the adaptations to training with LL-BFRE as a conditioning activity within a contrast training sequence.

5 PRACTICAL APPLICATIONS

Low-intensity resistance training with BFR could be implemented into an integrated strength training program with a combination of power or plyometric exercise to effectively improve the strength and jump height performance in lower limbs in preadolescent athletic populations. Our study has provided valuable implications for coaches working with elite young athletes, especially when using high loads in a contrast training structure is not possible.

6 CONCLUSION

Implementing LL-BFRE in place of HL-RE in a contrast training structure is safe and might be equally effective in improving lower-body strength and power in preadolescent trampoline gymnasts.

AUTHOR'S NOTE

The study was conducted at Shanghai's Chongming Training Base of Professional Sports.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://osf.io/789gy Name of repository/repositories: OSF.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Board of Research Committee of Shanghai Research Institute of Sports Science (No. 20J006, date: 30/09/2019). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SY, PZ, and BG contributed to the conception and design of the study. EC organized the database and performed the statistical analysis. SY, EC, and MS-S wrote the first draft of the manuscript. SY, PZ, DZ, JC, and JH contributed to data acquisition and/or interpretation of data. BG and EC supervised the study. All authors contributed to manuscript revision, read and approved the submitted version.

ACKNOWLEDGMENTS

The authors especially express their gratitude to head coach Hua Yu and to coaches Xiaojing Zhang, Jun Xie, and Qing Fan of the Shanghai Trampoline Team for their generous help.

REFERENCES

Abe, T., Kawamoto, K., Yasuda, T., Kearns, C. F., Midorikawa, T., and Sato, Y. (2005). Eight Days KAATSU-Resistance Training Improved Sprint but Not Jump Performance in Collegiate Male Track and Field Athletes. *Int. J. KAATSU Ttaining Res.* 1 (1), 19–23. doi:10.3806/ijktr.1.19

Bauer, P., Uebellacker, F., Mitter, B., Aigner, A. J., Hasenoehrl, T., Ristl, R., et al. (2019). Combining Higher-Load and Lower-Load Resistance Training Exercises: A Systematic Review and Meta-Analysis of Findings from Complex Training Studies. *J. Sci. Med. Sport* 22 (7), 838–851. doi:10.1016/j.jsams.2019.01.006

Behm, D. G., and Sale, D. G. (1993). Velocity Specificity of Resistance Training. *Sports Med.* 15 (6), 374–388. doi:10.2165/00007256-199315060-00003

Behm, D. G., Young, J. D., Whitten, J. H. D., Reid, J. C., Quigley, P. J., Low, J., et al. (2017). Effectiveness of Traditional Strength vs. Power Training on Muscle Strength, Power and Speed with Youth: A Systematic Review and Meta-Analysis. *Front. Physiol.* 8, 423. doi:10.3389/fphys.2017.00423

Behringer, M., vom Heede, A., Yue, Z., and Mester, J. (2010). Effects of Resistance Training in Children and Adolescents: A Meta-Analysis. *Pediatrics* 126, e1199–e1210. doi:10.1542/peds.2010-0445

Bishop, C., Pereira, L. A., Reis, V. P., Read, P., Turner, A. N., and Loturco, I. (2019). Comparing the Magnitude and Direction of Asymmetry during the Squat, Countermovement and Drop Jump Tests in Elite Youth Female Soccer Players. *J. Sports Sci.* 38 (11-12), 1296–1303. doi:10.1080/02640414.2019.1649525

Blazevich, A. J., and Babault, N. (2019). Post-activation Potentiation versus Post-Activation Performance Enhancement in Humans: Historical Perspective, Underlying Mechanisms, and Current Issues. *Front. Physiol.* 10, 1359. doi:10.3389/fphys.2019.01359

Bohm, S., Mersmann, F., and Arampatzis, A. (2015). Human Tendon Adaptation in Response to Mechanical Loading: a Systematic Review and Meta-Analysis of Exercise Intervention Studies on Healthy Adults. *Sports Med.-Open* 1 (1), 7. doi:10.1186/s40798-015-0009-9

Boullosa, D., Beato, M., Dello Iacono, A., Cuenca-Fernández, F., Doma, K., Schumann, M., et al. (2020). A New Taxonomy for Postactivation Potentiation in Sport. *Int. J. Sport Physiol.* 15 (8), 1197–1200. doi:10.1123/ijspp.2020-0350

Centner, C., and Lauber, B. (2020). A Systematic Review and Meta-Analysis on Neural Adaptations Following Blood Flow Restriction Training: What We Know and what We Don't Know. *Front. Physiol.* 11, 887. doi:10.3389/fphys.2020.00887

Chavda, S., Turner, A. N., Comfort, P., Haff, G. G., Williams, S., Bishop, C., et al. (2020). A Practical Guide to Analyzing the Force-Time Curve of Isometric Tasks in Excel. *Strength Cond. J.* 42, 26–37. doi:10.1519/SSC.0000000000000507

Cleary, C. J., and Cook, S. B. (2020). Postactivation Potentiation in Blood Flow-Restricted Complex Training. *J. Strength Cond. Res.* 34 (4), 905–910. doi:10.1519/JSC.0000000000003497

Cook, C. J., Kilduff, L. P., and Beaven, C. M. (2014). Improving Strength and Power in Trained Athletes with 3 Weeks of Occlusion Training. *Int. J. Sport Physiol.* 9 (1), 166–172. doi:10.1123/ijspp.2013-0018

Cuenca-Fernández, F., Smith, I. C., Jordan, M. J., MacIntosh, B. R., López-Contreras, G., Arellano, R., et al. (2017). Non Localized Postactivation Performance Enhancement (PAPE) Effects in Trained Athletes: a Pilot Study. *Appl. Physiol. Nutr. Metab.* 42 (10), 1122–1125. doi:10.1139/apnm-2017-0217

Doma, K., Leicht, A. S., Boullosa, D., and Woods, C. T. (2020). Lunge Exercises with Blood-Flow Restriction Induces Post-activation Potentiation and Improves Vertical Jump Performance. *Eur. J. Appl. Physiol.* 120 (3), 687–695. doi:10.1007/s00421-020-04308-6

Duthie, G. M., Young, W. B., and Aitken, D. A. (2002). The Acute Effects of Heavy Loads on Jump Squat Performance: an Evaluation of the Complex and Contrast Methods of Power Development. *J. Strength Cond. Res.* 16 (4), 530–538. doi:10.1519/1533-4287(2002)016<0530:taeohl>2.0.co;2

Faigenbaum, A. D., Kraemer, W. J., Blimkie, C. J. R., Jeffreys, I., Micheli, L. J., Nitka, M., et al. (2009). Youth Resistance Training: Updated Position Statement Paper from the National Strength and Conditioning Association. *J. Strength Cond. Res.* 23 (5 Suppl), S60–S79. doi:10.1519/JSC.0b013e31819df407

Faigenbaum, A. D., Milliken, L. A., and Westcott, W. L. (2003). Maximal Strength Testing in Healthy Children. *J. Strength Cond. Res.* 17 (1), 162–166. doi:10.1519/1533-4287(2003)017<0162:mstihc>2.0.co;2

Farrow, J., Steele, J., Behm, D. G., Skivington, M., and Fisher, J. P. (2021). Lighter-Load Exercise Produces Greater Acute- and Prolonged-Fatigue in Exercised and Non-exercised Limbs. *Res. Q. Exerc. Sport* 92 (3), 369–379. doi:10.1080/02701367.2020.1734521

Fathi, A., Hammami, R., Moran, J., Borji, R., Sahli, S., and Rebai, H. (2019). Effect of a 16-Week Combined Strength and Plyometric Training Program Followed by a Detraining Period on Athletic Performance in Pubertal Volleyball Players. *J. Strength Cond. Res.* 33 (8), 2117–2127. doi:10.1519/JSC.0000000000002461

Fenwick, A. J., Wood, A. M., and Tanner, B. C. W. (2017). Effects of Cross-Bridge Compliance on the Force-Velocity Relationship and Muscle Power Output. *PLOS ONE* 12 (12), e0190335. doi:10.1371/journal.pone.0190335

Flanagan, E. P., and Comyns, T. M. (2008). The Use of Contact Time and the Reactive Strength Index to Optimize Fast Stretch-Shortening Cycle Training. *Strength Cond. J.* 30 (5), 32–38. doi:10.1519/SSC.0b013e318187e25b

Folland, J. P., and Williams, A. G. (2007). The Adaptations to Strength Training: Morphological and Neurological Contributions to Increased Strength. *Sports Med.* 37 (2), 145–168. doi:10.2165/00007256-200737020-00004

Franco-Márquez, F., Rodríguez-Rosell, D., González-Suárez, J., Pareja-Blanco, F., Mora-Custodio, R., Yañez-García, J., et al. (2015). Effects of Combined Resistance Training and Plyometrics on Physical Performance in Young Soccer Players. *Int. J. Sports Med.* 36 (11), 906–914. doi:10.1055/s-0035-1548890

Freitas, E., Poole, C., Miller, R., Heishman, A., Kaur, J., Bemben, D., et al. (2017). Time Course Change in Muscle Swelling: High-Intensity vs. Blood Flow Restriction Exercise. *Int. J. Sports Med.* 38 (13), 1009–1016. doi:10.1055/s-0043-118342

Granacher, U., Goesele, A., Roggo, K., Wischer, T., Fischer, S., Zuerny, C., et al. (2011). Effects and Mechanisms of Strength Training in Children. *Int. J. Sports Med.* 32 (05), 357–364. doi:10.1055/s-0031-1271677

Granacher, U., Lesinski, M., Büsch, D., Muehlbauer, T., Prieske, O., Puta, C., et al. (2016). Effects of Resistance Training in Youth Athletes on Muscular Fitness and Athletic Performance: A Conceptual Model for Long-Term Athlete Development. *Front. Physiol.* 7, 1–14. doi:10.3389/fphys.2016.00164

Grapton, X., Lion, A., Gauchard, G. C., Barrault, D., and Perrin, P. P. (2013). Specific Injuries Induced by the Practice of Trampoline, Tumbling and Acrobatic Gymnastics. *Knee Surg. Sports Traumatol. Arthrosc.* 21 (2), 494–499. doi:10.1007/s00167-012-1982-x

Groeber, M., Stafilidis, S., and Baca, A. (2021). The Effect of Stretch-Shortening Magnitude and Muscle-Tendon Unit Length on Performance Enhancement in a Stretch-Shortening Cycle. *Sci. Rep.* 11 (1), 14605. doi:10.1038/s41598-021-94046-2

Haddock, B., Hansen, S. K., Lindberg, U., Nielsen, J. L., Frandsen, U., Aagaard, P., et al. (2020). Physiological Responses of Human Skeletal Muscle to Acute Blood Flow Restricted Exercise Assessed by Multimodal MRI. *J. Appl. Physiol.* 129 (4), 748–759. doi:10.1152/japplphysiol.00171.2020

Hansen, S. K., Ratzer, J., Nielsen, J. L., Suetta, C., Karlsen, A., Kvorning, T., et al. (2020). Effects of Alternating Blood Flow Restricted Training and Heavy-Load Resistance Training on Myofiber Morphology and Mechanical Muscle Function. *J. Appl. Physiology (1985)* 128 (6), 1523–1532. doi:10.1152/japplphysiol.00015.2020

Harries, S. K., Lubans, D. R., and Callister, R. (2012). Resistance Training to Improve Power and Sports Performance in Adolescent Athletes: A Systematic Review and Meta-Analysis. *J. Sci. Med. Sport* 15 (6), 532–540. doi:10.1016/j.jsams.2012.02.005

Harries, S. K., Lubans, D. R., and Callister, R. (2015). Systematic Review and Meta-Analysis of Linear and Undulating Periodized Resistance Training Programs on Muscular Strength. *J. Strength Cond. Res.* 29 (4), 1113–1125. doi:10.1519/JSC.0000000000000712

Horiuchi, M., Endo, J., Sato, T., and Okita, K. (2018). Jump Training with Blood Flow Restriction Has No Effect on Jump Performance. *Biol. Sport.* 35 (4), 343–348. doi:10.5114/biolsport.2018.78053

Jenkins, N. D. M., Miramonti, A. A., Hill, E. C., Smith, C. M., Cochrane-Snyman, K. C., Housh, T. J., et al. (2017). Greater Neural Adaptations Following High- vs. Low-Load Resistance Training. *Front. Physiol.* 8, 331. doi:10.3389/fphys.2017.00331

Jensen, P., Scott, S., Krustrup, P., and Mohr, M. (2013). Physiological Responses and Performance in a Simulated Trampoline Gymnastics Competition in Elite Male Gymnasts. *J. Sports Sci.* 31, 1761–1769. doi:10.1080/02640414.2013.803591

Lindner, K. J., and Caine, D. J. (1991). Injury Patterns of Female Competitive Club Gymnasts. *Clin. J. Sport Med.* 1 (4), 147–261. doi:10.1097/00042752-199104000-00023

Koo, T. K., and Li, M. Y. (2016). A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J. Chiropr. Med.* 15, 155–163. doi:10.1016/j.jcm.2016.02.012

Kozinc, Ž., Žitnik, J., Smajla, D., and Šarabon, N. (2021). The Difference between Squat Jump and Countermovement Jump in 770 Male and Female Participants from Different Sports. *Eur. J. Sport Sci.*, 1–9. doi:10.1080/17461391.2021.1936654

Lesinski, M., Prieske, O., and Granacher, U. (2016). Effects and Dose-Response Relationships of Resistance Training on Physical Performance in Youth Athletes: a Systematic Review and Meta-Analysis. *Br. J. Sports Med.* 50 (13), 781–795. doi:10.1136/bjsports-2015-095497 (Online ahead of print)

Loenneke, J. P., Fahs, C. A., Rossow, L. M., Abe, T., and Bemben, M. G. (2012a). The Anabolic Benefits of Venous Blood Flow Restriction Training May Be Induced by Muscle Cell Swelling. *Med. Hypotheses* 78 (1), 151–154. doi:10.1016/j.mehy.2011.10.014

Loenneke, J. P., Thiebaud, R. S., Abe, T., and Bemben, M. G. (2014). Blood Flow Restriction Pressure Recommendations: The Hormesis Hypothesis. *Med. Hypotheses* 82 (5), 623–626. doi:10.1016/j.mehy.2014.02.023

Loenneke, J. P., Wilson, J. M., Marín, P. J., Zourdos, M. C., and Bemben, M. G. (2012b). Low Intensity Blood Flow Restriction Training: a Meta-Analysis. *Eur. J. Appl. Physiol.* 112 (5), 1849–1859. doi:10.1007/s00421-011-2167-x

Lopez, P., Radaelli, R., Taaffe, D. R., Newton, R. U., Galvão, D. A., Trajano, G. S., et al. (2021). Resistance Training Load Effects on Muscle Hypertrophy and Strength Gain: Systematic Review and Network Meta-Analysis. *Med. Sci. Sports Exerc.* 53 (6), 1206–1216. doi:10.1249/MSS.0000000000002585

Luebbers, P. E., Witte, E. V., Oshel, J. Q., and Butler, M. S. (2019). Effects of Practical Blood Flow Restriction Training on Adolescent Lower-Body Strength. *J. Strength Cond. Res.* 33 (10), 2674–2683. doi:10.1519/JSC.0000000000002302

Manini, T. M., and Clark, B. C. (2009). Blood Flow Restricted Exercise and Skeletal Muscle Health. *Exerc. Sport Sci. Rev.* 37 (2), 78–85. doi:10.1097/JES.0b013e31819c2e5c

Marshall, J., Bishop, C., Turner, A., and Haff, G. G. (2021). Optimal Training Sequences to Develop Lower Body Force, Velocity, Power, and Jump Height: A Systematic Review with Meta-Analysis. *Sports Med.* 51 (6), 1245–1271. doi:10.1007/s40279-021-01430-z

Marshall, W. A., and Tanner, J. M. (1969). Variations in Pattern of Pubertal Changes in Girls. *Archives Dis. Child.* 44 (235), 291–303. doi:10.1136/adc.44.235.291

Marshall, W. A., and Tanner, J. M. (1970). Variations in the Pattern of Pubertal Changes in Boys. *Archives Dis. Child.* 45 (239), 13–23. doi:10.1136/adc.45.239.13

McBride, J. M., Triplett-McBride, T., Davie, A., and Newton, R. U. (2002). The Effect of Heavy- vs. Light-Load Jump Squats on the Development of Strength, Power, and Speed. *J. Strength Cond. Res.* 16 (1), 75–82. doi:10.1519/1533-4287(2002)016<0075:teohvl>2.0.co;2

Mcguigan, M. R., Doyle, T. L. A., Newton, M., Edwards, D. J., Nimphius, S., and Newton, R. U. (2006). Eccentric Utilization Ratio: Effect of Sport and Phase of Training. *J. Strength Cond. Res.* 20 (4), 992–995. doi:10.1519/R-19165.1

McMahon, J. J., Suchomel, T. J., Lake, J. P., and Comfort, P. (2018). Understanding the Key Phases of the Countermovement Jump Force-Time Curve. *Strength Cond. J.* 40, 96–106. doi:10.1519/SSC.0000000000000375

McQuilliam, S. J., Clark, D. R., Erskine, R. M., and Brownlee, T. E. (2020). Free-Weight Resistance Training in Youth Athletes: A Narrative Review. *Sports Med.* 50 (9), 1567–1580. doi:10.1007/s40279-020-01307-7

Mohamed, I. W., Rahim, M. F. A., and Shaharudin, S. (2017). Effects of Isokinetic versus Isotonic Training on Strength, Power and Muscular Balance of Rotator Cuff Muscles Among Advanced Level of Adolescent Weightlifters. *Int. J. Appl. Sports Sci.* 29 (2), 143–154. doi:10.24985/ijass.2017.29.2.143

Moran, J. J., Sandercock, G. R. H., Ramírez-Campillo, R., Meylan, C. M. P., Collison, J. A., and Parry, D. A. (2017). Age-Related Variation in Male Youth Athletes' Countermovement Jump after Plyometric Training: A Meta-Analysis of Controlled Trials. *J. Strength Cond. Res.* 31 (2), 552–565. doi:10.1519/JSC.0000000000001444

Nicol, C., Avela, J., and Komi, P. V. (2006). The Stretch-Shortening Cycle: Model to Study Naturally Occurring Neuromuscular Fatigue. *Sports Med.* 36 (11), 977–999. doi:10.2165/00007256-200636110-00004

Pearson, S. J., and Hussain, S. R. (2015). A Review on the Mechanisms of Blood-Flow Restriction Resistance Training-Induced Muscle Hypertrophy. *Sports Med.* 45 (2), 187–200. doi:10.1007/s40279-014-0264-9

Petronijevic, M. S., Garcia Ramos, A., Mirkov, D. M., Jaric, S., Valdevit, Z., and Knezevic, O. M. (2018). Self-Preferred Initial Position Could Be a Viable Alternative to the Standard Squat Jump Testing Procedure. *J. strength Cond. Res.* 32 (11), 3267–3275. doi:10.1519/JSC.0000000000002385

Pope, Z. K., Willardson, J. M., and Schoenfeld, B. J. (2013). Exercise and Blood Flow Restriction. *J. Strength Cond. Res.* 27 (10), 2914–2926. doi:10.1519/JSC.0b013e3182874721

Radnor, J. M., Oliver, J. L., Waugh, C. M., Myer, G. D., Moore, I. S., and Lloyd, R. S. (2018). The Influence of Growth and Maturation on Stretch-Shortening Cycle Function in Youth. *Sports Med.* 48 (1), 57–71. doi:10.1007/s40279-017-0785-0

Sale, D. G. (2002). Postactivation Potentiation: Role in Human Performance. *Exerc. Sport Sci. Rev.* 30 (3), 138–143. doi:10.1097/00003677-200207000-00008

Santos Nobre, J., and da Motta Singer, J. (2007). Residual Analysis for Linear Mixed Models. *Biom. J.* 49, 863–875. doi:10.1002/bimj.200610341

Suchomel, T. J., Nimphius, S., and Stone, M. H. (2016). The Importance of Muscular Strength in Athletic Performance. *Sports Med.* 46 (10), 1419–1449. doi:10.1007/s40279-016-0486-0

Tillin, N. A., and Bishop, D. (2009). Factors Modulating Post-Activation Potentiation and its Effect on Performance of Subsequent Explosive Activities. *Sports Med.* 39 (2), 147–166. doi:10.2165/00007256-200939020-00004

Van Cutsem, M., Duchateau, J., and Hainaut, K. (1998). Changes in Single Motor Unit Behaviour Contribute to the Increase in Contraction Speed after Dynamic Training in Humans. *J. Physiol.* 513 (Pt 1), 295–305. doi:10.1111/j.1469-7793.1998.295by.x

Van Hooren, B., and Zolotarjova, J. (2017). The Difference between Countermovement and Squat Jump Performances: A Review of Underlying Mechanisms with Practical Applications. *J. Strength Cond. Res.* 31 (7), 2011–2020. doi:10.1519/JSC.0000000000001913

Wilson, J. M., Lowery, R. P., Joy, J. M., Loenneke, J. P., and Naimo, M. A. (2013). Practical Blood Flow Restriction Training Increases Acute Determinants of Hypertrophy without Increasing Indices of Muscle Damage. *J. Strength Cond. Res.* 27 (11), 3068–3075. doi:10.1519/JSC.0b013e31828a1ffa

Yamanaka, T., Farley, R. S., and Caputo, J. L. (2012). Occlusion Training Increases Muscular Strength in Division IA Football Players. *J. Strength Cond. Res.* 26 (9), 2523–2529. doi:10.1519/JSC.0b013e31823f2b0e

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

BRIEF RESEARCH REPORT
published: 15 July 2022
doi: 10.3389/fphys.2022.864642

Check for updates

Muscle Deoxygenation Rates and Reoxygenation Modeling During a Sprint Interval Training Exercise Performed Under Different Hypoxic Conditions

Robert Solsona[1,2], Roméo Deriaz[1], Fabio Borrani[2*†] and Anthony M. J. Sanchez[1*†]

[1]Laboratoire Interdisciplinaire Performance Santé Environnement de Montagne (LIPSEM), Faculty of Sports Sciences, University of Perpignan Via Domitia (UPVD), Font-Romeu, France, [2]Institute of Sport Sciences, University of Lausanne, Lausanne, Switzerland

OPEN ACCESS

Edited by:
Gregory C. Bogdanis,
National and Kapodistrian University of Athens, Greece

Reviewed by:
Stéphane P. Dufour,
Université de Strasbourg, France
Argyris G. Toubekis,
National and Kapodistrian University of Athens, Greece

***Correspondence:**
Fabio Borrani
fabio.Borrani@unil.ch
Anthony M. J. Sanchez
anthony.sanchez@univ-perp.fr
anthony.mj.sanchez@gmail.com

†These authors have contributed equally to this work and share senior authorship

Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: 28 January 2022
Accepted: 15 June 2022
Published: 15 July 2022

Citation:
Solsona R, Deriaz R, Borrani F and Sanchez AMJ (2022) Muscle Deoxygenation Rates and Reoxygenation Modeling During a Sprint Interval Training Exercise Performed Under Different Hypoxic Conditions. Front. Physiol. 13:864642. doi: 10.3389/fphys.2022.864642

This study compared the kinetics of muscle deoxygenation and reoxygenation during a sprint interval protocol performed under four modalities: blood flow restriction at 60% of the resting femoral artery occlusive pressure (BFR), gravity-induced BFR (G-BFR), simulated hypoxia (FiO_2≈13%, HYP) and normoxia (NOR). Thirteen healthy men performed each session composed of five all-out 30-s efforts interspaced with 4 min of passive recovery. Total work during the exercises was 17 ± 3.4, 15.8 ± 2.9, 16.7 ± 3.4, and 18.0 ± 3.0 kJ for BFR, G-BFR, HYP and NOR, respectively. Muscle oxygenation was continuously measured with near-infrared spectroscopy. Tissue saturation index (TSI) was modelled with a linear function at the beginning of the sprint and reoxygenation during recovery with an exponential function. Results showed that both models were adjusted to the TSI (R^2 = 0.98 and 0.95, respectively). Greater deoxygenation rates were observed in NOR compared to BFR (p = 0.028). No difference was found between the conditions for the deoxygenation rates relative to sprint total work ($p > 0.05$). Concerning reoxygenation, the amplitude of the exponential was not different among conditions ($p > 0.05$). The time delay of reoxygenation was longer in BFR compared to the other conditions ($p < 0.05$). A longer time constant was found for G-BFR compared to the other conditions ($p < 0.05$), and mean response time was longer for BFR and G-BFR. Finally, sprint performance was correlated with faster reoxygenation. Hence, deoxygenation rates were not different between the conditions when expressed relatively to total sprint work. Furthermore, BFR conditions impair reoxygenation: BFR delays and G-BFR slows down reoxygenation.

Keywords: blood flow restriction, occlusion, hypoxia, skeletal muscle, exercise training, altitude, gravity-induced BFR

INTRODUCTION

Sprint interval training (SIT) is a training method in vogue that was found to shortly improve both aerobic performance and repeated sprint ability (Burgomaster et al., 2006; Brocherie et al., 2017). SIT includes long sprints (e.g., 30 s) interspaced with long recovery periods (between 2 and 4 min) (Buchheit and Laursen, 2013). In the past few years, it has been observed that additional hypoxic stress during repeated sprint sessions amplifies several training adaptations, including muscle phosphocreatine content, repeated sprint ability, the onset of blood lactate accumulation, single sprint and Yo-Yo test performance (Millet et al., 2019).

Among the known hypoxic methods, there is systemic hypoxia, provoked by natural altitude or simulated altitude with hypoxic or hypobaric chambers (HYP), and local hypoxia, which can be obtained using cuffed blood flow restriction (BFR) and gravity-induced blood flow restriction (G-BFR) (Preobrazenski et al., 2020, 2021; Solsona et al., 2021). BFR consists in placing compression cuffs around the proximal part of the exercising muscles which induces ischemia and/or altered venous return according to the pressure exerted (Patterson et al., 2019). G-BFR is an easy-to-use method consisting in the inclination of an ergocycle to place the heart beneath the lower limbs, thus reducing blood availability to the working muscles (Preobrazenski et al., 2020, 2021; Solsona et al., 2021). However, the acute physiological effects of these methods during SIT sessions remain underexplored.

Muscle oxygenation kinetics have been studied during constant-intensity submaximal exercise with or without BFR (Salzmann et al., 2021). In this study, it was found that BFR accelerated the deoxygenation phases compared to normoxia (NOR), and increased total deoxygenation amplitude, especially during the last phase of exercise. Another study previously examined the muscle oxygenation kinetics during an SIT session performed in NOR (Buchheit et al., 2012). The authors found an association between sprint performance and muscle deoxygenation, as well as an increase of the deoxygenation and reoxygenation rates across the sprint repetitions. Specifically, the SIT session elicited near-to-maximal $\dot{V}O_2$ peak values, which were associated with a high degree of muscle deoxygenation. These data support the highly energetic demand of SIT protocols at the muscular level.

However, muscle deoxygenation and reoxygenation kinetics have never been studied and compared under different hypoxic conditions. This focus is of importance since muscle deoxygenation rates and the kinetics of muscle reoxygenation may be linked to performance and the replenishment of energy substrates. Indeed, previous studies showed differences in muscle oxygen availability and substrate utilization during sustained intermittent intense and continuous submaximal exercises (Christmass et al., 1999). Hence, the aim of this study was to compare the muscle deoxygenation rates and reoxygenation kinetics during an SIT exercise performed under different hypoxic protocols (BFR, G-BFR, HYP, and NOR) with a randomized crossover design. For this purpose, two models were used: a linear model for muscle deoxygenation at the onset of sprints and an exponential model during recovery. The hypotheses were that different deoxygenation rates would be observed according to the condition, with higher values in NOR due to more oxygen availability, compared to the other conditions, and according to the sprint number due to fatigue accumulation. Furthermore, muscle reoxygenation would be limited by the different hypoxic conditions.

METHODS

Participants

The data have been collected during a previous experiment that aimed to examine the effects of SIT conducted in hypoxia or with BFR on mechanical, cardiorespiratory, and muscular O_2 extraction responses (Solsona et al., 2021). Thirteen healthy young moderately trained men (mean ± standard deviation, age 24 ± 3 years; weight 73.8 ± 6.5 kg; height 179 ± 6 cm; body fat percentage 12.5 ± 2.1%; training frequency 8 ± 4 h per week) volunteered to participate in the study. They gave written consent to participate in the experiment, which was approved by the local ethics committee (VD-2021-00597). Participants completed the Physical Activity Readiness Questionnaire prior to the first session. All experiments were performed in accordance with the last Declaration of Helsinki. The participants were asked to maintain their dietary habits and to avoid alcohol consumption 48 h before each test. They did not take medication or dietary supplements during the studied period.

Study Design

This crossover study aimed to compare the deoxygenation rates during an SIT session under different hypoxic conditions. Participants performed four SIT sessions under different conditions in a random order over 4 weeks. Sessions took place at least 5 days apart to avoid fatigue-related bias. Trials were performed at the same time of the day and within the same environmental conditions to minimize the effects of circadian cycles. Anthropometric measurements were carried out on the first visit and body fat percentage was estimated with the four skinfold method (Durnin and Womersley, 1974). Inflation cuffs (SC12D, cuff size 13 × 85 cm) and an inflation apparatus (E20/AG101 Rapid Cuff Inflation System, D. E Hokanson Inc., Bellevue, WA, United States) were used for BFR, which was only applied during the first 2 min of recovery at 60% of resting arterial occlusive pressure (AOP). Preliminary work determined these were the longest time and the highest pressure that could be tolerated by participants. Resting AOP was measured with an ultrasound linear probe (EchoWave II 3.4.4, Telemed Medical Systems, Milan, Italy) in a seated position on the right leg the day participants undertook the BFR condition. The pressure was progressively increased until no blood flow was detected in the femoral artery. A total of three measurements were taken with a one-minute recovery between each evaluation. The highest value recorded was retained and 60% of this value was used for the cuffs that were placed bilaterally during the exercise session. The cuffs were inflated immediately after the sprints for 2 min. Concerning G-BFR, a structure was built to allow participants to pedal in the supine position. The structure also permitted handgrip to mimic conventional cycling and to avoid body displacements during exercise. Mean vertical distance between the horizontal plane and the crank axis was about 35 cm. The laying position was adopted at the end of the warm-up and maintained until the end of the protocol. Regarding HYP, the inspired dioxygen fraction (FiO_2) was set at 13.0% in a normobaric hypoxic chamber (ATS altitude training, Sydney, Australia). The warm-up was performed in HYP for this condition. NOR was performed below 400 m of altitude. The configuration (height and length) of both the saddle and the handlebars was recorded on the first visit to be reproduced in the subsequent tests. Participants had to maintain saddle contact and were verbally encouraged to provide maximal effort. Researchers did not provide verbal indications of time to avoid pacing strategies. Muscle oxygenation was continuously measured with a near-infrared spectroscopy (NIRS) probe (OxiplexTS, ISS, Champagne, United States). The device was calibrated before each session and was placed on the distal part of the vastus lateralis (VL) muscle. It was wrapped with an elastic band to limit extraneous light and movement.

Sprint Interval Training Exercise

Exercise sessions consisted of a standardized warm-up of 16 min including 10 min at 100 W and 85 rpm, followed by two six-second sprints preceded by 54 s of resting. Thereafter, 4 min of passive recovery were allowed before the beginning of the SIT session, which comprised five all-out efforts of 30 s with 4 min of passive recovery. The session lasted until the recovery of the fifth sprint. The sessions took place in a controlled indoor environment with an ergocycle (Lode Excalibur Sport 911905, Lode B.V., Groningen, Netherlands) set on constant torque (0.8 $Nm\cdot kg^{-1}$). A three-second countdown indicated the beginning of the sprint, which was performed with a standing start (i.e., without inertia).

Data Treatment

The acquisition frequency was 50 Hz and data were averaged every second. Tissue saturation index (TSI) was calculated as follows by the NIRS (Barstow, 2019):

$$TSI = \frac{[O_2Hb]}{[tHb]} \times 100$$

$[O_2Hb]$ and [tHb] represent the concentration of oxygenated haemoglobin and total haemoglobin concentrations, respectively. Then, data were treated with a low-pass second-order Butterworth filter with a cutoff frequency of 0.1 Hz. The slopes (a) and TSI_0 (intercepts) of the TSI during the first 9 s of each sprint were calculated. This allowed to obtain a modeled TSI (mTSI) with a linear function (Bae et al., 2000):

$$mTSI_{(t)} = a \times t + TSI_0$$

With t being the time (in seconds) elapsed from the start of the sprint. The slope represents the rate of deoxygenation per second (Buchheit et al., 2012). TSI_0 is the intercept, corresponding with the TSI at the beginning of the sprint. The equation allowed the calculation of the coefficient of determination (R^2) between the mTSI and the TSI data. The first 10 consecutive points (i.e., 9 s) were selected. Finally, the relative rate of deoxygenation (a_{adj}) according to the sprint total work (W) was calculated as follows (Buchheit et al., 2012):

$$a_{adj} = \frac{a}{W}$$

Of note, TSI is a better indicator of muscle oxygenation than deoxygenated haemoglobin when blood flow is not constant (Wolf et al., 2007). **Figure 1** represents the measured and modelled TSI during a representative 30-second sprint.

ΔTSI is the absolute difference between maximal sprint TSI and minimal sprint TSI.

Muscle reoxygenation kinetics (TSIk) was modelled with an exponential function:

$$TSIk_{(t)} = TSIb + A\left(1 - e^{\frac{t-TD}{\tau}}\right)$$

With TSIb corresponding to the TSI at the beginning of recovery, A being total reoxygenation amplitude of the first exponential, TD is the time delay, τ is the exponential time constant and mean response time (MRT) equals to TD + τ. A′ is the amplitude of reoxygenation from the beginning of the exponential curve until the end of recovery (Tend), which was calculated as follows:

$$A' = A\left(1 - e^{\frac{-Tend-TD}{\tau}}\right)$$

The parameters of the model for deoxygenation (a, TSI_0) and reoxygenation (A′, TD, τ, MRT) were determined with an iterative procedure by minimizing the sum of the mean squares of the differences between the estimated mTSI and TSIk models and the measured TSI. Power decrease percentage was calculated as follows (Glaister et al., 2008):

$$Power\ decrease\ percentage =$$

$$100 \times \frac{Sum\ of\ mean\ power\ of\ all\ the\ sprints}{Best\ mean\ power \times number\ of\ sprints} - 100$$

Statistical Analysis

The statistical analyses were performed using Jamovi (Version 1.6.23). Figures were designed with Microsoft Excel and PowerPoint. Linear mixed models were used to compare the conditions and the sprints number. The significance level was set at 0.05. Post hoc analyses were performed using pairwise comparisons with Holm's correction. Effect sizes (d) are provided (trivial effect 0.10 < d < 0.20, small effect 0.20 < d < 0.50, medium effect 0.50 < d < 0.80 and large effect d > 0.80) (Cohen, 1992). Spearman correlations were performed between deoxygenation rates, reoxygenation kinetics and the other variables.

Furthermore, the coefficient of determination (R^2) and the adjusted coefficient of determination (adjR^2) were calculated from the beginning of the exponential until Tend:

$$\text{adj}R^2 = 1 - \left(1 - R^2\right)\frac{n-1}{n-k-1}$$

The coefficient k corresponds to the number of degrees of freedom of the model (i.e., three), n is the sample size.

RESULTS

No condition*sprint number interaction was detected for any variable.

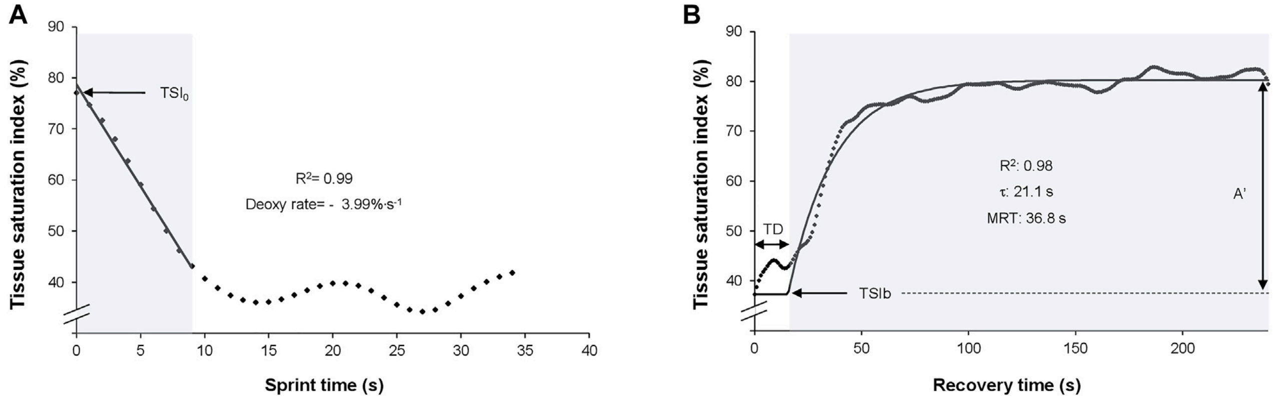

FIGURE 1 | Measured (rhombuses) and modelled (line) tissue saturation index during a 30 s sprint **(A)** and during recovery **(B)** for a representative subject. Grey zone: modelled sections; TSI_0: Tissue saturation index at the beginning of the sprint; R2: determination coefficient between measured and modelled data; Deoxy rate: deoxygenation rate per second (i.e., model slope). TSIb, TSI at the beginning of recovery; A', amplitude of the exponential; TD, time delay from the beginning of recovery until the beginning of the exponential; τ, time constant of the exponential; MRT, mean response time of the exponential. Of note, the values are representative and correspond to a subject's illustrative sprint.

TABLE 1 | Peak and mean power output during sprints under the different conditions.

	BFR	G-BFR	HYP	NOR
Peak power (W)	766.6 ± 174.2	717.8 ± 135.0	783.0 ± 149.6	835.4 ± 176.0†
Mean power (W)	551.9 ± 107.4†	533.8 ± 97.6	557.4 ± 82.8†	593.4 ± 98.6†
Power decrease (%)	−16.1 ± 8.5	−12.7 ± 7.3	−12.5 ± 5.2	−12.9 ± 7.2

†significantly different from G-BFR (p < 0.05). Data are shown as mean ± standard deviation.
BFR, blood flow restriction; G-BFR, gravity-induced blood flow restriction; HYP, hypoxia; NOR, normoxia. Power decrease, percentage decrease between the best sprint and the mean sprints power.

Performance

Peak power was lower in G-BFR compared to NOR ($p < 0.01$) and mean power was lower in G-BFR compared to the other conditions ($p < 0.05$). No difference between conditions was found ($p > 0.05$) in the performance decrease percentage (**Table 1**). Sprint exercises mean total work was 17 ± 3.4, 15.8 ± 2.9, 16.7 ± 3.4 and 18.0 ± 3.0 kJ for BFR, G-BFR, HYP and NOR, respectively. Mean total work was lower in G-BFR compared to the other conditions ($p < 0.05$).

Goodness of the Fit and Coefficient of Determination for Deoxygenation Rates and Reoxygenation Kinetics

A total of 210/260 (R^2>0.80) sprint exercises were modelled with the linear function and 148/260 (R^2>0.80) sprint exercises were modelled with the exponential function. Indeed, an R > 0.90 (i.e., R^2>0.80) represents a strong relationship between two variables (Taylor, 1990). In the linear model of muscle deoxygenation, the mean R^2 between TSI and mTSI was 0.98 ± 0.02 (**Figure 1**). The coefficient of determination, as well as the adjusted coefficient of determination of the exponential model were 0.95 ± 0.04 (**Figure 1**).

Muscle Deoxygenation Rates

An effect of condition was detected for absolute deoxygenation rates (p = 0.014). According to post hoc tests, greater deoxygenation rates were observed in NOR compared to BFR (p = 0.028; d = 0.21, **Figure 2A**). The means were −2.4 ± 1.0% s^{-1} and −2.6 ± 1.2% s^{-1}, respectively. However, when deoxygenation rates were expressed relatively to sprint total work, there was no significant difference ($p > 0.05$, **Figure 2B**): −0.15 ± 0.06% s^{-1} kJ for both BFR and NOR. Regarding sprint number, no difference on absolute deoxygenation rate was found ($p > 0.05$, **Figure 2C**). An effect of sprint number was found for adjusted deoxygenation rates (p = 0.030). Post hoc analyses showed that adjusted deoxygenation rates were higher in the fifth sprint compared to the first sprint (p = 0.041; d = 0.39, **Figure 2D**).

Importantly, significant differences were found regarding TSI_0 between conditions: values were higher in BFR compared to G-BFR and HYP ($p < 0.001$; d = 1.11 and p = 0.014; d = 0.60, respectively, **Figure 2E**). TSI_0 was also higher in HYP compared to G-BFR ($p < 0.001$; d = 0.77) and in NOR compared to G-BFR and HYP ($p < 0.001$; d = 0.99 and p = 0.035; d = 0.41, respectively, **Figure 2E**). Mean TSI_0 values were 80.0 ± 4.4%, 72.4 ± 8.6%, 77.6 ± 3.7% and 79.2 ± 4.5% for BFR; G-BFR, HYP and NOR, respectively. Finally, regarding the sprint number, no difference was observed concerning TSI_0 ($p > 0.05$, **Figure 2F**).

Muscle Reoxygenation

The amplitude of the exponential (A') did not present an effect of condition or sprint number ($p > 0.05$; **Table 2**). On the other

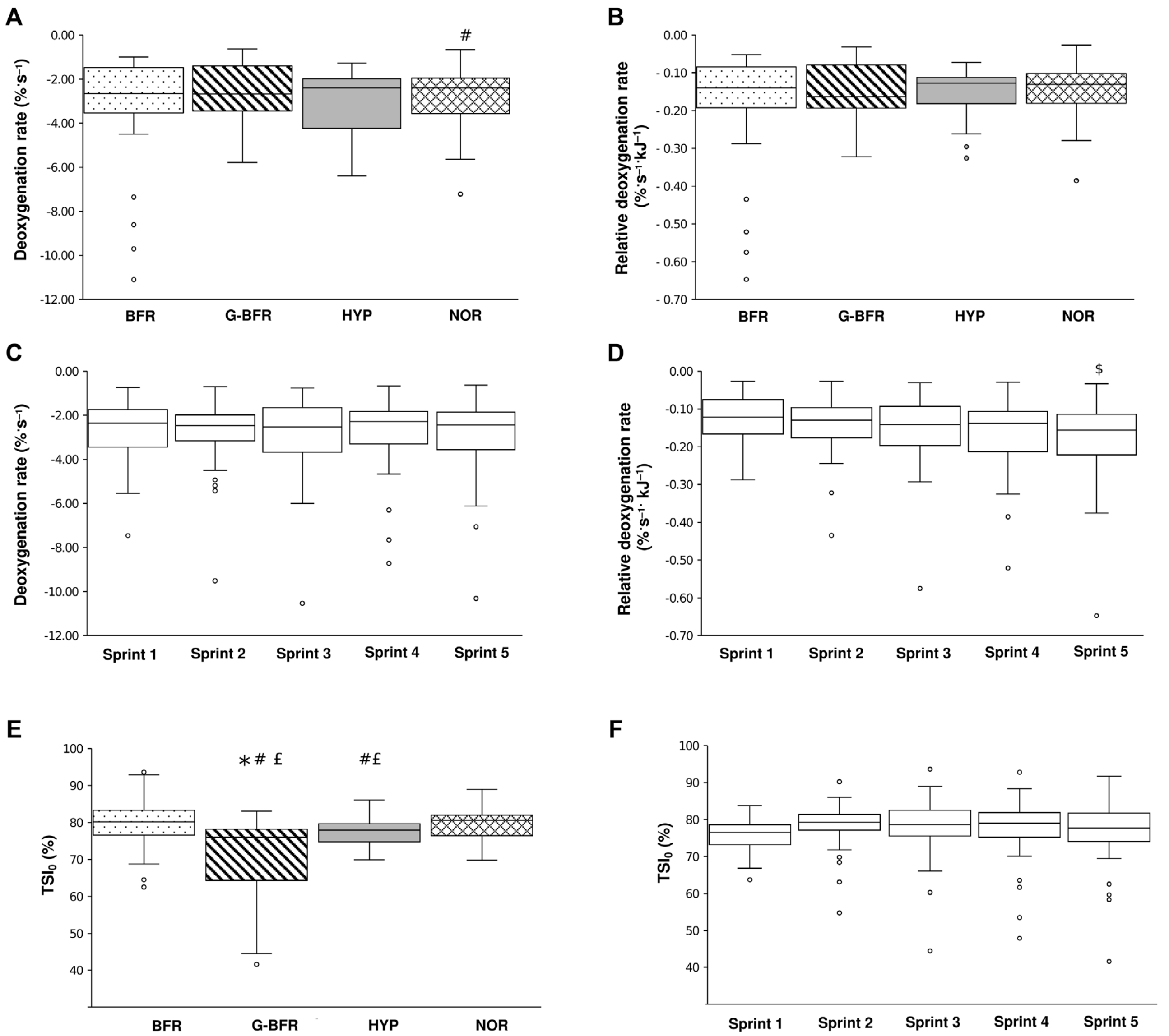

FIGURE 2 | Deoxygenation rate and relative deoxygenation rate between conditions (**A** and **B** respectively) and between sprints (**C** and **D** respectively). Deoxygenation rates correspond to the slopes of the tissue saturation index (TSI)/time (in seconds) relationship. Relative deoxygenation rate considers total sprint work. Pre-sprint tissue saturation index (TSI_0) comparison between conditions **(E)** and between sprints **(F)**. The dots represent outlier data points, the whiskers minimal and maximal values, the boxes the interquartile region, the horizontal line the median. Quartiles are also shown. £, significantly different from NOR; $, significantly different from sprint 1. *, significantly different from HYP; #, significantly different from BFR. Of note, condition graphs **(A,B,E)** include the five sprints averaged and sprint number graphs **(C,D,F)** include the four conditions averaged.

TABLE 2 | Parameters estimated for exponential curve fitting of individual reoxygenation response.

	BFR	G-BFR	HYP	NOR
A' (%)	23.04 ± 7.12	29.34 ± 5.87	28.44 ± 9.98	27.05 ± 8.69
TD (s)	52.57 ± 40.20	24.20 ± 12.05$^{\#}$	18.54 ± 15.15$^{\#}$	14.71 ± 14.45$^{\#}$
τ (s)	50.12 ± 33.82†	60.82 ± 53.38	30.87 ± 16.77†	26.68 ± 15.77†
MRT (s)	102.69 ± 50.48	85.02 ± 55.55	49.41 ± 19.90$^{\#\dagger}$	41.38 ± 17.68$^{\#\dagger}$

$^{\#}$*significantly different from BFR (p < 0.05).*
†*significantly different from G-BFR (p < 0.05). Data are shown as mean ± standard deviation.*
BFR, blood flow restriction; G-BFR, gravity-induced blood flow restriction; HYP, hypoxia; NOR, normoxia. A', amplitude of the exponential of the modelled TSI; TD, time delay of the exponential; τ, time constant of the exponential; MRT, mean response time of the exponential.

hand, TD presented an effect of condition ($p < 0.001$). According to post hoc tests, TD was higher in BFR compared to G-BFR ($p < 0.001$; d = 0.96), HYP ($p < 0.001$; d = 1.12) and NOR ($p < 0.001$; d = 1.25). TSIb also showed an effect of condition ($p < 0.001$). Post hoc analyses revealed that TSIb was higher in BFR compared to G-BFR ($p < 0.001$; d = 1.35) and HYP ($p = 0.001$; d = 0.95). TSIb presented an effect of sprint ($p = 0.017$). According to post hoc analyses it was higher after sprints one and two compared to sprint five ($p = 0.024$; d = 0.65 and $p = 0.011$; d = 0.80, respectively). τ presented an effect of condition ($p < 0.001$), with higher values observed in G-BFR compared to BFR ($p = 0.033$; d = 0.24), HYP ($p < 0.001$; d = 0.76) and NOR ($p < 0.001$; d = 0.87). MRT was also different among the conditions ($p < 0.001$). MRT was higher in both BFR and G-BFR compared to HYP ($p < 0.001$; d = 1.39 and $p < 0.001$; d = 0.85, respectively) and NOR ($p < 0.001$; d = 1.62 and $p < 0.001$; d = 1.06, respectively).

Correlations

Negative correlations with deoxygenation rates were found for mean power (r = −0.16; $p = 0.025$), peak power (r = −0.26; $p < 0.001$), TSI_0 (r = −0.31; $p < 0.001$) and ΔTSI (r = −0.78; $p < 0.001$). TSI_0 was positively correlated to ΔTSI (r = 0.30; $p < 0.001$). Furthermore, mean power was negatively correlated with τ (r = −0.39; $p < 0.001$) and with MRT (r = −0.33; $p < 0.001$). Finally, peak power was positively associated with A' (r = 0.28; $p < 0.001$), and negatively correlated to τ (r = −0.31; $p < 0.001$), TSIb (r = −0.22; $p = 0.008$) and MRT (r = −0.28; $p < 0.001$).

DISCUSSION

This crossover study aimed to model and to compare the muscle deoxygenation rates and reoxygenation kinetics during an SIT exercise performed under different hypoxic conditions in moderately trained men. An R^2 of 0.98 was obtained between the measured and modelled TSI during sprints, which means that deoxygenation at the first phase of the sprint was linear. In addition, the exponential model fitted satisfactorily reoxygenation during the recovery periods. The present data show that, even if greater deoxygenation rates were observed in NOR compared to BFR, this difference disappeared when the deoxygenation rates were adjusted with sprint total work. Moreover, BFR delays and G-BFR slows down reoxygenation kinetics.

According to the data, absolute deoxygenation rates were not different between the sprints. However, greater adjusted deoxygenation rates were found in the fifth sprint compared to the first sprint, unlike the results of Buchheit and colleagues, who found a significant decrease in the adjusted deoxygenation rates with the repetition of sprints (Buchheit et al., 2012). However, it has been shown that glycogenolysis decreased since the second 30-s sprint (Bogdanis et al., 1996). It is also known that energy production from substrates depends less on phosphocreatine with the repetition of sprints (Parolin et al., 1999). Altogether, muscle energetic metabolism relies more on oxygen as long intermittent high intensity bouts are repeated. Of note, muscle contraction efficiency decreases with fatigue (Barclay, 1996), which would explain the increased deoxygenation rates for a given mechanical work during the last sprint. Furthermore, TSI_0 was different between the conditions except between NOR and BFR. Specifically, HYP reduced TSI_0, and G-BFR decreased it further. This result means that HYP, but mostly G-BFR, decreased basal TSI, but without any effect on the deoxygenation rates. Thus, while adding different hypoxic stress to an SIT session does not impact the muscular deoxygenation rate, it does affect pre-sprint TSI. Interestingly, this result suggests that basal TSI does not have an impact on deoxygenation rates during the current protocol. Lastly, the current study showed that TSI_0 was lower in G-BFR compared to the other conditions. This result is in agreement with previous work from our laboratory, which showed that mean session TSI was also lower in G-BFR compared to BFR, NOR and HYP (Solsona et al., 2021).

A recent study from our laboratory highlighted that BFR could accelerate the decrease of TSI during constant-load submaximal exercise (Salzmann et al., 2021). Accordingly, a study with a repeated sprint protocol (i.e., 10-s sprints) showed that continuous BFR increases the amplitude of deoxyhaemoglobin, suggesting that deoxygenation rates were higher in this condition (Willis et al., 2019). The present study showed the opposite result, at least in the absolute deoxygenation rate values, probably because of the intermittent application of BFR. It could be speculated that deoxygenation rates would have been higher in BFR if it was applied during the sprints. On the other hand, as TSI represents the ratio of oxygenated haemoglobin to total haemoglobin, it is not possible to rule out an alteration of oxygen-rich blood delivery and/or an increase of total haemoglobin concentrations. Yet, both have recently been shown to increase proportionally during the present protocol under the BFR condition (Solsona et al., 2021), which would not affect the ratio and thus lead to an unmodified TSI.

The amplitude of reoxygenation was not limited by the different hypoxic conditions. Hence, 4 min of recovery are sufficient to reoxygenate muscles after SIT exercises under these conditions. Importantly, BFR delayed recovery compared to the other conditions (higher TD). On the other hand, τ was higher in G-BFR compared to BFR, NOR and HYP, meaning that the exponential curve increased slower, and that muscle reoxygenation is delayed by gravity. Indeed, we previously showed that mean session TSI was lower under this condition (Solsona et al., 2021). Moreover, TSIb was higher in BFR compared to HYP and G-BFR, which agrees with the higher minimal TSI value observed during the sprints (Solsona et al., 2021). Furthermore, MRT was longer under BFR and G-BFR compared to NOR and HYP. Blood flow restriction methods delay post-sprint recovery differently: while TD increased in BFR, τ increased in G-BFR. These results mean that BFR delays the beginning of the exponential and G-BFR slows down reoxygenation.

Deoxygenation rates were inversely correlated to peak power output, mean power, TSI_0 and ΔTSI. This result means that performance is associated with higher deoxygenation rates, lower TSI_0 and higher deoxygenation amplitude. On the other hand, TSI_0 was correlated to ΔTSI, which suggests that higher pre-sprint TSI permits higher deoxygenation amplitudes. Finally, several reoxygenation variables were correlated with performance. Specifically, the amplitude of reoxygenation was correlated with peak power, meaning that higher levels of reoxygenation (because of lower post-sprint values) are useful for performance during SIT. Participants showing high power outputs also presented lower TSIb, reflecting their ability to further deoxygenate muscles during sprints. Finally, τ and MRT were shorter on participants who were able to achieve higher mean and peak power outputs. This result suggests that performance in the current protocol was associated with faster reoxygenation.

Some limitations must be acknowledged. Indeed, TSI is influenced by microvascular blood flow variation induced by thermoregulation (Grassi and Quaresima, 2016). Nevertheless, trials were performed in a laboratory environment with non-significant changes in temperature. In addition, oxygenation was measured in a small part of the VL muscle, making it difficult to extrapolate the results in the whole muscle. However, for this issue, a study demonstrated that deoxyhaemoglobin kinetics were similar between all the muscles of the quadriceps femoris during a moderate-intensity knee extension exercise (duManoir et al., 2010).

In conclusion, this study shows that adding different hypoxic stress to an SIT session did not have an impact on muscle deoxygenation rates in moderately trained athletes when total work was considered. Indeed, sprinting seems sufficient to cause high levels of deoxygenation rates, as it is observed in NOR. However, pre-sprint muscle oxygen availability was lower in HYP and G-BFR compared to both BFR and NOR, with a more pronounced effect observed for G-BFR compared to HYP. In addition, according to the exponential fitting, BFR delays and G-BFR slows down reoxygenation kinetics. Importantly, data also suggest that sprint performance is associated with faster reoxygenation and with higher amplitude of both deoxygenation and reoxygenation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Commission cantonale d'éthique de la recherche sur l'être humain, Canton de Vaud, CER-VDVD-2021-00597. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: RS, RD, FB, and AS. Performed the experiments: RS, RD, FB, and AS. Analyzed the data: RS, RD, FB, and AS. Designed the tables and figures: RS, RD, FB, and AS. Wrote the paper: RS, RD, FB, and AS. RS, RD, FB, and AS read the manuscript and approved the final version.

FUNDING

This project was funded by the University of Lausanne and the University of Perpignan Via Domitia (Bonus Qualité Recherche). Open access funding was provided by the University of Lausanne.

ACKNOWLEDGMENTS

The authors thank the participants for their engagement and the University of Lausanne for their support.

REFERENCES

Bae, S. Y., Hamaoka, T., Katsumara, T., Shiga, T., Ohno, H., and Haga, S. (2000). Comparison of Muscle Oxygen Consumption Measured by Near Infrared Continuous Wave Spectroscopy During Supramaximal and Intermittent Pedalling Exercise. *Int. J. Sports Med.* 21, 168–174. doi:10.1055/s-2000-8880

Barclay, C. J. (1996). Mechanical Efficiency and Fatigue of Fast and Slow Muscles of the Mouse. *J. Physiol.* 497 (Pt 3), 781–794. doi:10.1113/jphysiol.1996.sp021809

Barstow, T. J. (2019). Understanding Near Infrared Spectroscopy and its Application to Skeletal Muscle Research. *J. Appl. Physiology* 126 (126), 1360–1376. doi:10.1152/japplphysiol.00166.2018

Bogdanis, G. C., Nevill, M. E., Boobis, L. H., and Lakomy, H. K. (1996). Contribution of Phosphocreatine and Aerobic Metabolism to Energy Supply During Repeated Sprint Exercise. *J. Appl. Physiology* 80, 876–884. doi:10.1152/jappl.1996.80.3.876

Brocherie, F., Girard, O., Faiss, R., and Millet, G. P. (2017). Effects of Repeated-Sprint Training in Hypoxia on Sea-Level Performance: A Meta-Analysis. *Sports Med.* 47, 1651–1660. doi:10.1007/s40279-017-0685-3

Buchheit, M., Abbiss, C. R., Peiffer, J. J., and Laursen, P. B. (2012). Performance and Physiological Responses During a Sprint Interval Training Session: Relationships with Muscle Oxygenation and Pulmonary Oxygen Uptake Kinetics. *Eur. J. Appl. Physiol.* 112, 767–779. doi:10.1007/s00421-011-2021-1

Buchheit, M., and Laursen, P. B. (2013). High-Intensity Interval Training, Solutions to the Programming Puzzle. *Sports Med.* 43, 313–338. doi:10.1007/s40279-013-0029-x

Burgomaster, K. A., Heigenhauser, G. J. F., and Gibala, M. J. (2006). Effect of Short-Term Sprint Interval Training on Human Skeletal Muscle Carbohydrate Metabolism During Exercise and Time-Trial Performance. *J. Appl. Physiology* 100 (100), 2041–2047. doi:10.1152/japplphysiol.01220.2005

Christmass, M. A., Dawson, B., Passeretto, P., and Arthur, P. G. (1999). A Comparison of Skeletal Muscle Oxygenation and Fuel Use in Sustained Continuous and Intermittent Exercise. *Eur. J. Appl. Physiol.* 80, 423–435. doi:10.1007/s004210050614

Cohen, J. (1992). A Power Primer. *Psychol. Bull.* 112, 155–159. doi:10.1037//0033-2909.112.1.15510.1037/0033-2909.112.1.155

duManoir, G. R., DeLorey, D. S., Kowalchuk, J. M., and Paterson, D. H. (2010). Kinetics of VO2 Limb Blood Flow and Regional Muscle Deoxygenation in Young Adults During Moderate Intensity, Knee-Extension Exercise. *Eur. J. Appl. Physiol.* 108, 607–617. doi:10.1007/s00421-009-1263-7

Durnin, J. V. G. A., and Womersley, J. (1974). Body Fat Assessed from Total Body Density and its Estimation from Skinfold Thickness: Measurements on 481 Men and Women Aged from 16 to 72 Years. *Br. J. Nutr.* 32, 77–97. doi:10.1079/BJN19740060

Ferrari, M., Ferrari, M., and Quaresima, V. (2007). Progress of Near-Infrared Spectroscopy and Topography for Brain and Muscle Clinical Applications. *J. Biomed. Opt.* 12, 062104. doi:10.1117/1.2804899

Glaister, M., Howatson, G., Pattison, J. R., and McInnes, G. (2008). The Reliability and Validity of Fatigue Measures During Multiple-Sprint Work: An Issue Revisited. *J. Strength Cond. Res.* 22, 1597–1601. doi:10.1519/JSC.0b013e318181ab80

Grassi, B., and Quaresima, V. (2016). Near-infrared Spectroscopy and Skeletal Muscle Oxidative Functionin Vivoin Health and Disease: A Review from an Exercise Physiology Perspective. *J. Biomed. Opt.* 21, 091313. doi:10.1117/1.JBO.21.9.091313

Millet, G., Girard, O., Beard, A., and Brocherie, F. (2019). Repeated Sprint Training in Hypoxia - An Innovative Method. *Dtsch. Z Sportmed.* 2019, 115–122. doi:10.5960/dzsm.2019.374

Parolin, M. L., Chesley, A., Matsos, M. P., Spriet, L. L., Jones, N. L., and Heigenhauser, G. J. F. (1999). Regulation of Skeletal Muscle Glycogen Phosphorylase and PDH During Maximal Intermittent Exercise. *Am. J. Physiology-Endocrinology Metabolism* 277, E890–E900. doi:10.1152/ajpendo.1999.277.5.E890

Patterson, S. D., Hughes, L., Warmington, S., Burr, J., Scott, B. R., Owens, J., et al. (2019). Blood Flow Restriction Exercise: Considerations of Methodology, Application, and Safety. *Front. Physiol.* 10, 533. doi:10.3389/fphys.2019.00533

Preobrazenski, N., Islam, H., Drouin, P. J., Bonafiglia, J. T., Tschakovsky, M. E., and Gurd, B. J. (2020). A Novel Gravity-Induced Blood Flow Restriction Model Augments ACC Phosphorylation and PGC-1α mRNA in Human Skeletal Muscle Following Aerobic Exercise: A Randomized Crossover Study. *Appl. Physiol. Nutr. Metab.* 45, 641–649. doi:10.1139/apnm-2019-0641

Preobrazenski, N., Islam, H., and Gurd, B. J. (2021). Molecular Regulation of Skeletal Muscle Mitochondrial Biogenesis Following Blood Flow-Restricted Aerobic Exercise: A Call to Action. *Eur. J. Appl. Physiol.* 121, 1835–1847. doi:10.1007/s00421-021-04669-6

Salzmann, K., Sanchez, A. M. J., and Borrani, F. (2021). Effects of Blood Flow Restriction on O2 Muscle Extraction and O2 Pulmonary Uptake Kinetics During Heavy Exercise. *Front. Physiol.* 12, 722848. doi:10.3389/fphys.2021.722848

Solsona, R., Berthelot, H., Borrani, F., and Sanchez, A. M. J. (2021). Mechanical, Cardiorespiratory, and Muscular Oxygenation Responses to Sprint Interval Exercises Under Different Hypoxic Conditions in Healthy Moderately Trained Men. *Front. Physiol.* 12, 2263. doi:10.3389/fphys.2021.773950

Taylor, R. (1990). Interpretation of the Correlation Coefficient: A Basic Review. *J. Diagnostic Med. Sonogr.* 6, 35–39. doi:10.1177/875647939000600106

Willis, S. J., Peyrard, A., Rupp, T., Borrani, F., and Millet, G. P. (2019). Vascular and Oxygenation Responses of Local Ischemia and Systemic Hypoxia During Arm Cycling Repeated Sprints. *J. Sci. Med. Sport* 22, 1151–1156. doi:10.1016/j.jsams.2019.05.001

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Physiology

TYPE Original Research
PUBLISHED 15 December 2022
DOI 10.3389/fphys.2022.1083299

Check for updates

OPEN ACCESS

EDITED BY
J. Grant Mouser,
Troy University, United States

REVIEWED BY
Scott Dankel,
Rowan University, United States
Robert Spitz,
University of Mississippi, United States

*CORRESPONDENCE
Gregory C. Bogdanis,
gbogdanis@phed.uoa.gr

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

RECEIVED 28 October 2022
ACCEPTED 03 December 2022
PUBLISHED 15 December 2022

CITATION
Salagas A, Tsoukos A, Terzis G, Paschalis V, Katsikas C, Krzysztofik M, Wilk M, Zajac A and Bogdanis GC (2022), Effectiveness of either short-duration ischemic pre-conditioning, single-set high-resistance exercise, or their combination in potentiating bench press exercise performance. *Front. Physiol.* 13:1083299. doi: 10.3389/fphys.2022.1083299

Effectiveness of either short-duration ischemic pre-conditioning, single-set high-resistance exercise, or their combination in potentiating bench press exercise performance

Andreas Salagas[1†], Athanasios Tsoukos[1†], Gerasimos Terzis[1], Vassilis Paschalis[1], Christos Katsikas[1], Michal Krzysztofik[2], Michal Wilk[2], Adam Zajac[2] and Gregory C. Bogdanis[1*]

[1]School of Physical Education and Sports Science, National and Kapodistrian University of Athens, Athens, Greece, [2]Institute of Sport Sciences, Jerzy Kukuczka Academy of Physical Education in Katowice, Katowice, Poland

This study compared the effects of short-duration ischemic preconditioning, a single-set high-resistance exercise and their combination on subsequent bench press performance. Twelve men (age: 25.8 ± 6.0 years, bench press 1-RM: 1.21 ± 0.17 kg kg^{-1} body mass) performed four 12 s sets as fast as possible, with 2 min of recovery between sets, against 60% 1-RM, after: a) 5 min ischemic preconditioning (IPC; at 100% of full arterial occlusion pressure), b) one set of three bench press repetitions at 90% 1-RM (PAPE), c) their combination (PAPE + IPC) or d) control (CTRL). Mean barbell velocity in ischemic preconditioning was higher than CTRL (by 6.6–9.0%, $p < 0.05$) from set 1 to set 3, and higher than PAPE in set 1 (by 4.4%, $p < 0.05$). Mean barbell velocity in PAPE was higher than CTRL from set 2 to set 4 (by 6.7–8.9%, $p < 0.05$), while mean barbell velocity in PAPE + IPC was higher than CTRL only in set 1 (+5.8 ± 10.0%). Peak barbell velocity in ischemic preconditioning and PAPE was higher than CTRL (by 7.8% and 8.5%, respectively; $p < 0.05$). Total number of repetitions was similarly increased in all experimental conditions compared with CTRL (by 7.0–7.9%, $p < 0.05$). Rating of perceived exertion was lower in ischemic preconditioning compared with CTRL ($p < 0.001$) and PAPE ($p = 0.045$), respectively. These results highlight the effectiveness of short-duration ischemic preconditioning in increasing bench press performance, and suggest that it may be readily used by strength and conditioning coaches during resistance training due to its brevity and lower perceived exertion.

KEYWORDS

velocity-based training, warm-up, performance enhancement, post-activation potentiation, blood flow restricted exercise

Introduction

Two of the most common pre-conditioning methods used by athletes and coaches are the post-activation performance enhancement (PAPE) and ischemic pre-conditioning (IPC) (Kilduff et al., 2013; Blazevich and Babault, 2019; Krzysztofik et al., 2020, 2021; Wilk et al., 2021). PAPE has been defined as an acute enhancement of muscle performance following pre-conditioning using a series of maximal or submaximal muscle actions (Tillin and Bishop, 2009; Tsoukos et al., 2016). These muscle actions usually involve resistance or plyometric exercises, and have been shown to acutely increase muscular strength and power (Conrado de Freitas et al., 2021; Tsolakis et al., 2011), movement velocity (Tsoukos et al., 2021a), rate of force development (Arabatzi et al., 2014) and total work of training (Alves et al., 2019). The optimal recovery time between the pre-conditioning exercises and subsequent muscular performance varies from a few seconds (French et al., 2003) to 20 min (Gilbert and Lees, 2005) and depends on the balance between PAPE and fatigue (Rassier and Macintosh, 2000). Previous research has shown that the PAPE effect is greater when using heavy compared with light loads (Rahimi, 2007; Bogdanis et al., 2014; Tsoukos et al., 2019; Tsoukos et al., 2021a; Krzysztofik et al., 2021). However, fatigue is also enhanced when resistance is high (Tsoukos et al., 2021b), and thus a longer recovery time (4–20 min) may be necessary between the pre-conditioning exercise with heavy loads and subsequent performance (Gilbert and Lees, 2005; Tsoukos et al., 2019; Tsoukos et al., 2021a; Krzysztofik et al., 2021). Moreover, improving explosive performance, PAPE has been shown to increase the total number of repetitions, total work, and total time under tension (TUT) during resistance exercise protocols performed to exhaustion (Alves et al., 2019; Krzysztofik et al., 2020). However, limited information exists regarding the effects of PAPE protocols on barbell velocity and total volume during repeated sets performed with maximum intended velocity for a set duration (10–30 s), mimicking high-intensity functional training (HIFT) with free weights which is a popular training modality in gym settings (Feito et al., 2018; Kapsis et al., 2022).

Ischemic preconditioning (IPC) is another pre-conditioning technique which consists of one extended (e.g., several repeated periods or "cycles" (usually 3-4 x 5 min) of ischemia, followed by equal duration reperfusion periods (Sharma et al., 2015). A series of studies found that IPC may increase performance in different exercise modalities where the oxidative or the glycolytic energy systems dominate (Incognito et al., 2016; Salvador et al., 2016). IPC results in enhanced VO_2 kinetics (Walsh et al., 2002), muscle oxygenation (Kido et al., 2015), power output (Kraus et al., 2015) applied force (Paradis-Deschênes et al., 2016), as well as higher training load (Carvalho and Barroso, 2019). These benefits seem to be observed as a result of greater metabolic efficiency (Murry et al., 1990; Andreas et al., 2011), increased blood flow (Cunniffe et al., 2017) and higher neural activation (de Oliveira Cruz et al., 2017). Few studies have examined the effect of IPC during resistance exercise on barbell velocity, total number of repetitions performed and total volume during resistance exercise, and found improvements (Carvalho and Barroso, 2019; Guilherme Da Silva Telles et al., 2020; da Silva Novaes et al., 2021; Wilk et al., 2021). However, in all these studies the authors used either 4 cycles of 5 min of occlusion at cuff pressure of 220 Hg, alternated by equal periods of reperfusion prior to exercise (Carvalho and Barroso, 2019; Guilherme Da Silva Telles et al., 2020; da Silva Novaes et al., 2021), or occlusion applied during the recovery between sets of resistance exercise with very short reperfusion periods (Wilk et al., 2021). From a practical viewpoint, these approaches require a long period of pre-conditioning before the execution of the exercise sets, or may cause discomfort and performance drop if IPC is used during exercise (Paixão et al., 2014; Cocking et al., 2018). To our knowledge, no study has examined IPC of very brief duration on subsequent performance during resistance training, and it would be of great practical interest if only one cycle of IPC is adequate to cause performance enhancement. Therefore, we examined the effects of: a) a single 5-min period of IPC at full occlusion pressure [100% of full arterial occlusion pressure (AOP)], followed by 5 min of reperfusion, b) a high-resistance PAPE protocol (1 set of 3 repetitions at 90% of 1-RM) and c) the combination of IPC and PAPE protocols, on barbell velocity, training load (total number of repetitions) and rating of perceived exertion during four sets of the bench press exercise against a load of 60% of 1-RM.

Methods

Experimental design

A randomized and counterbalanced repeated measures latin square design was used. The participants completed two preliminary sessions, followed by three experimental and one control session, 1 week apart. The three experimental sessions involved short-duration IPC, PAPE, and a combined IPC + PAPE intervention, while during the control condition the participants rested for 10.5 min (Figure 1). After each intervention, subjects performed 4 sets of 12 s duration each, of bench presses executed as fast as possible against a load of 60% of 1-RM on a Smith machine. Each set was followed by 2 min of passive recovery. The 60% of 1-RM load was chosen because it has been shown to combine the characteristics of the high average surface electromyographic (sEMG) activity of heavier loads, and the high total integrated sEMG observed at lighter loads, when sets are executed as fast as possible until exhaustion (Tsoukos et al., 2021b). During the first preliminary visit, anthropometric data were obtained and the maximum dynamic bench press strength (1-RM) was measured. In the second preliminary visit, the individual full arterial occlusion

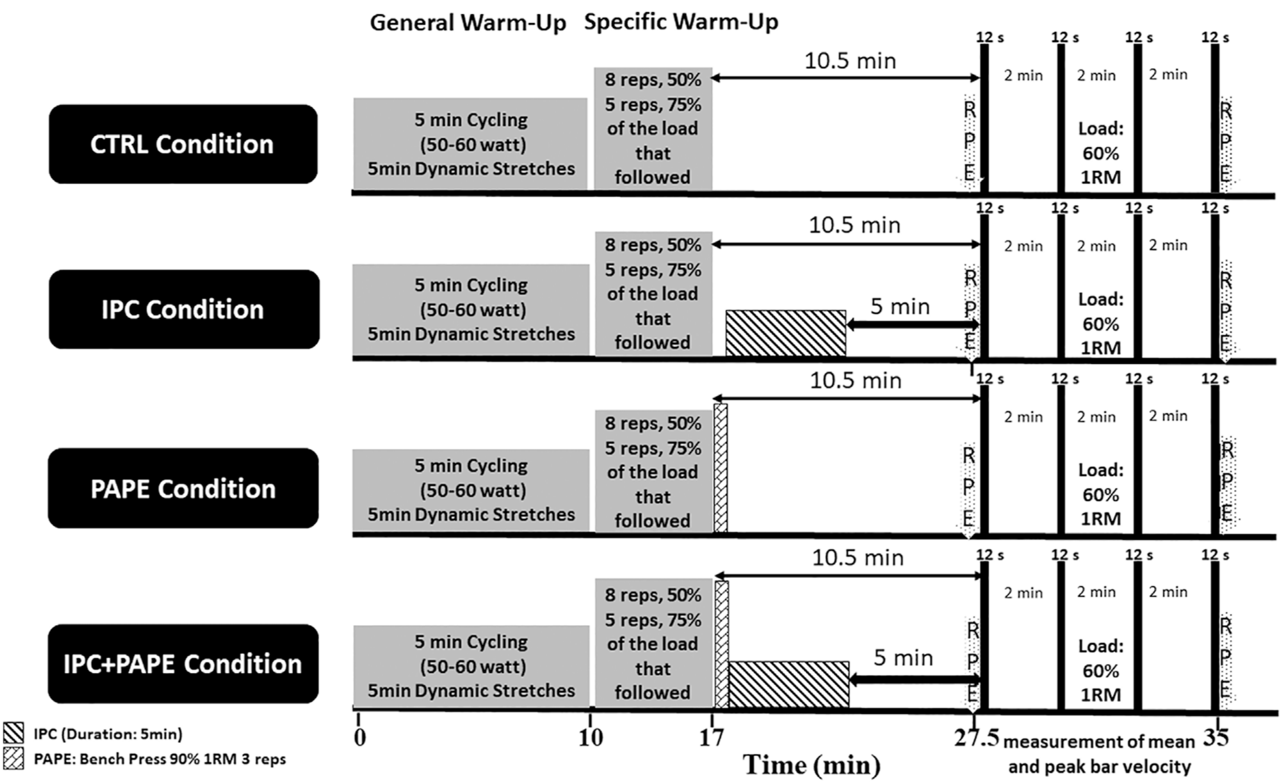

FIGURE 1
Schematic representation of the experimental design.

pressure (AOP) was determined, and the participants were familiarized with executing the bench press exercise as fast as possible from the first repetition. The dependent variables were: the average mean barbell velocities of all the repetitions in each set, the average peak barbell velocities of all the repetitions in each set, the total number of repetitions, and the rating of perceived exertion (RPE).

Subjects

Twelve healthy men participated in the study after completing an informed consent form (age: 25.8 ± 6.0 years, weight: 79.7 ± 8.9 kg, height: 1.82 ± 0.04 m, bench press 1-RM: 95.8 ± 13.3 or 1.21 ± 0.17 kg kg^{-1} body mass). The following inclusion criteria were used to select participants: a) they were healthy and physically active for at least 6 months before the study, b) their bench press 1 RM exceeded their body weight. Exclusion criteria were: a) any musculoskeletal injuries of the upper body for at least 6 months prior to the study, b) any blood or intraocular pressure problems.

The participants were instructed to maintain their habitual dietary routine over the course of the study and to abstain from the use of any supplements or stimulants during the experiment. Before providing their written consent, they were informed about the benefits and the risks of the study, and also about their right to withdraw from the study at any time without providing any explanation. The protocol of the study was approved by the Bioethics Committee of the School of Physical Education and Sport Science of Athens, Greece (1279/14-4-2021), and the experimental procedures were in accordance with the Declaration of Helsinki, 1983.

Procedures

Familiarization session and the 1 RM strength test

Before the main experiment, the participants performed two preliminary sessions. In the first of the two preliminary sessions, anthropometric data were collected, and the 1-RM bench-press strength was measured on a Smith machine. The subjects warmed-up on a cycle ergometer for 5 min at (50–60 W) followed by 5 min upper body dynamic stretching for chest and arms (Tsoukos et al., 2019; Tsoukos et al., 2021a). After the completion of the general warm-up, the participants were instructed to follow the procedure outlined by the National Strength and Conditioning Association (Gregory Haff and Travis Triplett, 2016). The feet were placed flat on the floor with a knee angle of approximately 90 and the head, shoulders and hips were supported by the bench. Assistance was provided throughout the test by two experienced spotters, who were qualified strength coaches. The participants were instructed to grasp the bar with a narrow width at 100% of bi-acromial distance (Barnett et al., 1995). The distance between hands was measured and kept the same for all sessions. During the procedure verbal encouragement was given to all participants. The ICC for the 1-RM measurement in our laboratory is 0.92 (Tsoukos et al., 2021a). Twenty minutes after the completion of the 1-RM test, subjects were familiarized with the occlusion cuffs, which included a manometer (Fit Cuffs Arms, Odder, Denmark, cuff width: 7.5 cm). The cuffs were worn near the axillary's fossa of both arms, while subjects lay on the bench. Cuffs were inflated to 140 mmHg and this pressure was maintained for 3 min.

In the second preliminary session, the participants wore the occlusion cuffs in close proximity to the axillary's fossa of both arms, lay on the bench for 10 min, and the individual cuff pressure at 100% of full arterial occlusion (AOP: 146.7 ± 15.0 mmHg) was determined using a pulse oximeter (Contec Holter ABPM50, Contec Medical Systems, Qinhuangdao, Hebei Province, China). This measurement was conducted twice on each arm (total of four times) with a 10 min interval. Ten minutes after the determination of the individual AOP, the participants were familiarized with the ischemic pre-conditioning and the PAPE protocol. Immediately after the completion of the standardized general and specific warm-up (see Figure 1), subjects performed one set of bench press, comprising three repetitions at 90% of 1-RM on a Smith machine. Thirty seconds after the end of warm-up, the cuffs were inflated at 100% AOP for 5 min, followed by a 5-min period of reperfusion. Afterwards, subjects performed two sets of 12 s duration each, at 60% of 1 RM with 2 min rest intervals between them with the intention to move as fast as possible from the first to the last repetition. The intention of movement was required to be maximal for both the eccentric and the concentric phase of the movement for each repetition (Wilk et al., 2020a; Wilk et al., 2020b).

Measurements

Movement velocity was recorded with a linear position transducer (Tendo Power analyzer System v. 314, TENDO Sports Machines, Trencin, Slovak Republic). The string of the linear position transducer was positioned vertically to the barbell of the Smith machine. The position of the transducer was set up by hanging a small weight from the bar to the floor before the start of any condition. This procedure was done to secure that the vertical velocity of the barbell was measured correctly. The validity and reliability of this system has been presented elsewhere (Garnacho-Castaño et al., 2014). The average of mean barbell velocities (AMV) was determined as the mean value of all mean velocities of the repetitions in each set. The average of peak barbell velocities (APV) ($m \cdot s^{-1}$) was determined as the mean value of all peak velocities of all repetitions in every set. The ICCs for these measurements in our laboratory are as follows: MV [0.983 (95% CI: 0.962–0.995)] and PV [0.971 (95% CI: 0.932–0.992)] (Tsoukos et al., 2019; Tsoukos et al., 2021a). Rating of Perceived Exertion (RPE) was obtained using the Borg RPE Scale (ranging from 0 to 10) and ratings were collected before and immediately after performance of the 4 × 12 s bench press sets in every condition (Figure 1) (Lagally and Amorose, 2007).

Experimental conditions

During all experimental conditions the participants completed a general warm-up which included 5-min of low intensity cycling (50–60 W), followed by 5-min of upper body dynamic stretching for chest and arms (Tsoukos et al., 2019; Tsoukos et al., 2021a). Subsequently, the participants performed a specific warm-up which included: a) a set of 8 repetitions at 50% of the load that followed (either 60% 1-RM in IPC condition or 90% 1-RM in the PAPE and combined IPC + PAPE conditions) and b) a set of five repetitions at 75% of the load that followed, with 3 min rest intervals between the sets. Warm-up sets with the submaximal loads were performed with a controlled movement velocity in order to limit the development of PAPE and neuromuscular fatigue (Rahimi, 2007; García et al., 2022).

After the general and the specific warm-up, the participants performed four experimental conditions in randomized and counterbalanced order:

1) short-duration IPC (5 min): In this condition, 100%AOP was applied for 5 min on both arms, starting 30 s after the end of the specific warm-up (Figure 1). After 5 min of occlusion, the cuffs were deflated, and the participants rested for 5 min (reperfusion period) before they executed the four bench press sets
2) PAPE protocol: In this condition the participants performed a set of 3 repetitions at 90% of 1-RM, within 30 s after the end of the specific warm-up. Then, the participants rested for 5 min before executing the four bench press sets,
3) combination of PAPE and IPC: In this condition, participants performed a bench press set of 3 repetitions at 90% of 1-RM on a Smith machine, within 30 s after the end of the specific warm-up, followed by 5 min of IPC at 100%AOP. Then, the participants rested for 5 min before executing the four bench press performance sets,
4) control condition (CTRL): During the CTRL condition, the participants performed the general and specific warm-up, and

then rested for 10.5 min before executing the four bench press performance sets (Figure 1).

Each of the four bench press performance sets lasted 12 s, and the load was 60% of 1-RM, while a 2 min rest was applied between sets. All bench press sets were executed on a Smith machine with a pre-determined grip width. During each set subjects were instructed to move the barbell as fast as possible during both the concentric and eccentric phases. The time was measured by an electronic countdown timer and when the 12th second was reached the participants were informed to stop the movement by a loud audio signal generated by the timer. A spotter assisted the subject to stop the movement by grasping the barbell on the timer signal. If a repetition was stopped during the eccentric phase or at the start of the concentric phase, it was not considered for data analysis.

Statistical analysis

All results are presented as mean ± standard deviations (SD). Statistical analyses were conducted using the SPSS v. 23 (IBM-SPSS Inc. Armonk, New York, United States). Differences between the four conditions were examined using two-way repeated measures ANOVA (4 conditions x 4 sets). Statistical significance was set at $p < 0.05$. A Tukey's post hoc test was performed when a significant main effect or interaction was observed. Partial eta square (η^2) value was used to evaluate the effect size for the interactions and main effects. Partial eta squared values were classified as large (> 0.137), moderate (0.06–0.137) and small (0.01–0.059). For pairwise comparisons, the effect size (ES) was determined by Hedges' g (small, < 0.3; medium, 0.3–0.8; and large, > 0.8).

Results

Average of mean barbell velocities (AMV) in each set

The time-course of changes in peak and mean bar velocity per repetition and set in the four experimental conditions is presented in Figure 2 for visual inspection. Regarding the comparisons of AMV, the 2-way ANOVA revealed a significant interaction ($p = 0.009$, $\eta^2 = 0.19$). Tukey post hoc tests showed that AMV significantly decreased from set 1 to set 4 (set 1 > set 2 > set 3 > set 4; $p < 0.01$) (Table 1) in all four conditions. Post-hoc tests showed that AMV in set 1 was higher in IPC compared with CTRL (+9.0 ± 4.0%) and with PAPE (+4.4 ± 8.9%) ($p < 0.01$; g = 0.77 and $p < 0.05$, g = 0.32, respectively). Also, AMV in set 1 was higher in PAPE + IPC (+5.8 ± 10.0%) compared with CTRL ($p < 0.01$ and g = 0.39). In sets 2 and 3, AMV was higher in IPC (set 2: by 7.0 ± 5.9%, $p < 0.01$ and set 3: by 6.6 ± 5.5%, $p < 0.05$; g = 0.68 and g = 0.64) and PAPE (set 2: by 6.7 ± 10.8%, set 3: by 8.9 ± 12.6%, $p < 0.01$; g = 0.51 and g = 0.74) compared with CTRL. During the fourth set, only PAPE was significantly higher compared with the CTRL (set 4: by 7.6 ± 9.7%, $p < 0.05$, g = 0.64).

Average of peak barbell velocities (APV) in each set

No significant interaction was observed for APV ($p = 0.98$, $\eta^2 = 0.02$). However, the two-way ANOVA showed a significant main effect for condition ($p = 0.02$, $\eta^2 = 0.25$) and set ($p < 0.001$, $\eta^2 = 0.91$). APV significantly decreased from set to set ($p < 0.001$, g = 0.91–2.77). Tukey's post hoc tests revealed that APV was higher during IPC (+7.8 ± 7.7%, $p = 0.044$, g = 0.40) and PAPE (+8.5 ± 9.6%, $p = 0.026$, g = 0.40) compared with CTRL irrespective of the set (Figure 3).

Number of repetitions

No significant interaction was observed for the number of repetitions in each set ($p = 0.10$, $\eta^2 = 0.13$). However, the two-way ANOVA showed a significant main effect for condition ($p = 0.008$, $\eta^2 = 0.30$) and set ($p < 0.001$, $\eta^2 = 0.86$). Tukey's *post hoc* tests revealed that the total number of repetitions was higher during IPC (+7.6 ± 9.5%, $p = 0.019$, g = 0.42), PAPE (+7.4 ± 11.3%, $p = 0.036$, g = 0.41) and PAPE + IPC (+8.0 ± 11.5%, $p = 0.016$, g = 0.43) compared with CTRL (Figure 4). There was also a time effect, showing that number of repetitions significantly decreased from set to set ($p < 0.01$, g = from 0.59 to 2.33).

Rating of perceived exertion (RPE)

The 2-way ANOVA revealed a significant interaction for RPE ($p = 0.016$, $\eta^2 = 0.27$). Tukey *post hoc* tests showed that RPE after the completion of the four bench press performance sets was lower in IPC compared with CTRL ($p < 0.001$; g = 1.19) and with PAPE conditions ($p = 0.045$; g = 0.69, Figure 5). There was also a trend for PAPE + IPC to be higher than IPC ($p = 0.076$; g = 0.78).

Discussion

The aim of the present study was to examine the acute effects of short-duration IPC (1 cycle of 5 min at 100% of full arterial occlusion pressure (AOP) and a very low-volume, high-resistance PAPE protocol (1 set of 3 repetitions at 90% of 1-RM in the bench press exercise), as well as their combination (PAPE + IPC) on performance during repeated sets of the bench press exercise. The main finding of the present study was that

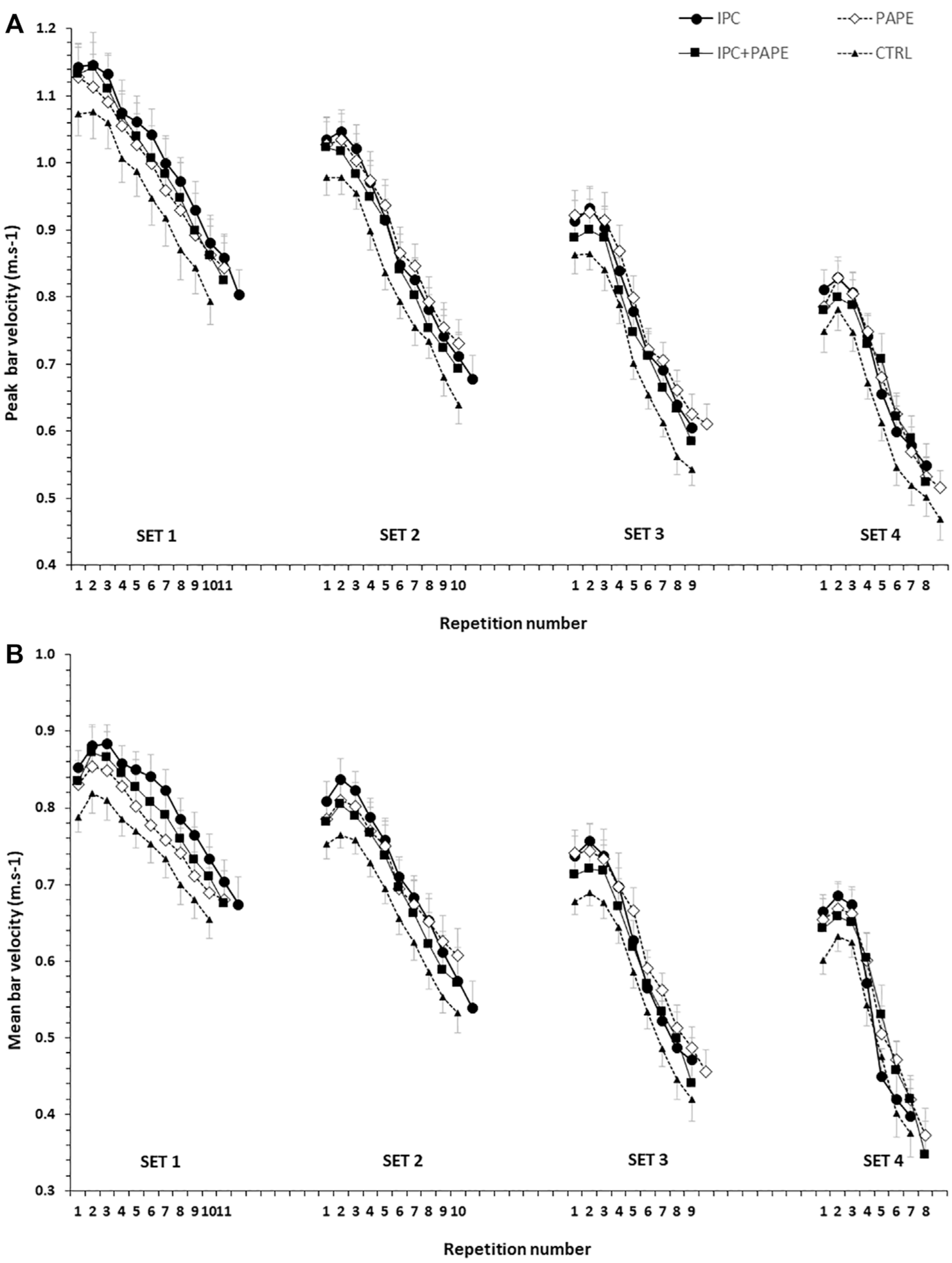

FIGURE 2
Peak (upper panel) and mean bar velocities (lower panel) per repetition in the four sets (set 1 to set 4) of each experimental condition (CTRL: control, IPC: ischemic pre-conditioning, PAPE: post-activation performance enhancement, PAPE + IPC: combination of PAPE and IPC conditions).

short-duration IPC, PAPE and their combination resulted in similar overall improvements in bench press performance compared with CTRL condition. However mean barbell velocity was improved in first set only in IPC. Interestingly, the improvement in performance after IPC was accompanied by almost 2 a. u. Lower RPE than CTRL (IPC: 5.2 ± 0.5 vs. CTRL: 6.9 ± 0.5, $p < 0.001$; g = 1.19), indicating a beneficial effect of IPC on performance vs perceived effort relationship. The PAPE protocol was as effective as IPC only in sets 2-4, while AMV in set 1 was higher in IPC. Also, RPE in PAPE was not different from CTRL. The combination of PAPE + IPC resulted in improved AMV only in set 1, while performance in subsequent tests did not differ from CTRL, possibly due to prevalence of fatigue over performance enhancement.

To our knowledge this is the first study examining the effects of short-duration IPC on the volume of training and

TABLE 1 The average mean barbell velocities (AMV) in each experimental condition. CTRL: control; IPC: ischemic pre-conditioning; PAPE: post-activation performance enhancement; PAPE + IPC: post-activation performance enhancement and ischemic pre-conditioning.

	AMV ($m \cdot s^{-1}$)			
Condition	SET 1	SET 2	SET 3	SET 4
CTRL	0.74 ± 0.07	0.66 ± 0.06*	0.57 ± 0.06*	0.49 ± 0.06*
IPC	0.80 ± 0.08#‡	0.71 ± 0.08*#	0.61 ± 0.06*†	0.52 ± 0.07*
PAPE	0.77 ± 0.10	0.70 ± 0.09*#	0.62 ± 0.07*#	0.53 ± 0.06*†
PAPE + IPC	0.78 ± 0.12#	0.68 ± 0.12*	0.59 ± 0.10*	0.52 ± 0.09*

*: $p<0.01$ from the previous set; # and †: $p < 0.01$ and $p < 0.05$ from CTRL; ‡: $p < 0.05$ from PAPE.

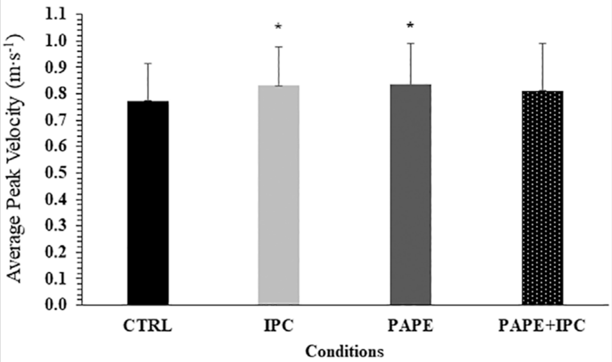

FIGURE 3
Average peak bar velocities (APV) in each experimental condition (CTRL: control, IPC: ischemic pre-conditioning, PAPE: post-activation performance enhancement, PAPE + IPC: combination of PAPE and IPC conditions). *: $p < 0.05$ from CTRL.

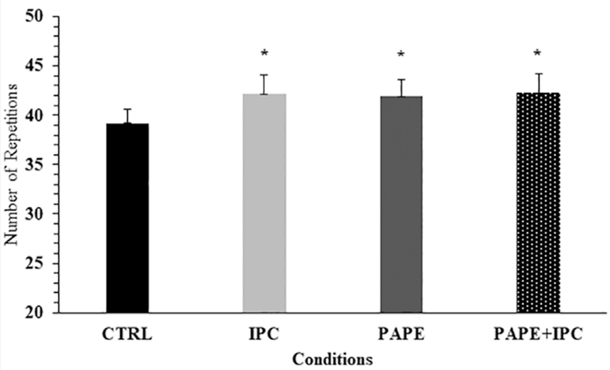

FIGURE 4
Total number of repetitions (all sets included) in each experimental condition (CTRL: control, IPC: ischemic pre-conditioning, PAPE: post-activation performance enhancement, PAPE + IPC: combination of PAPE and IPC conditions). *: $p < 0.05$ from CTRL.

performance of repeated bench press sets. The beneficial effects of such a short-duration IPC are of great practical interest, as they can be easily applied to training. Only a short period of time (10 min) is required to potentiate performance during repeated bouts of the bench press exercise, compared with the previous studies where a total of 30–40 min at much higher occlusion pressures (e.g., 220 mmHg) were required to induce beneficial effects on resistance exercise performance (Carvalho and Barroso, 2019; Guilherme Da Silva Telles et al., 2020; da Silva Novaes et al., 2021). Thus, it is evident that a single 5-min cycle of IPC is adequate to induce significant increases in mean barbell velocity (from 6.6 ± 5.5% to 9.0 ± 4.0%) and total number of repetitions (7.6 ± 9.5%), compared with the CTRL condition, and so practitioners may easily apply it in exercise training. So far, only a limited number of studies have examined short duration IPC, and this was on single effort explosive muscle performance (Beaven et al., 2012). For example, two short bouts of IPC (2 × 3 min) applied on the thighs, resulted in a (9.0 ± 9.1%) improvement in jump height (Beaven et al., 2012).

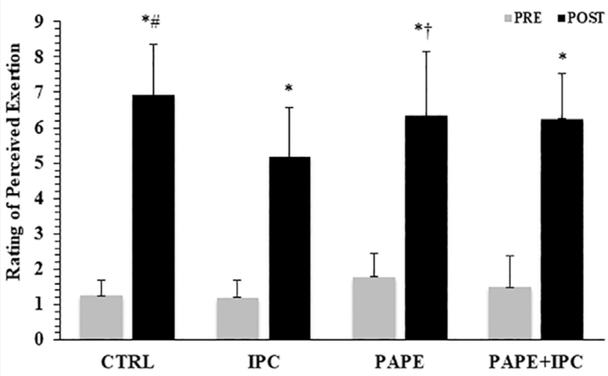

FIGURE 5
Rating of perceived exertion (RPE) before and after the execution of the four sets in the bench press exercise in each experimental condition (CTRL: control, IPC: ischemic pre-conditioning, PAPE: post-activation performance enhancement, PAPE + IPC: combination of PAPE and IPC conditions). *: $p < 0.05$ from PRE, # and †: $p < 0.01$ and $p < 0.05$ from IPC.

Research has shown conflicting results regarding the effects of IPC on subsequent performance. Some authors found no difference between the IPC protocol (220 mmHg of cuff pressure) and a sham condition (20 mmHg of cuff pressure) (Marocolo et al., 2016a; Marocolo et al., 2016b), while others reported acute increases in strength and power performance (Paradis-Deschênes et al., 2016; de Oliveira Cruz et al., 2019; Jarosz et al., 2021; Wilk et al., 2021). For example, Marocolo et al. (Marocolo et al., 2016a) evaluated the effects of IPC (4 × 5-min occlusion at 220 mmHg) and a sham condition on resistance exercise performance in the lower and upper limbs and found that both IPC or sham may enhance performance during resistance exercise with no difference between them. The authors concluded that the same number of repetitions performed by both groups (IPC or sham) were due to the higher psychological motivation and could not be attributed to physiological mechanisms. In contrast, several studies have shown a beneficial effect of IPC, compared with sham and control conditions. Paradis-Deschênes et al. (Paradis-Deschênes et al., 2016) found an increase in peak and average force after IPC (3×5-min IPC/5-min reperfusion cycles at 200 mm Hg) compared with a sham condition, while Wilk and colleagues (Wilk et al., 2021) showed that ischemia (80% of AOP) applied between five sets of bench press exercise at 60% 1-RM, enhanced peak velocity and peak power during the third, fourth and fifth set by 7.5%, 7.3%, 8.6% respectively, compared with the control condition (Wilk et al., 2021). These improvements may be attributed to acute increases in: 1) neuromuscular activation (overall sEMG amplitude), 2) the accumulated oxygen deficit, 3) the amplitude of blood lactate kinetics, 4) the total amount of oxygen consumed during recovery, 5) muscle deoxygenation kinetics, 6) oxygen uptake (VO2) peak (de Oliveira Cruz et al., 2017) 7) muscle oxygenation and 8) phosphocreatine (PCr) resynthesis (Andreas et al., 2011). Regarding the neuromuscular activation, de Oliveira Cruz et al. (de Oliveira Cruz et al., 2016, 2019) observed a parallel increase in performance and electromyographic activity after an intermittent bilateral cuff inflation [4 × (5 min of blood flow restriction + 5-min reperfusion)] (de Oliveira Cruz et al., 2016, 2019). Higher neural activation may be caused by an increase in concentration of metabolic byproducts, such as hypoxia-inducible factor 1a (HIF 1a), opioid peptides, endogenous cannabinoids and other factors which may cause a decrease in the activation of the group III and IV muscle afferent fibers (de Oliveira Cruz et al., 2017). Ischemia may also trigger an increase in ATP production by glycolytic and phosphagen paths (Janier et al., 1994; Mendez-Villanueva et al., 2012). The physiological basis of the increase in movement velocity may be explained by changes in the metabolic substrates and energy metabolism (Kraemer et al., 1987; Robergs et al., 1991). In the present study we observed a significant difference between the CTRL condition and IPC in AMV from the first until the third set. This greater maintenance of AMV during the IPC condition may be due to an increase in blood volume which is observed after the use of IPC (Cunniffe et al., 2017). It has also been shown that higher blood flow caused by higher concentration in adenosine and nitric oxide that leads to opening of K_{ATP} potassium channels which result in greater vessel diameter (Rosenberry and Nelson, 2020). The higher blood flow might cause greater oxygen supply to the muscle and thus a faster PCr resynthesis (Hogan et al., 1999). Faster PCr resynthesis is critical in exercise performance, particularly during repeated efforts of high intensity contractions with incomplete recovery (Bogdanis et al., 1996; Mendez-Villanueva et al., 2012).

Another fact that merits discussion regarding the results of the present study was that ischemic preconditioning was applied distally to the pectoralis major and anterior deltoid muscles, which are among the prime movers of the bench press exercise. The positive effect of such cuff placement has been considered "a paradox" and may be induced by a greater muscle activation of the muscles that are proximal to the pressure cuffs. (Yasuda et al., 2010; Hedt et al., 2022).

The higher total number of repetitions observed in our study is in line with previews studies which found a 12–17% increase following several-fold longer IPC (Paradis-Deschênes et al., 2016; Tanaka et al., 2016). This improvement may be due to increased muscle oxygenation and muscle blood volume (45,56), implying higher blood flow to the exercising muscle (Incognito et al., 2016), which may also lead to faster removal of metabolic byproducts and lower peripheral fatigue (Amann and Calbet, 2008). Furthermore, an increase in muscle blood flow and water content of the muscle has been proposed as one of the main physiological mechanisms of PAPE which has been shown to substantially enhance muscle force and shortening velocity (Blazevich and Babault, 2019). This might be the reason of the greater total volume of training. The higher total number of repetitions in PAPE and PAPE + IPC may be beneficial during systematic training when the aim is to maximize muscle hypertrophy (Schoenfeld et al., 2021), by inducing greater anabolic intracellular signaling (Terzis et al., 2010), higher protein synthesis rate (Burd et al., 2010) and enhanced satellite cell responses (Hanssen et al., 2013).

Alongside with the greater mean and peak barbell velocity, which was observed in IPC, there was also a lower RPE. These results are in line with a previous study during maximal constant-load cycling, which reported lower RPE after 4 × 5 min high pressure IPC (220 mmHg), and a parallel increase in peak VO_2, faster oxygen kinetics and higher vastus lateralis sEMG activity (de Oliveira Cruz et al., 2015). Furthermore, a recent study examining the origin of fatigue during an intermittent isometric protocol of the knee extensor muscles at 40% of MVC till exhaustion, found that the ergogenic effect of IPC has a neural origin which lowers neuromuscular fatigue (Pethick et al., 2021). Therefore, the improvement in performance and the lower RPE observed in the present study following IPC may be explained by the above-mentioned mechanisms.

The participants of the present study achieved higher mean (from 6.7 ± 10.8% to 8.9 ± 12.6%) and peak (8.5 ± 9.6% overall irrespective of the set) velocities in the bench press exercise after the PAPE protocol compared with the control condition. This finding confirms previous results and demonstrates the beneficial effects of very low volume, high-intensity conditioning exercise on subsequent performance during training and competition in different sports, such as track and field, gymnastics and team sports (Jemni et al., 2006; Takanashi et al., 2020; Gonçalves et al., 2021). Although the effects of PAPE in power and movement velocity are well known (Tsolakis et al., 2011; Tsoukos et al., 2021a), few studies have investigated the influence of this method on the total number of repetitions (Alves et al., 2019; Krzysztofik et al., 2020). Alves et al. (Alves et al., 2019) used a similar conditioning protocol with the present study (3 repetitions at 90% of 1-RM) and found an increase in the number of repetitions performed during three sets of the bench press against 75% 1-RM to failure with 1.5-min rest interval between sets (Alves et al., 2019). In contrast, Krzysztofik and colleagues (Krzysztofik et al., 2020) examined the effects of a PAPE protocol on resistance training volume during the bench press exercise and found slightly different results compared with our study. Specifically, the authors did not find a statistically significant difference between the PAPE protocol and the control condition for barbell velocity and the number of repetitions performed, although a greater total time under tension was found (Krzysztofik et al., 2020). The lack of an increase in barbell velocity and the number of repetitions in that study may be due to the larger volume of the PAPE protocol used, i.e., 3 sets of 3 repetitions at 85% of 1-RM (Krzysztofik et al., 2020), which was 3-fold higher than that used in the present study. Thus, the prevalence of fatigue may outweigh the beneficial effects of PAPE on total number of repetitions, lending further support to the use of very low volume, high-intensity protocols for optimal results.

This study is the first to examine the effect of a combined PAPE and IPC protocol (PAPE + IPC) on performance and volume of training. The combined protocol induced an increase in mean barbell velocity compared with CTRL only in the first of the four sets (Table 1), while peak barbell velocity was unaffected. In contrast when PAPE or IPC were applied, we observed higher barbell velocities compared with CTRL. A possible explanation may be that the combination of PAPE + IPC resulted in greater muscle fatigue, which counteracted the positive effects of each intervention on barbell velocity. However, the effects of PAPE + IPC on total number of repetitions were similar to the other interventions, and therefore cumulative and not peak performance was enhanced by this combination of pre-activation protocols. A limitation of the present study is that we did not use the inverse order of interventions in the combined condition. That is, to use first the IPC and then the PAPE set. This combination could have resulted in improvements in barbell velocity and should be examined in future studies, along with the physiological mechanisms involved.

In conclusion, short duration IPC (5 min), using a relatively moderate cuff pressure (i.e., 100% AOP; 146.7 ± 15.0 mmHg) enhanced performance during repeated sets of the bench press exercise, by inducing increases in mean barbell velocity (AMV: from 6.6 ± 5.5% to 9.0 ± 4.0%) and total number of repetitions (by 7.6 ± 9.5%) of the session. Notably, this improvement in performance after IPC was accompanied by lower perception of effort (i.e., lower RPE than CTRL). In addition, the PAPE protocol less effective than IPC in set 1, but equally effective in sets 2-4, while RPE was higher, and similar to CTRL. The combination of PAPE + IPC resulted in improved mean barbell velocity only in set 1, while performance in subsequent tests did not differ from CTRL, possibly due to prevalence of fatigue over performance enhancement. Compared to CTRL, all interventions resulted in improved total number of repetitions during the repeated sets of bench press exercise, executed as fast as possible against 60% 1-RM. Due to its brief duration and lower discomfort and perceived exertion, short-duration IPC may be used to enhance power output during training and competition requiring fast repeated muscle actions, as well as when athletes aim to maximize total training volume during muscle hypertrophy protocols.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Bioethics Committee of the School of Physical Education and Sport Science of Athens, Greece (1279/14-4-2021). The patients/participants provided their written informed consent to participate in this study.

Author contributions

GB, AT, and AS conceptualized the study. GB supervised the study. AT and AS drafted the manuscript. AT, AS, GT, VP, and CK performed data collection. MK, MW, AZ, AS, and AT analyzed the data and performed the statistical analysis. GB, AT, GT, MK, and MW, authors revised the manuscript and approved its current form.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Alves, R. R., Viana, R. B., Silva, M. H., Guimarães, T. C., Vieira, C. A., Santos, D. D. A. T., et al. (2019). Postactivation potentiation improves performance in a resistance training session in trained men. *J. Strength Cond. Res.* 35, 3296–3299. doi:10.1519/jsc.0000000000003367

Amann, M., and Calbet, J. A. L. (2008). Convective oxygen transport and fatigue. *J. Appl. Physiol.* 104, 861–870. doi:10.1152/japplphysiol.01008.2007

Andreas, M., Schmid, A. I., Keilani, M., Doberer, D., Bartko, J., Crevenna, R., et al. (2011). Effect of ischemic preconditioning in skeletal muscle measured by functional magnetic resonance imaging and spectroscopy: A randomized crossover trial. *J. Cardiovasc. Magn. Reson.* 13, 32. doi:10.1186/1532-429X-13-32

Arabatzi, F., Patikas, D., Zafeiridis, A., Giavroudis, K., Kannas, T., Gourgoulis, V., et al. (2014). The post-activation potentiation effect on squat jump performance: Age and sex effect. *Pediatr. Exerc. Sci.* 26, 187–194. doi:10.1123/pes.2013-0052

Barnett, C., Kippers, V., and Turner, P. (1995). Effects of variations of the bench press exercise on the EMG activity of five shoulder muscles. *J. Strength Cond. Res.* 9, 222–227. doi:10.1519/00124278-199511000-00003

Beaven, C. M., Cook, C. J., Kilduff, L., Drawer, S., and Gill, N. (2012). Intermittent lower-limb occlusion enhances recovery after strenuous exercise. *Appl. Physiol. Nutr. Metab.* 37, 1132–1139. doi:10.1139/H2012-101

Blazevich, A. J., and Babault, N. (2019). Post-activation potentiation versus post-activation performance enhancement in humans: Historical perspective, underlying mechanisms, and current issues. *Front. Physiol.* 10, 1359. doi:10.3389/FPHYS.2019.01359

Bogdanis, G. C., Nevill, M. E., Boobis, L. H., and Lakomy, H. K. (1996). Contribution of phosphocreatine and aerobic metabolism to energy supply during repeated sprint exercise. *J. Appl. Physiol.* 80, 876–884. doi:10.1152/jappl.1996.80.3.876

Bogdanis, G. C., Tsoukos, A., Veligekas, P., Tsolakis, C., and Terzis, G. (2014). Effects of muscle action type with equal impulse of conditioning activity on postactivation potentiation. *J. Strength Cond. Res.* 28, 2521–2528. doi:10.1519/JSC.0000000000000444

Burd, N. A., Holwerda, A. M., Selby, K. C., West, D. W. D., Staples, A. W., Cain, N. E., et al. (2010). Resistance exercise volume affects myofibrillar protein synthesis and anabolic signalling molecule phosphorylation in young men. *J. Physiol.* 588, 3119–3130. doi:10.1113/jphysiol.2010.192856

Carvalho, L., and Barroso, R. (2019). Ischemic preconditioning improves strength endurance performance. *J. strength Cond. Res.* 33, 3332–3337. doi:10.1519/JSC.0000000000002846

Cocking, S., Wilson, M. G., Nichols, D., Cable, N. T., Green, D. J., Thijssen, D. H. J., et al. (2018). Is there an optimal ischemic-preconditioning dose to improve cycling performance? *Int. J. Sports Physiol. Perform.* 13, 274–282. doi:10.1123/ijspp.2017-0114

Conrado de Freitas, M., Rossi, F. E., Colognesi, L. A., de Oliveira, J. V. N. S., Zanchi, N. E., Lira, F. S., et al. (2021). Postactivation potentiation improves acute resistance exercise performance and muscular force in trained men. *J. strength Cond. Res.* 35, 1357–1363. doi:10.1519/JSC.0000000000002897

Cunniffe, B., Sharma, V., Cardinale, M., and Yellon, D. (2017). Characterization of muscle oxygenation response to vascular occlusion: Implications for remote ischaemic preconditioning and physical performance. *Clin. Physiol. Funct. Imaging* 37, 785–793. doi:10.1111/cpf.12353

da Silva Novaes, J., da Silva Telles, L. G., Monteiro, E. R., da Silva Araujo, G., Vingren, J. L., Silva Panza, P., et al. (2021). Ischemic preconditioning improves resistance training session performance. *J. strength Cond. Res.* 35, 2993–2998. doi:10.1519/JSC.0000000000003532

de Oliveira Cruz, R. S., de Aguiar, R. A., Turnes, T., Pereira, K. L., and Caputo, F. (2015). Effects of ischemic preconditioning on maximal constant-load cycling performance. *J. Appl. Physiol.* 119, 961–967. doi:10.1152/japplphysiol.00498.2015

de Oliveira Cruz, R. S., de Aguiar, R. A., Turnes, T., Salvador, A. F., and Caputo, F. (2016). Effects of ischemic preconditioning on short-duration cycling performance. *Appl. Physiol. Nutr. Metab.* 41, 825–831. doi:10.1139/apnm-2015-0646

de Oliveira Cruz, R. S., Pereira, K. L., de Aguiar, R. A., Turnes, T., Denadai, B. S., and Caputo, F. (2019). Effects of ischemic conditioning on maximal voluntary plantar flexion contractions. *J. Electromyogr. Kinesiol.* 48, 37–43. doi:10.1016/j.jelekin.2019.06.004

de Oliveira Cruz, R. S., Pereira, K. L., Lisbôa, F. D., and Caputo, F. (2017). Could small-diameter muscle afferents be responsible for the ergogenic effect of limb ischemic preconditioning? *J. Appl. Physiol.* 122, 718–720. doi:10.1152/japplphysiol.00662.2016

Feito, Y., Heinrich, K., Butcher, S., and Poston, W. (2018). High-intensity functional training (HIFT): Definition and research implications for improved fitness. *Sports* 6, 76. doi:10.3390/sports6030076

French, D. N., Kraemer, W. J., and Cooke, C. B. (2003). Changes in dynamic exercise performance following a sequence of preconditioning isometric muscle actions. *J. Strength Cond. Res.* 17, 678–685. doi:10.1519/1533-4287(2003)017<0678:cidepf>2.0.co;2

García, J. M. Y., Mora-Custodio, R., Ribas-Serna, J., González-Badillo, J. J., and Rodríguez-Rosell, D. (2022). Movement velocity as a determinant of actual intensity in resistance exercise. *Int. J. Sports Med.* 43, 1033–1042. doi:10.1055/a-1834-6693

Garnacho-Castaño, M. V., López-Lastra, S., and Maté-Muñoz, J. L. (2014). Reliability and validity assessment of a linear position transducer. *J. Sport. Sci. Med.* 14, 128–136.

Gilbert, G., and Lees, A. (2005). Changes in the force development characteristics of muscle following repeated maximum force and power exercise. *Ergonomics* 48, 1576–1584. doi:10.1080/00140130500101163

Gonçalves, C. A., Lopes, T. J. D., Nunes, C., Marinho, D. A., and Neiva, H. P. (2021). Neuromuscular jumping performance and upper-body horizontal power of volleyball players. *J. Strength Cond. Res.* 35, 2236–2241. doi:10.1519/JSC.0000000000003139

Gregory Haff, G., and Travis Triplett, N. (2016). *Essentials of strength & conditioning*. Champaign, IL, United States: Human Kinetics Fourth Edition.

Guilherme Da Silva Telles, L., Cristiano Carelli, L., Dutra Bráz, I., Junqueira, C., Rios Monteiro, E., Machado Reis, V., et al. (2020). Effects of ischemic preconditioning as a warm-up on leg press and bench press performance. *J. Hum. Kinet.* 75, 267–277. doi:10.2478/HUKIN-2020-0055

Hanssen, K. E., Kvamme, N. H., Nilsen, T. S., Rønnestad, B., Ambjørnsen, I. K., Norheim, F., et al. (2013). The effect of strength training volume on satellite cells, myogenic regulatory factors, and growth factors. *Scand. J. Med. Sci. Sports* 23, 728–739. doi:10.1111/j.1600-0838.2012.01452.x

Hedt, C., McCulloch, P. C., Harris, J. D., and Lambert, B. S. (2022). Blood flow restriction enhances rehabilitation and return to sport: The paradox of proximal performance. *Arthrosc. Sports Med. Rehabil.* 4, e51–e63. doi:10.1016/J.ASMR.2021.09.024

Hogan, M. C., Kohin, S., Stary, C. M., and Hepple, R. T. (1999). Rapid force recovery in contracting skeletal muscle after brief ischemia is dependent on O2 availability. *J. Appl. Physiol.* 87, 2225–2229. doi:10.1152/jappl.1999.87.6.2225

Incognito, A. V., Burr, J. F., and Millar, P. J. (2016). The effects of ischemic preconditioning on human exercise performance. *Sports Med.* 46, 531–544. doi:10.1007/s40279-015-0433-5

Janier, M. F., Vanoverschelde, J. L. J., and Bergmann, S. R. (1994). Ischemic preconditioning stimulates anaerobic glycolysis in the isolated rabbit heart. *Am. J. Physiol.* 267, H1353–H1360. doi:10.1152/ajpheart.1994.267.4.h1353

Jarosz, J., Trybulski, R., Krzysztofik, M., Tsoukos, A., Filip-Stachnik, A., Zajac, A., et al. (2021). The effects of ischemia during rest intervals on bar velocity in the bench press exercise with different external loads. *Front. Physiol.* 12, 1289. doi:10.3389/fphys.2021.715096

Jemni, M., Sands, W. A., Friemel, F., Stone, M. H., and Cooke, C. B. (2006). Any effect of gymnastics training on upper-body and lower-body aerobic and power components in national and international male gymnasts? *J. Strength Cond. Res.* 20, 899–907. doi:10.1519/R-18525.1

Kapsis, D. P., Tsoukos, A., Psarraki, M. P., Douda, H. T., Smilios, I., and Bogdanis, G. C. (2022). Changes in body composition and strength after 12 Weeks of high-intensity functional training with two different loads in physically active men and women: A randomized controlled study. *Sports* 10, 7. doi:10.3390/sports10010007

Kido, K., Suga, T., Tanaka, D., Honjo, T., Homma, T., Fujita, S., et al. (2015). Ischemic preconditioning accelerates muscle deoxygenation dynamics and enhances exercise endurance during the work-to-work test. *Physiol. Rep.* 3, e12395. doi:10.14814/phy2.12395

Kilduff, L. P., Finn, C. V., Baker, J. S., Cook, C. J., and West, D. J. (2013). Preconditioning strategies to enhance physical performance on the day of competition. *Int. J. Sports Physiol. Perform.* 8, 677–681. doi:10.1123/ijspp.8.6.677

Kraemer, W. J., Noble, B. J., Clark, M. J., and Culver, B. W. (1987). Physiologic responses to heavy-resistance exercise with very short rest periods. *Int. J. Sports Med.* 8, 247–252. doi:10.1055/s-2008-1025663

Kraus, A. S., Pasha, E. P., Machin, D. R., Alkatan, M., Kloner, R. A., and Tanaka, H. (2015). Bilateral upper limb remote ischemic preconditioning improves anaerobic power. *Open Sport. Med. J.* 9, 1–6. doi:10.2174/1874387001509010001

Krzysztofik, M., Wilk, M., Filip, A., Zmijewski, P., Zajac, A., and Tufano, J. J. (2020). Can post-activation performance enhancement (PAPE) improve resistance training volume during the bench press exercise? *Int. J. Environ. Res. Public Health* 17, 2554. doi:10.3390/ijerph17072554

Krzysztofik, M., Wilk, M., Stastny, P., and Golas, A. (2021). Post-activation performance enhancement in the bench press throw: A systematic review and meta-analysis. *Front. Physiol.* 11, 598628. doi:10.3389/fphys.2020.598628

Lagally, K. M., and Amorose, A. J. (2007). The validity of using prior ratings of perceive exertion to regulate resistance exercise intensity. *Percept. Mot. Ski.* 104, 534–542. doi:10.2466/PMS.104.2.534-542

Marocolo, M., Marocolo, I. C., Da Mota, G. R., Simão, R., Maior, A. S., and Coriolano, H. J. A. (2016a). Beneficial effects of ischemic preconditioning in resistance exercise fade over time. *Int. J. Sports Med.* 37, 819–824. doi:10.1055/s-0042-109066

Marocolo, M., Willardson, J. M., Marocolo, I. C., Ribeiro Da Mota, G., Simão, R., and Maior, A. S. (2016b). Ischemic preconditioning and placebo intervention improves resistance exercise performance. *J. Strength Cond. Res.* 30, 1462–1469. doi:10.1519/JSC.0000000000001232

Mendez-Villanueva, A., Edge, J., Suriano, R., Hamer, P., and Bishop, D. (2012). The recovery of repeated-sprint exercise is associated with PCr resynthesis, while muscle pH and EMG amplitude remain depressed. *PLoS One* 7, e51977. doi:10.1371/journal.pone.0051977

Murry, C. E., Richard, V. J., Reimer, K. A., and Jennings, R. B. (1990). Ischemic preconditioning slows energy metabolism and delays ultrastructural damage during a sustained ischemic episode. *Circ. Res.* 66, 913–931. doi:10.1161/01.RES.66.4.913

Paixão, R. C., Da Mota, G. R., and Marocolo, M. (2014). Acute effect of ischemic preconditioning is detrimental to anaerobic performance in cyclists. *Int. J. Sports Med.* 35, 912–915. doi:10.1055/s-0034-1372628

Paradis-Deschênes, P., Joanisse, D. R., and Billaut, F. (2016). Ischemic preconditioning increases muscle perfusion, oxygen uptake, and force in strength-trained athletes. *Appl. Physiol. Nutr. Metab.* 41, 938–944. doi:10.1139/apnm-2015-0561

Pethick, J., Casselton, C., Winter, S. L., and Burnley, M. (2021). Ischemic preconditioning blunts loss of knee extensor torque complexity with fatigue. *Med. Sci. Sports Exerc.* 53, 306–315. doi:10.1249/MSS.0000000000002475

Rahimi, R. (2007). The acute effects of heavy versus light-load squats on sprint performance. *Phys. Educ. Sport* 5, 163–169.

Rassier, D. E., and Macintosh, B. R. (2000). Coexistence of potentiation and fatigue in skeletal muscle. *Braz. J. Med. Biol. Res.* 33, 499–508. doi:10.1590/s0100-879x2000000500003

Robergs, R. A., Pearson, D. R., Costill, D. L., Fink, W. J., Pascoe, D. D., Benedict, M. A., et al. (1991). Muscle glycogenolysis during differing intensities of weight-resistance exercise. *J. Appl. Physiol.* 70, 1700–1706. doi:10.1152/jappl.1991.70.4.1700

Rosenberry, R., and Nelson, M. D. (2020). Reactive hyperemia: A review of methods, mechanisms, and considerations. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 318, R605–R618. doi:10.1152/AJPREGU.00339.2019

Salvador, A. F., De Aguiar, R. A., Lisbôa, F. D., Pereira, K. L., De Cruz, R. S. O., and Caputo, F. (2016). Ischemic preconditioning and exercise performance: A systematic review and meta-analysis. *Int. J. Sports Physiol. Perform.* 11, 4–14. doi:10.1123/ijspp.2015-0204

Schoenfeld, B., Fisher, J., Grgic, J., Haun, C., Helms, E., Phillips, S., et al. (2021). Resistance training recommendations to maximize muscle hypertrophy in an athletic population: Position stand of the IUSCA. *Int'l. J. Strength &. Cond* 1. doi:10.47206/ijsc.v1i1.81

Sharma, V., Marsh, R., Cunniffe, B., Cardinale, M., Yellon, D. M., and Davidson, S. M. (2015). From protecting the heart to improving athletic performance – The benefits of local and remote ischaemic preconditioning. *Cardiovasc. Drugs Ther.* 29, 573–588. doi:10.1007/s10557-015-6621-6

Takanashi, Y., Kohmura, Y., and Aoki, K. (2020). Evaluation of explosive strength ability of the upper body for athletic throwers. *jhse.* 17. doi:10.14198/jhse.2022.171.19

Tanaka, D., Suga, T., Tanaka, T., Kido, K., Honjo, T., Fujita, S., et al. (2016). Ischemic preconditioning enhances muscle endurance during sustained isometric exercise. *Int. J. Sports Med.* 37, 614–618. doi:10.1055/s-0035-1565141

Terzis, G., Spengos, K., Mascher, H., Georgiadis, G., Manta, P., and Blomstrand, E. (2010). The degree of p70 S6k and S6 phosphorylation in human skeletal muscle in response to resistance exercise depends on the training volume. *Eur. J. Appl. Physiol.* 110, 835–843. doi:10.1007/s00421-010-1527-2

Tillin, N. A., and Bishop, D. (2009). Factors modulating post-activation potentiation and its effect on performance of subsequent explosive activities. *Sports Med.* 39, 147–166. doi:10.2165/00007256-200939020-00004

Tsolakis, C., Bogdanis, G. C., Nikolaou, A., and Zacharogiannis, E. (2011). Influence of type of muscle contraction and gender on postactivation potentiation of upper and lower limb explosive performance in elite fencers. *J. Sport. Sci. Med.* 10, 577–583.

Tsoukos, A., Bogdanis, G. C., Terzis, G., and Veligekas, P. (2016). Acute improvement of vertical jump performance after isometric squats depends on knee angle and vertical jumping ability. *J. Strength Cond. Res.* 30, 2250–2257. doi:10.1519/JSC.0000000000001328

Tsoukos, A., Brown, L. E. L. E., Veligekas, P., Terzis, G., and Bogdanis, G. C. G. C. (2019). Postactivation potentiation of bench press throw performance using velocity-based conditioning protocols with low and moderate loads. *J. Hum. Kinet.* 68, 81–98. doi:10.2478/hukin-2019-0058

Tsoukos, A., Brown, L. E., Terzis, G., Veligekas, P., and Bogdanis, G. C. (2021a). Potentiation of bench press throw performance using a heavy load and velocity-based repetition control. *J. strength Cond. Res.* 35, S72–S79. doi:10.1519/JSC.0000000000003633

Tsoukos, A., Brown, L. E., Terzis, G., Wilk, M., Zajac, A., and Bogdanis, G. C. (2021b). Changes in EMG and movement velocity during a set to failure against different loads in the bench press exercise. *Scand. J. Med. Sci. Sports* 31, 2071–2082. doi:10.1111/SMS.14027

Walsh, M. L., Takahashi, A., Endo, M., Miura, A., and Fukuba, Y. (2002). Effects of ischaemia on subsequent exercise-induced oxygen uptake kinetics in healthy adult humans. *Exp. Physiol.* 87, 227–235. doi:10.1113/eph8702262

Wilk, M., Gepfert, M., Krzysztofik, M., Mostowik, A., Filip, A., Hajduk, G., et al. (2020a). Impact of duration of eccentric movement in the one-repetition maximum test result in the bench press among women. *J. Sport. Sci. Med.*

Wilk, M., Golas, A., Zmijewski, P., Krzysztofik, M., Filip, A., Coso, J. D., et al. (2020b). The effects of the movement tempo on the one-repetition maximum bench press results. *J. Hum. Kinet.* 72, 151–159. doi:10.2478/hukin-2020-0001

Wilk, M., Krzysztofik, M., Jarosz, J., Krol, P., Leznicka, K., Zajac, A., et al. (2021). Impact of ischemic intra-conditioning on power output and bar velocity of the upper limbs. *Front. Physiol.* 12, 1–8. doi:10.3389/fphys.2021

Yasuda, T., Fujita, S., Ogasawara, R., Sato, Y., and Abe, T. (2010). Effects of low-intensity bench press training with restricted arm muscle blood flow on chest muscle hypertrophy: A pilot study. *Clin. Physiol. Funct. Imaging* 30, 338–343. doi:10.1111/j.1475-097X.2010.00949.x

frontiers | Frontiers in Physiology

TYPE Review
PUBLISHED 30 March 2023
DOI 10.3389/fphys.2023.1089065

Check for updates

OPEN ACCESS

EDITED BY
Adam Zajac,
University School of Physical Education in Wroclaw, Poland

REVIEWED BY
J. Derek Kingsley,
Kent State University, United States
Corbin Hedt,
Houston Methodist Hospital,
United States

*CORRESPONDENCE
Nicholas Rolnick,
nrolnick@gmail.com

SPECIALTY SECTION
This article was submitted to Exercise Physiology,
a section of the journal
Frontiers in Physiology

RECEIVED 03 November 2022
ACCEPTED 06 March 2023
PUBLISHED 30 March 2023

CITATION
Rolnick N, Kimbrell K and de Queiros V (2023), Beneath the cuff: Often overlooked and under-reported blood flow restriction device features and their potential impact on practice—A review of the current state of the research. *Front. Physiol.* 14:1089065.
doi: 10.3389/fphys.2023.1089065

Beneath the cuff: Often overlooked and under-reported blood flow restriction device features and their potential impact on practice—A review of the current state of the research

Nicholas Rolnick[1]*, Kyle Kimbrell[2] and Victor de Queiros[3]

[1]The Human Performance Mechanic, CUNY Lehman College, NY, United States, [2]Owens Recovery Science, San Antonio, TX, United States, [3]Graduate Program in Health Sciences, Federal University of Rio Grande do Norte (UFRN), NatalRN, Brazil

Training with blood flow restriction (BFR) has been shown to be a useful technique to improve muscle hypertrophy, muscle strength and a host of other physiological benefits in both healthy and clinical populations using low intensities [20%–30% 1-repetition maximum (1RM) or <50% maximum oxygen uptake (VO_{2max})]. However, as BFR training is gaining popularity in both practice and research, there is a lack of awareness for potentially important design characteristics and features associated with BFR cuff application that may impact the acute and longitudinal responses to training as well as the safety profile of BFR exercise. While cuff width and cuff material have been somewhat addressed in the literature, other cuff design and features have received less attention. This manuscript highlights additional cuff design and features and hypothesizes on their potential to impact the response and safety profile of BFR. Features including the presence of autoregulation during exercise, the type of bladder system used, the shape of the cuff, the set pressure *versus* the interface pressure, and the bladder length will be addressed as these variables have the potential to alter the responses to BFR training. As more devices enter the marketplace for consumer purchase, investigations specifically looking at their impact is warranted. We propose numerous avenues for future research to help shape the practice of BFR that may ultimately enhance efficacy and safety using a variety of BFR technologies.

KEYWORDS

safety, autoregulation, bladder, kaatsu, occlusion training, BFR training

1 Introduction

The interest and adoption of blood flow restriction (BFR) training in the rehabilitation and fitness settings has increased substantially in recent years (de Queiros et al., 2021; Mills et al., 2021; Cuffe et al., 2022). Fueled at least in part by its ability to generate musculoskeletal and cardiovascular performance benefits with reduced mechanical loads (Lixandrão et al., 2018; Formiga et al., 2020), this interest has also fueled an in-kind response from the device manufacturing market. As is true of all product markets, manufacturers have included a variety of different features to their respective BFR cuffs to appeal to the consumer. Apart from cuff width, little is known regarding most features that make one cuff different from the next. Device features that impact the delivery of pressure to the limb are of particular importance given pressure's impact on acute responses to the exercise technique (Hughes et al., 2018; Jacobs et al., 2023). These acute responses will have safety implications due to their impact on hemodynamics but may also have longitudinal influence given the associated perceptual responses (Rossow et al., 2012).

To the authors' knowledge, Loenneke et al. (Loenneke et al., 2012) was the first to suggest that applied BFR pressures be standardized relative to the cuff and the individual using arterial occlusion pressure (AOP). AOP is the minimum pressure needed to completely occlude arterial inflow and venous return to the limb (Patterson et al., 2019). The use of AOP has its roots in the surgical world where it has been suggested both safety and post-operative pain are affected; increased use in the BFR literature has been both encouraged by a group of experienced researchers and reported in recent reviews and trials (AORN Recommended Practices Committee, 2007; Morehouse et al., 2021; Murray et al., 2021). This approach inherently controls for variances in cuff widths (Mouser et al., 2018; Evin et al., 2021), limb circumferences and participant blood pressures (Loenneke et al., 2015). Left uncontrolled, other applied pressure schemes common in the BFR literature (e.g., 200 mmHg, 1.3x systolic blood pressure, etc.) may unfavorably impact acute responses to BFR exercise, reducing adherence while increasing the potential for exercise to be carried out under full occlusion (Chulvi-Medrano et al., 2023). Moreover, the use of personalized pressures prescribed as a %AOP may reduce the heterogeneity observed in the systematic reviews and meta-analyses (Lixandrão et al., 2018; Clarkson et al., 2019; Formiga et al., 2020; Grønfeldt et al., 2020), leading to more precise estimates on the magnitude of the effects of BFR exercise and a greater ability to generalize research findings to practice.

For example, one study compared the acute muscular and perceptual responses to a bout of four sets of biceps curl performed with either a 3 cm wide Kaatsu® (Kaatsu Master, Sato Sports Plaza, Tokyo Japan) elastic cuff inflated to an arbitrary 160 mmHg applied pressure or a 5 cm wide Hokanson (Hokanson, Bellevue, WA, United States) nylon cuff inflated to 40% AOP (Dankel et al., 2017). Despite similar cellular swelling, electromyographic amplitudes and post-exercise torque production, the nylon cuff condition reported greater number of repetitions performed during sets 2 and 3, lower rate of perceived exertion during set one and lower rate of perceived discomfort during all sets compared to the elastic cuff condition. The discrepancy between conditions in perceptual responses and repetitions to failure may be explained by the higher relative applied pressure of the elastic cuff (~65 ± 19% AOP) compared to the nylon cuff (40% AOP). Giving further support, when cuffs of different widths and materials are standardized to a %AOP, the physiologic and perceptual responses are largely equivocal (Loenneke et al., 2012; Loenneke et al., 2013; Buckner et al., 2017) indicating that much of the differences observed following arbitrary pressure application protocols are likely due to varied degrees of relative personalized pressures.

BFR cuff systems marketed to consumers may possess modifications in shape, bladder construction, pressure control, material qualities or the ability to adjust pressure in response to contracting muscle that likely affect the delivery of pressure to the limb and/or ability to determine a personalized pressure. However, many of these device features have little to no evidence the end user can reference to support prioritizing certain features over others. The purpose of this manuscript is to expound upon these cuff features, reviewing what evidence we possess and illustrating the importance of continued empirical investigations into these features so that practitioners can make informed decisions and device manufacturers can continue to innovate.

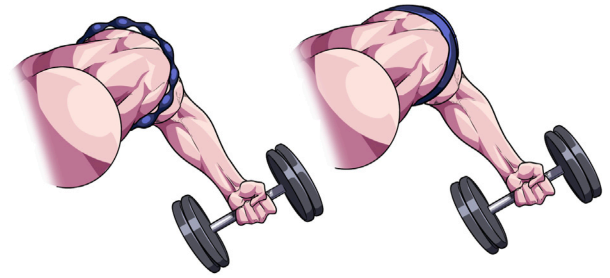

FIGURE 1
Multi-chambered versus single-chambered bladder cuff design. As opposed to traditional tourniquets whose function is to occlude arterial flow, multi-chambered bladders are composed of sequential bladders that when inflated, leave regions where minimal compression occurs. This cuff feature reduces the ability for the device to occlude arterial flow making it difficult to obtain a personalized pressure. The inability to occlude has been hypothesized to enhance safety during BFR exercise.

2 The impact of lesser-known cuff features on personalized pressure application and responses to BFR exercise

2.1 Multi-vs. Single-chambered bladder system

A tourniquet—by definition—is designed to occlude arterial flow (Noordin et al., 2009). This function forms the basis for the majority of BFR cuffs on the marketplace and in research because it allows a personalization of applied pressure with additional technology (e.g., doppler ultrasound, pulse pressor sensors, etc.) (Patterson et al., 2019). The bladder in a single-chambered system completely encircles the limb and inflates with air to apply pressure to the limb. Studies indicate that these types of bladder systems interact with cardiovascular and perceptual responses which may impact tolerability or the potential safety of the approach (Rossow et al., 2012), while a few studies note attenuated hypertrophy of the muscles underneath the cuff (Kacin and Strazar, 2011; Ellefsen et al., 2015). However, the attenuated hypertrophy underneath the cuff observed in some studies appears to not occur when pressure is personalized using %AOP (Laurentino et al., 2016).

Recently, commercially available devices have entered the marketplace that consist of numerous sequential bladders that according to the manufacturer (B-Strong™ Bands (B-Strong Training Systems™, Park City, UT, United States); B3 BFR

TABLE 1 Summary of available acute and chronic blood flow restriction training studies using a multi-chambered bladder system.

Reference	Sample (M/F)	Study design	Duration (Weekly frequency)	Intensity	Volume	Device (cuff width)	Pressure	Outcomes	Conclusions
Chronic studies									
Early et al. (2020)	31 healthy adults (11/20)	Randomized controlled trial (Between-subjects)	8 weeks (2-3)	LL-BFR: 30-50% 1-RM HL-RT: 60-100% 1-RM	LL-BFR: 3x10 reps HL-RT: 3x30 reps	B-Strong™ Bands (Arms: 5.5 cm/Legs: 7.0 cm)	Arms: 250 mmHg Legs: 350 mmHg	Artery diameter (FMD) Blood pressure Pain Muscle strength Muscle endurance	There was no significant difference between interventions for strength, endurance, or cardiovascular outcomes. Pain was lower in B-Strong™ bands after the last session.
Wang et al. (2022)	18 collegiate volleyball players (18/0)	Randomized controlled trial (Between-subjects)	8 weeks (3)	LL-BFR: 30% 1-RM HL-BFR: 70% 1-RM HL-RT: 70% 1-RM	LL-BFR: 4x10 reps HL-RT: 4x8 reps	B-Strong™ Bands (7.0 cm)	50% estimated AOP based on thigh circumference	Muscle strength Vertical jump	For muscle strength, there were significant differences between groups, favoring high-load interventions. Only HL-BFR promoted improved jumping performance.
Wooten et al. (2022)	21 older patients with abdominal cancer	Cohort	4 weeks (5-6)	NR	NR	B-Strong™ Bands (NR)	NR	Length of hospital stay Postoperative complications Readmission rate Mortality at 90 days post-surgery	BFR training plus sports nutrition supplementation was effective in reducing postoperative complications and length of hospital stay.
Acute studies									
Bordessa et al. (2021)	34 healthy adults (18/16)	Crossover randomized trial	—	LL-BFR: 30% 1-RM HL-RT: 80% 1-RM	LL-BFR: 1x30 + 3x15 HL-RT: 2x8 + 2x6	B-StrongTM Bands (5.0 cm) Delfi Personalized Tourniquet System (11.5 cm)	250-310 mm Hg 80% AOP	RPE Pain EMG	Resistance exercise with B-Strong™ bands induced less pronounced perceptual responses.
Callanan et al. (2022)	15 healthy adults (8/7)	Crossover randomized trial	—	NR for both free-flow and BFR conditions	3x3 minutes of VersaClimber	BStrong™ Bands (Arms: 5.0 cm/Legs: 7.5 cm)	NR	WBC Platelets Neutrophils Lymphocytes CD34+ Lactate Blood glucose RPE	RPE significantly greater in B-Strong™ bands above free-flow and both groups improved in WBC, platelets, lymphocytes, CD34+ and blood glucose and decreased peripheral neutrophils post-exercise. No significant differences between groups.

(Continued on following page)

10.3389/fphys.2023.1089065

TABLE 1 (*Continued*) **Summary of available acute and chronic blood flow restriction training studies using a multi-chambered bladder system.**

Reference	Sample (M/F)	Study design	Duration (Weekly frequency)	Intensity	Volume	Device (cuff width)	Pressure	Outcomes	Conclusions
Citherlet et al. (2022)	11 healthy adults (4/7)	Crossover randomized trial	—	—	—	B-Strong™ Bands (Arms: 5.0 cm/Legs: 7.5 cm)	200, 250, 300, 350, and 400 mmHg 0, 40 and 60% AOP	Blood flow	Both devices were able to reduce blood flow. For B-Strong™ bands, this response was achieved only with 350 and 400 mmHg. With Hokanson, the two pressures tested were able to reduce blood flow.
						E20 rapid cuff inflator, Hokanson (Arms: 5 cm; Legs: 10 cm)			
Machek et al. (2022)	18 recreationally active adults (18/0)	Crossover randomized trial	—	LL-BFR: 20% 1-RM	LL-BFR: 1x30 + 3x15 + 2 sets to failure	B3 Bands (9.525 cm)	80% AOP	RPE	Betaine supplementation 14 days prior did not provide additive benefit to outcomes in any loading condition. However, HL-RT increased lactate concentrations post-exercise over B3 Bands condition and B3 Bands condition had higher RPE and discomfort than HL-RT.
				HL-RT: 70% 1-RM	HL-RT: 4x10 + 2 sets to failure			Discomfort	
								Lactate	
								Serum GH, IGF-1, and HCY	
Stray-Gundersen et al. (2020)	15 healthy adults (9/6)	Crossover randomized trial	—	0.9 m/s (Walking)	5x2 minutes	B-Strong™ Bands (5 cm)	160 mmHg	Blood lactate	Walking with B-Strong™ bands induced less pronounced responses than Hokanson cuff.
						E20 rapid cuff inflator, Hokanson (18 cm)	300 mmHg	RPE	
								Blood pressure	
								Heart rate	
								Arterial stiffness	
Wilburn et al. (2021)	1 healthy adult (1/0)	Case report	—	LL-BFR: 30% 1-RM	LL-BFR: 1x30 + 3x15 + 2 sets to failure	B3 Bands (9.525 cm)	80% AOP	Muscle damage	Muscle damage appeared to be elevated in the HL-RT condition compared to B3 Bands condition. Sarcomere orientation and sarcomere length differed post-exercise, with wave-like orientation and intracellular abnormalities observed in B3 Bands condition.
				HL-RT: 70% 1-RM	HL-RT: 4x10 + 2 sets to failure			Sarcomere orientation	
								Sarcomere area	
								Sarcomere lengh	
								M-band width (all via electron micrograph)	
Wooten et al. (2020)	20 healthy adults (10/10	Crossover randomized trial	—	20 Yoga poses	LL-BFR: N/R	B-Strong™ Bands (6 cm arms; 6 cm legs)	300 mm Hg	RPE	No significant differences between conditions were observed except for a greater increase in lactate levels in the B-Strong™ cuff condition.
					LL: N/R			CAVI	
								Blood pressure	
								HR	
								Double product	
								FMD	
								Lactate	

1-RM, 1 repetition maximum; AOP, arterial occlusion pressure; BFR, blood flow restriction; EMG, electromyography; F, female; FMD, flow-mediated dilation, HL, high-load; LL, low-load; RPE, rate of perceived exertion; NR, not reported; WBC, white blood cell; GH, Growth hormone; IGF-1, Insulin-like growth factor 1; HCY, Homocysteine; CAVI, cardio-ankle vascular index; HR, heart rate

10.3389/fphys.2023.1089065

Bands (B3 Sciences, Frisco, TX, United States) are designed to reduce the potential for arterial occlusion and may result in a non-uniform circumferential pressure during exercise (Figure 1) (Early et al., 2020). As the multi-chambered bladder system is not designed to occlude, measurement of AOP is largely unfeasible in most individuals (Citherlet et al., 2022), so the manufacturer recommends pressures of 250 mmHg for the upper body and 350 mmHg for the lower body (Early et al., 2020) or a pressure based on individual factors using an app (Bordessa et al., 2021; Callanan et al., 2022). These cuff systems do appear to induce additional acute physiological stress over work-matched free flow exercise (Stray-Gundersen et al., 2020; Wooten et al., 2020), indicating that they have the potential to produce beneficial adaptations in a longitudinal training approach. However, as noted earlier, it is difficult to personalize pressure relative to the individual with this cuff design. Not personalizing the pressure may alter magnitude of the BFR stimulus and subsequent adaptation profile.

To the authors' knowledge, only three training studies utilizing a multi-chambered bladder system have been published and none of those studies were constructed in a manner that the results might elucidate the potential efficacy of the bladder type with respect to blood flow restricted exercise (Table 1). We will discuss each of these studies briefly to inform the reader of the state of the body of research and comment on their potential implications to our understanding of BFR exercise with multi-chambered bladder cuff systems.

Early et al. (Early et al., 2020) compared the muscular performance, pain and vascular function following 8 weeks of BFR exercise performed with the B-Strong™ cuff in 31 healthy participants (n = 20 females). They randomized participants to either a traditional resistance exercise (3 × 10 repetitions at 60% 1RM), BFR exercise (3 × 30 repetitions or to failure at 30% 1RM), or a non-exercise control group. Participants in the exercise groups performed 20 exercise sessions (2–3x/week) over the training period with seven upper and lower body exercises performed in each session. Load was progressed 10% every second week in both groups, but the BFR group was capped at 50% 1RM. Applied pressure in the BFR condition ranged between 250 mmHg in the upper body to 350 mmHg in the lower body and was kept on continuously and deflated only when changing from upper body to lower body exercise. Results showed that after 8 weeks, BFR was able to elicit similar vascular adaptations (evidenced by small [~0.5–1%] improvements in flow mediated dilatation; $p = 0.006$) and strength gains as traditional resistance exercise in all 1RM tests ($p > 0.05$) with less perceived muscle pain (evidenced by the visual analog scale) during the last session ($p < 0.05$). The conclusions support the use of a multi-chambered bladder system to induce comparable physiological changes as traditional resistance exercise. However, as the study design had some participants exercise to failure in the BFR group and did not include a low load control group or monitor volume load (reps x sets x load) between groups, it is difficult to surmise any potential impact of the bladder system on the outcomes of the study. This is relevant to the discussion of bladder type because low-load exercise with- and without BFR to muscular fatigue has been shown to improve muscle mass and strength to a similar degree (Fahs et al., 2015; Pignanelli et al., 2020). To date, no study has investigated longitudinal musculoskeletal outcomes and tracked volume load when exercise is performed to failure between low-loads with and without different BFR bladder designs and high loads (>70% 1-repetition maximum).

The second study analyzed the benefits of a 4-week multi-modal prehabilitation program combining exercise with B-Strong™ bands and a sports nutrition supplement in 21 patients with abdominal cancer (Wooten et al., 2022). While the results of the study indicated a beneficial effect on reducing complications ($p = 0.03$) and length of hospital stay (~5.5 fewer days, $p = 0.02$) as well as a 58% increase in step count 5-day post-op ($p = -.043$), the comparison group was retrospectively analyzed (n = 71) and underwent usual standard of care without BFR or sports supplementation. Therefore, the study design was unable to determine whether the positive impact of the trial was due to the inclusion of the B-Strong™ cuffs, the sports nutrition supplement, or a combination of both.

The third and most recently published study (Wang et al., 2022) investigated the impact of backsquat exercise performed with BFR on performance and muscular strength following 8 weeks of 3x/week training in male resistance-trained volleyball players (n = 18; ~20 years old). Three experimental groups (n = 6 per group) were randomly formed: low-load BFR performed with 30% 1RM, high load strength training with 70% 1RM, and high load strength training with BFR using 70% 1RM. BFR was applied to the bilateral thighs using B-Strong™ cuffs at 50% estimated arterial occlusion pressure and was on continuously in all BFR conditions (e.g., was inflated before the exercise and released after the exercise only). The low-load BFR group exercised with the commonly recommended BFR fixed repetition scheme of 30–15–15–15 with 60 s of interset rest whereas the high load strength training with- and without BFR was done for four sets of eight repetitions with 60 s of interset rest. After 8 weeks (24 sessions), max backsquat strength improved for all groups compared to baseline, but the high load strength training group with- (28.6%; $p = 0.00$) and without BFR (17.3%; $p = 0.003$) improved more ($p = 0.19$) than the low-load BFR group (9.9%; $p = 0.001$). Additional muscle strength results measuring peak isokinetic knee flexion and extension torques (at 60°/s) exhibited a similar trend. The high load strength training groups with- and without BFR improved peak knee extension (between 11.7%–17.7%, $p < 0.01$–$p < 0.05$) and flexion (10.9%–16.5%, $p < 0.01$–$p < 0.05$) torques to a greater degree ($p = 0.005$–0.048) over low-load BFR (between 5.1%–8.7% in both muscle groups) with no between-group differences ($p > 0.05$). Last, jump performance as assessed by a squat jump and three-footed takeoff test improved only in the high load strength training group with BFR ($p = 0.015$–$p = 0.02$) with significantly larger improvements than the low load BFR group ($p = 0.002$–0.039). The results of this study support that BFR using the B-Strong™ cuffs with high load strength training to maximize muscle strength and jump performance in trained athletes. Of note, BFR exercise has been recommended to be performed with low-intensity exercise (e.g., 20%–40% 1RM or <50% VO_2max) (Patterson et al., 2019), so the results of this study challenge current recommendations for practice. Further, as hemodynamics were not assessed in the study design, it is not known the impact of exercising with BFR using heavier loads and possible safety risk. This is particularly relevant given the current body of evidence showing that hemodynamic responses are predominantly driven by load lifted (MacDougall et al., 1985; Sale et al., 1994) and also by the application of BFR (Domingos and Polito, 2018).

This study highlights an important reason why this manuscript is being written. The authors attempted to apply BFR at 50% estimated AOP using an algorithm based on thigh circumference, but did not consider that the algorithm was created in reference to single-chambered bladder nylon and elastic BFR systems (Loenneke et al., 2012). Thus, it is likely not valid for use in a multi-chambered bladder system such as the B-Strong™ cuffs. Prior research has shown that the addition of blood flow restriction to high load strength exercise does not augment muscular activation (Dankel et al., 2018; Teixeira et al., 2018) or produce superior muscular hypertrophy or strength compared to the same exercise performed without BFR in single-chambered bladder systems (Laurentino et al., 2008). Of note, the longitudinal study (Laurentino et al., 2008) performed exercise at 100% AOP, had BFR applied intermittently (e.g., released during the rest period), and used loads between six- and 12-RM; so differences do exist between studies that limit strong comparisons. Nonetheless, the misapplication of the limb circumference algorithm in the current study could lead to misinterpretations regarding the effectiveness of BFR using heavier loading schemes with single-chamber bladder BFR cuff systems. Future studies should take care to apply algorithms designed for single-chambered bladder systems in investigations where single-chambered bladder systems are used to avoid potentially compromised study designs and conclusions.

Within the current BFR body of literature, there are three published studies that compared the acute responses of a multi-chambered bladder system to a single-bladder system (Stray-Gundersen et al., 2020; Bordessa et al., 2021; Citherlet et al., 2022) and four studies on multi-chambered bladder systems compared to a free-flow control (Wooten et al., 2020; Wilburn et al., 2021; Callanan et al., 2022; Machek et al., 2022) (Table 1). For completion's sake, we have displayed the four additional multi-chambered bladder investigations that compared responses to free-flow exercise to highlight the limited overall body of research in this area (Table 1).

All studies save two (Wilburn et al., 2021; Machek et al., 2022) have similar methodological issues due to the multi-chambered cuff construction preventing researchers from making pressures relative to that induced by the single chamber systems. Presumably, this results in a greater magnitude of AOP achieved by the single chambered systems in comparison studies, affecting acute cardiovascular, neuromuscular, and perceptual measures, leading to potentially faulty conclusions on safety risk and/or longitudinal outcomes.

Only two (Bordessa et al., 2021; Citherlet et al., 2022) of the three comparison studies set pressures in the single-chambered system relative to %AOP in the comparison condition, whereas the other study (Stray-Gundersen et al., 2020) assigned an arbitrary pressure. Despite the limitation mentioned, all three studies provide important context to the discussion of the potential impact of bladder design on the BFR stimulus.

The first published comparison study between different BFR cuff bladder designs compared the acute perceptual and hemodynamic responses between the B-Strong™ cuff (5-cm cuff width) and Hokanson rapid-inflator research device (Hokanson, Bellevue, WA, United States) (18-cm cuff width) inflated to 300 mmHg and 160 mmHg, respectively (Stray-Gundersen et al., 2020). The results support the use of the B-Strong™ cuff for BFR walking aerobic exercise as the Hokanson device promoted greater increases in heart rate, blood pressure, and double product during exercise with elevated perceptual demands (all measures $p < 0.05$). Lactate levels were observed to be significantly greater in the Hokanson condition as well, indicating that metabolic stress was likely greater than in the B-Strong™ condition, given that exercise-induced increases in lactate can be an indirect marker for signaling cell metabolic conditions that may induce metabolic acidosis (Robergs et al., 2004). This possibly resulted in a larger stimulation of the afferents governing the muscle metaboreflex response, increasing cardiovascular and perceptual responses (Boushel, 2010). Considering the width of the Hokanson cuff (18 cm), the magnitude of pressure used (160 mmHg), and the demographics of the participants, the authors of this manuscript conjecture that most were exercising very near 100% AOP. For comparison, Hughes et al. (Hughes et al., 2018) used a narrower Hokanson cuff (13 cm v 18 cm width) and reported full arterial occlusion in 18 subjects at 163.33 ± 17.06 mmHg (Hughes et al., 2018). The Hughes et al. cohort likely had higher AOP values than the Stray-Gunderson et al. cohort given the subject pool was entirely male, had higher BMI values (23 ± 3 vs. 28.94 ± 3.28), and higher resting systolic blood pressure (116 ± 11 mmHg vs. 129 ± 9 mmHg), all factors that have been shown *via* direct or indirect evidence to influence AOP.

The second publication compared two commercially available BFR devices [B-Strong™ and Delfi Personalized Tourniquet device (Delfi Medical Innovations®, Vancouver, BC, Canada)] at 30% 1RM against a high load strength training control group performed at 80% 1RM. Using a within-subjects design (n = 34; 18 males), muscle excitation and training-related rate of perceived exertion and muscle pain in a fixed repetition (e.g., 30–15–15–15) design during a leg press exercise was assessed (Bordessa et al., 2021). The B-Strong™ cuff was inflated to between 250–310 mmHg based upon participant characteristics while the Delfi Personalized Tourniquet device was inflated to 80% AOP (between 104–208 mmHg), the maximum recommended pressure for practical use (Patterson et al., 2019). Results show similar muscle activation (as evidenced by electromyography) between cuffs conditions ($p > 0.05$), but both were less than the high load exercise condition ($p < 0.01$). In addition, the B-Strong™ cuff elicited significantly less discomfort ($p < 0.001$) and perceptual exertion ($p < 0.001$) than the Delfi Personalized Tourniquet device condition and were greater than the high load strength condition ($p < 0.001$). As the Delfi Personalized Tourniquet device is a single-chambered bladder tourniquet (Weatherholt et al., 2019), the exercisers in this trial were likely experiencing a greater magnitude of muscle fatigue and were probably significantly closer to failure than those exercising in the B-Strong™ cuff trial given the B-Strong™ cuffs are not designed to occlude blood flow (Early et al., 2020). Research has shown that proximity to failure augments the perceptual responses experienced (Santos et al., 2021), so it is likely that the higher applied pressures in the Delfi Personalized Tourniquet device trial augmented muscle pain and perceived exertion during exercise. As such, the study's conclusions stated that B-Strong™ was more tolerable than the Delfi Personalized Tourniquet device while providing similar electromyographic activation of the quadriceps. Practitioners may assume from the study that the B-Strong™ cuff is just as effective as the Delfi Personalized Tourniquet device in a longitudinal program with better participant tolerability and similar muscle activation given the acute responses observed. However, without considering the impact of each cuff on occlusive capabilities and subsequent fatigue accumulation during exercise, extrapolating effectiveness should be done with caution. As accelerated muscle fatigue is likely the primary way BFR induces its beneficial effect on muscle (Jessee et al., 2018), the design of Bordessa et al. (Bordessa et al., 2021) gives limited guidance to the potential efficacy of the B-Strong™ cuff bladder system compared to the Delfi Personalized Tourniquet device as both exercised in a work-matched fashion, limiting our understanding of the proximity to failure between conditions and related perceptual factors. Future research comparing the two bladder types during exercise could include repetitions to momentary muscular failure anchored with a low-load free-flow group. This design could help practitioners understand the magnitude of muscle fatigue induced by the different bladders as evidenced by repetitions to momentary muscular failure in each condition. Similarly, longitudinal work-matched, non-failure training studies can help shed light on the adaptation profiles (e.g., muscle mass and strength) that can help form practical recommendations, particularly if adaptations are similar with lower exercise-induced discomfort in multi-chambered systems.

The most recent study published in late 2022 compared the B-Strong™ cuff to the Hokanson research tourniquet on capacity to modulate resting limb blood flow in the upper and lower limbs (Citherlet et al., 2022). Eleven healthy participants (n = 7 females) had all their extremities assessed with both cuffs and their resting blood flow monitored following application of different pressures (e.g., 40%–60% AOP with Hokanson and 200–400 mmHg pressures with B-Strong™). The authors noted that AOP was unable to be determined in any individual with the B-Strong™ cuff and that resting blood flow was only slightly altered from resting conditions at 350 mmHg ($p = 0.016$, d = 0.688) and 400 mmHg ($p = 0.002$, d = 0.805). Conversely, the Hokanson cuff was able to modulate blood flow from rest in both the 40% AOP ($p = 0.009$, d = 0.715) and 60% AOP ($p < 0.001$, d = 0.948) conditions using pressures between 83–125 mmHg. However, both cuffs displayed an inability to regulate blood flow according to the pressure applied (e.g., exhibiting a direct negative linear relationship with increasing pressure), although this observation was more evident with the B-Strong™ cuff ($p > 0.05$). The results of this study indicate that even at the highest pressures, the multi-chambered bladder system cannot effectively modulate limb blood flow whereas a single-chambered bladder system applied at the lowest minimal recommended pressure can modulate blood flow.

Lastly, although not a direct comparison to other BFR cuff types, Callanan et al. (Callanan et al., 2022) sought to examine the systemic hematopoetic stem cell response to an acute bout of lower extremity exercise using B-Strong™ cuffs. This lab has published previous work demonstrating exercise with Delfi Personalized Tourniquet device as well as Vasper system (Vasper Systems, Mountain View, CA) elicits significant increases in platelets, lactate and hematopoetic stem cells (Callanan et al., 2021a; Callanan et al., 2021b). The authors hypothesize this increase in hematopoetic stem cell response may have clinical utility to ensure a more uniform quality of orthobiologic injections. Thus, determining whether a device like B-Strong™ can achieve a similar result is important. To test this, subjects exercised intensely on a VersaClimber for 9 min while wearing the B-Strong™ cuffs on all four limbs at the manufacturer's recommended pressures based on anthropometric data and sex of the participant (pressures not described in text). Interestingly, while significant increases in platelets, lymphocytes, $CD34^+$ cells, and white blood cells were observed, the B-Strong™ condition did not elicit a response that was different than the free flow condition. This is a departure from the results of the other studies performed by the same author group (Callanan et al., 2021a; Callanan et al., 2021b). However, some of the discrepancy in outcomes between studies could be explained by the differences in the amount of volume performed in each of the exercise protocols.

While it does not appear the occlusion of arterial flow is a mandatory aspect of BFR application, reduction of arterial inflow is believed to be important for reducing oxygen delivery, promoting earlier type 2 muscle fiber recruitment, and accelerating muscular fatigue and metabolic stress (Jessee et al., 2018). Currently, no research exists on comparative effectiveness between bladder types in a longitudinal program. The current body of BFR research indicates that higher applied pressures—at least 50% AOP in the lower extremities–are needed to accelerate the fatigue response beyond that of low-load training (Cerqueira et al., 2021). Devices unable to determine a personalized pressure above 40%–50% AOP (Counts et al., 2016; Cerqueira et al., 2021) risk not applying enough pressure to the limb to elicit a fatiguing stimulus beyond that provided with low-load training alone, potentially leading to conclusions that may contradict the existing body of research using single-chambered bladder systems. Particularly susceptible to this issue are studies that exercise participants in a non-failure, work-matched fashion where proximity to failure is not known. Therefore, cuffs that are unable to occlude arterial inflow to determine a personalized pressure may present difficulties in studies when compared to a personalized pressure application.

To reduce flaws in comparisons between devices with different bladders, future studies should investigate the magnitude of post-exercise muscle fatigue (e.g., isometric/dynamic torque loss) following various application parameters. Of most value to practice are acute studies that compare repetitions to failure between different bladder types applied at recommended application settings (e.g., 250/350 mmHg in multi-chambered bladder systems and 40%–80% AOP in single-bladder systems) and longitudinal studies that track volume load, relevant outcomes, and occurrence of adverse events in non-failure and failure repetition schemes. These experimental designs will greatly increase practical relevancy, thus helping practitioners make informed decisions regarding the device they choose to use with their clients and patients.

2.2 Autoregulation of applied pressure

Autoregulation refers to the capability of a device to adjust pressure within the cuff during an inflation cycle. In theory, the result is a more consistent application of pressure to an exercising limb as muscular contractions against the cuff will create spikes in pressure, potentially affecting comfort, hemodynamics, and causing air to escape, possibly reducing the pressure in the cuff for the rest of the session (Kacin et al., 2015; Hughes et al., 2018) (Figure 2).

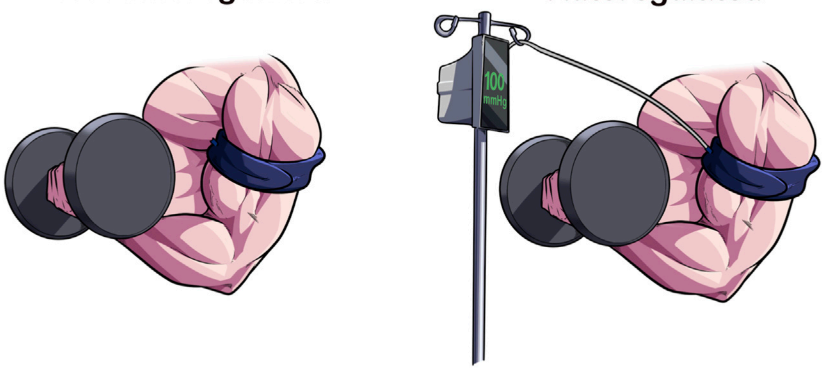

FIGURE 2
Autoregulation of Applied Pressures. Autoregulation is a design feature that accommodates for the changes in limb circumference because of muscular contraction. In current available devices, the BFR cuff is attached to a pneumatic air compressor *via* an air tubing that adjusts according to the pressure sensed at the cuff-limb interface. The speed at which this adjustment occurs varies across devices, making it a cuff-specific feature. Autoregulation may enhance the acute safety of BFR exercise.

Manual pneumatic cuffs (e.g., non-autoregulated) do not automatically adjust pressure during the inflation cycle; although the user may add pressure lost back into the cuff *via* sphygmomanometer. Until recently, all but one BFR device on the market would be classified as non-autoregulated. Now with multiple devices in the space possessing autoregulation technology, the responsiveness, or speed with which the device can sense and adjust pressure, becomes an important variable in assessing the impact of the feature. Therefore, whether a BFR device has an autoregulation feature, and how that feature performs may be an important variable to report and examine in future investigations.

Currently, Jacobs et al. (Jacobs et al., 2023) is the only study that has directly investigated autoregulation as a primary variable in a within-subjects research design. Using a cohort of 56 healthy, physically active men and women they compared the acute cardiovascular, perceptual, and performance outcomes during a 20% 1-RM leg extension exercise performed at fixed and failure repetition schemes with- and without autoregulation of applied pressures using an identical width (10.16 cm) Smartcuffs™ BFR cuff (Smart Tools Plus LLC, Strongsville, OH, United States). Exercise was performed at 60% AOP (determined in sitting) with a 4 s cadence (2 s concentric/2 s eccentric) per repetition. They also monitored for the occurrence of adverse responses to BFR exercise. Their results showed a 3x risk reduction in the odds of experiencing a minor adverse event (e.g., lightheadedness) compared to the non-autoregulated condition. In addition, during four sets of exercise to failure, the autoregulated condition performed significantly more volume than the non-autoregulated condition (~199 reps vs. ~161 reps, $p < 0.001$) with less delayed onset muscle soreness [3 ± 2.2 vs. 4 ± 2.6, $p < 0.001$; 95% confidence interval (CI): 0.544–1.022] and similar blood pressure responses. Though small, they also noted that autoregulation appeared to reduce the perceptual demands during both repetition schemes ($p <$ 0.028–<0.001). Thus, results indicate a beneficial impact of the autoregulation feature of the Smartcuffs™ BFR cuff system.

A recent preprint provided additional context to the discussion of autoregulation of applied pressures during BFR exercise. In another within-subject design, Rolnick et al. (Rolnick et al., 2023) investigated the acute central stiffness and muscle morphological responses to four sets of exhaustive wall squat exercise. Squats were performed at 20% 1-RM in 20 healthy, physically active men and women with- and without autoregulation of applied BFR pressures using the Delfi Personalized Tourniquet device. Participants exercised with 60% of supine AOP in a 4 s per repetition (2 s concentric/2 s eccentric) cadence. Their results are in contrast to Jacobs et al. (Jacobs et al., 2023) as they found no differences in volume performed between BFR conditions nor in rate of perceived exertion and rate of perceived discomfort. However, they did note that autoregulation blunted the exercise-induced increases in central stiffness compared to both non-autoregulation [Mean difference, [MD] = 0.57 ± 1.12 m/s, 95% CI (0.05–1.09), $p = 0.017$, effect size [ES] = 0.51] and low-load exercise [MD = 0.63 ± 1.42 m/s, 95% CI (+0.04–1.3), $p = 0.032$, ES = 0.44], albeit with wide CIs. The non-autoregulated cuff condition also produced significantly greater increases in post-exercise muscle swelling and potentially muscle damage than the autoregulated condition as evidenced by greater muscle cross-sectional area (MD = 0.61 ± 1.03 cm^2, 95% CI = 0.13–1.09, $p < 0.01$, ES = 0.59) and echo intensity [MD = 5.84 ± 8.89 au, 95% CI (1.67–9.99), $p < 0.01$, ES = 0.66]. While muscle damage was not directly sampled, prior research has indicated that post-exercise muscle swelling is a likely indicator of muscle damage, particularly if increased echo intensities along with larger muscle cross-sectional areas are observed (Damas et al., 2016). Of note, this study did not record any adverse events in either BFR condition throughout the study.

The divergent results on performance, rate of perceived exertion, rate of perceived pain and incidence of adverse events may be partially explained by differences in autoregulation capacity of the different BFR devices, participant characteristics, or type of exercise performed. Of potential relevancy is the practical observation that commercially available BFR devices vary in their capacity to provide quick adjustments to applied pressure during exercise, likely limiting conclusions about autoregulation to a particular device and not the feature itself. Future BFR research should specifically report the

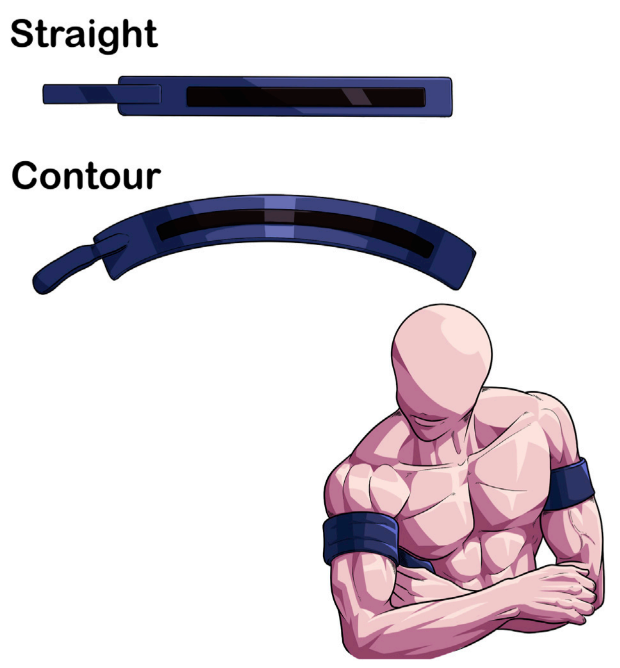

FIGURE 3
Differences in limb fit between contoured and straight BFR cuffs. contour cuffs provide a more secure fit due to the conical shape of the limb compared to a straight cuff. This may enhance the safety profile of BFR exercise.

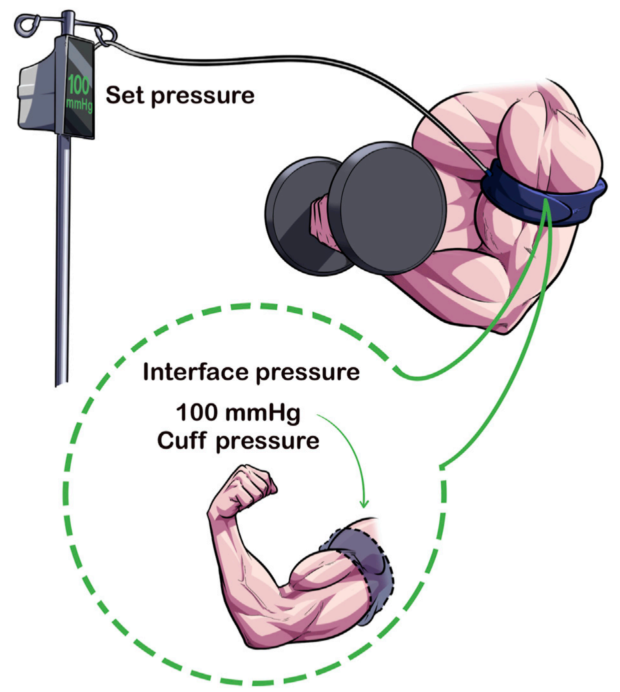

FIGURE 4
Set Pressure Versus Interface Pressure. The set pressure is the pressure that the pneumatic cuff is inflated to by the clinician/exerciser/researcher whereas the interface pressure is the amount of pressure applied to the limb from the cuff. Cuffs that can maintain a similar set and interface pressures may enhance acute safety of BFR exercise.

presence or absence of autoregulation given the preliminary body of research indicating it may impact BFR exercise responses.

2.3 Contour vs. straight cuff

Cuff shape has been shown to impact the amount of applied pressure needed to determine AOP (Figure 3) (Younger et al., 2004). Contour cuff shapes are longer at the top and shorter at the bottom, creating a tapered fit on the limb due to differences in diameter. Contoured cuffs also can be manufactured with variable contour shape, a design feature that allows for an even more secure fit to the limb as the device fastener apparatus can account for small differences in extremity size and shape (Tourniquet technology, 2017). Nonetheless, the difference in proximal to distal diameter of a contoured cuff reduces AOP slightly (~−25.4 ± 16.1 mmHg measured with doppler ultrasound) compared to a straight cuff (e.g., cuff that is similar length on the top and the bottom) in the lower body (Pedowitz et al., 1993). Small differences were also noted in the upper body AOP (124.2 ± 10.5 mmHg vs. 128.5 ± 13.9 mmHg in contoured and straight cuffs, respectively), but are likely practically insignificant (Pedowitz et al., 1993).

Further, the occlusive stimulus may be different as straight cuffs are more likely to apply asymmetric pressures to the limb given the change in limb circumference proximally to distally in the extremities (Noordin et al., 2009). In populations where pressures during BFR exercise may want to be minimized to reduce the pressor response (Spranger et al., 2015), the use of a contoured cuff may be preferred to accommodate for the conical limb shape, particularly in the lower extremities. To date, no study has directly compared the acute and longitudinal responses to a BFR exercise regimen using cuffs of similar widths but varying in cuff shape, so this area of research is largely unknown.

2.4 Set pressure versus pressure applied to the limb

The pressure that is set for BFR (i.e., "the set pressure") may not be the same pressure that is applied to the limb, known as the "interface pressure" (Figure 4) (Hughes et al., 2018). Hughes et al. (Hughes et al., 2018) showed that when the Delfi Personalized Tourniquet device (automatic autoregulated; cuff width = 11.5 cm; contoured cuff shape) was inflated to 40% and 80% AOP in a resting condition, the interface pressure was 8 ± 4 mmHg (95% CI: 16.84 to −0.17) and 9 ± 4 mmHg (95% CI: 16.80 to −0.32) lower than the set pressure ($p < 0.05$). When the manual cuff [Occlusion Cuff (The Occlusion Cuff LTD., Belfast, Ireland), cuff width = 8 cm; straight cuff shape] was inflated to similar relative pressures, the interface pressure was 20 ± 10 mmHg (95% CI: 39.16 to −1.40) and 37 ± 13 mmHg (95% CI: 62.12 to −11.88) lower than the set pressure ($p < 0.05$). Thus, despite personalizing the pressure to %AOP, the amount of applied pressure to the limb during resting conditions varied significantly between devices.

Preliminary results from Hughes et al. (Hughes et al., 2018) also indicated that cardiovascular and perceptual experiences were heightened in the manual cuff compared to the autoregulated cuff during exercise, with interface pressures greatly exceeding the clinical recommendation of ±15 mmHg applied pressure for safe tourniquet application (McEwen, 1981). Paradoxically compared to the lower interface pressures recorded during rest, the interface pressure compared to the set pressure during exercise was significantly elevated ranging between 37 ± 36 mmHg [95% CI: 33.79–108.01] in set 4 to 62 ± 35 mmHg (95% CI: 6.79–130.57) in set one; all $p < 0.01$]. In contrast, the Delfi Personalized Tourniquet device maintained the set and interface pressure during exercise and did not exceed ±15 mmHg in any of the four sets measured ($p > 0.05$). Elevations observed in the manual cuff over the Delfi Personalized Tourniquet device in rates of perceived exertion (e.g., 17 ± 2 vs. 15 ± 2 after set 4, 95% CI: 0.794–3.095, $p < 0.01$), rates of perceived pain (e.g., 8.3 ± 2.3 vs. 5.7 ± 2.0 after set 4, 95% CI: 1.359–3.808, $p < 0.01$) and mean arterial pressure 1-min post-exercise (11 ± 6 mmHg, 95% CI: 5.558–16.190, $p < 0.01$) may be at least partially explained by differences in the pressure applied to the underlying limb during exercise.

Despite setting AOP to a similar percentage based on the cuff (80% AOP), the comparison was not direct as cuff widths varied between devices, the Delfi Personalized Tourniquet device is autoregulated, and their cuff shapes varied. Insomuch as what's currently known from the devices in the consumer market, the Delfi Personalized Tourniquet device has been shown to apply a pressure within measurement error and safe tourniquet use (±15 mmHg), ensuring a stimulus that is like the set pressure during exercise conditions. If possible, future studies should integrate measurements for determining interface pressures, particularly when novel devices are being investigated. Special attention should be paid to studies using lower (40%–50% AOP) pressures in their lower body interventions as this may impact the clinical relevance given lower pressures in this range have been shown to be ineffective at accelerating fatigue accumulation in BFR exercise (Cerqueira et al., 2021). If a cuff used in a lower pressure intervention was shown to be ineffective, researchers should determine if it was ineffective due to the parameters set (e.g., lower pressure) or inadequate cuff restrictive capabilities.

Lastly, in addition to cuff design features, interface pressure may be impacted by how snugly the cuff is applied, affecting pressure transmission to the limb by as much as 50% (Graham et al., 1993). It may be important for researchers to attempt to standardize a baseline level of tightness for everyone to reduce the impact of a too tightly or loosely fitting initial pressure. It also should be mentioned that cuff overlap impacts the applied pressure to the limb and has been recommended to be between 3–6 inches (Kumar et al., 2016). Values within this range likely apply a more uniform pressure to the underlying limb and may result in a more accurate interface pressure relative to the set pressure.

2.5 Presence/absence of an internal stiffener

A stiffener is a feature of a tourniquet that directs the pressure from the bladder onto the limb and helps maintain the cuff's position when inflated to prevent slippage or skin pinching (McEwen et al., 2015; Tourniquet technology, 2017). The presence of an internal stiffener may impact the degree of AOP and/or the exerciser's perceptual experiences during exercise as its presence increases the resistance to cuff deformation with muscular contraction (Tourniquet technology, 2017; McEwen et al., 2019). With respect to BFR exercise, no study has investigated the impact of an internal stiffener on cuffs with similar widths to determine its effect on acute- and longitudinal training outcomes. Future studies should determine its relevance with BFR exercise as more devices are being purchased and used in practice (Cuffe et al., 2022).

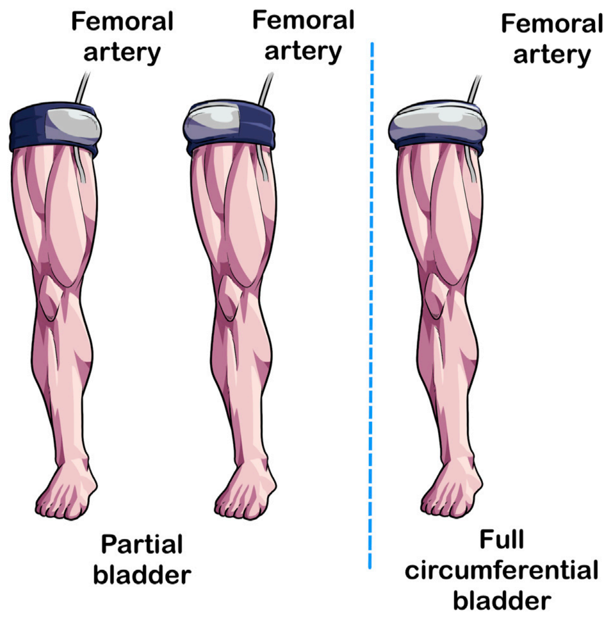

FIGURE 5
Partial circumferential versus circumferential bladder length. In traditional tourniquets, the bladder extends the length of the cuff (Right Image) whereas in some BFR cuffs, the bladder extends partially not covering the entirety of the length of the cuff (Left and Center Illustrations). Studies implementing BFR cuffs with partial circumference bladders should specify the position of the bladder because its placement may impact acute responses to BFR exercise.

2.6 Bladder length—circumferential vs. partial circumferential

The last cuff feature that can impact BFR exercise is the length of the bladder (Figure 5). In traditional tourniquets, the bladder circumferentially envelopes the limb (Kumar et al., 2016). In partial circumferential bladders, the bladder does not extend the length of the cuff, leaving areas without pneumatic pressure application that instead relies on compression from the sleeve of the device. As most, but not all [e.g., Airbands/SAGA Fitness Cuffs (VALD Health, VALD Pty Ltd., Newstead QLD, Australia)] BFR devices on the marketplace have circumferential bladders, little is known about the acute responses associated with differences in bladder length.

Currently, three studies exist utilizing partial circumferential bladders related to BFR (Spitz et al., 2020; Keller et al., 2023; Królikowska et al., 2023) but none of them have been used in the context of measuring acute- or longitudinal exercise responses. Two studies focused on methodological aspects of the partial bladder design (Spitz et al., 2020; Keller et al., 2023) and one investigated the impact of BFR on post-exercise joint position sense in recreational athletes (Królikowska et al., 2023). We want to briefly highlight the two studies (Spitz et al., 2020; Keller et al., 2023) investigating the methodological aspects associated with a partial bladder design and comment on their potential impact in practice and research design.

In a crossover within-subjects design (n = 32; 13 males), Spitz et al. (Spitz et al., 2020) showed that positioning the bladder on the outside of the thigh produced a greater AOP than when the bladder was positioned on the inside of the thigh (median difference of 13.56 mmHg, 95% CI: 7.29–19.84, Bayes factor $[BF]_{10}$ = 437.52). In addition, agreement between bladder positions was worse with individuals with larger limb circumferences (r = 0.558, 95% CI: 0.24–0.74, BF_{10} = 42.863), highlighting the relative importance of standardizing the bladder position in research and practice with partial circumferential cuff designs. The difference in AOP between positions was attributed to the location of the femoral artery, the main conduit artery of the lower extremity. As the femoral artery is located anteromedially and not anterolaterally, the inside position required less pressure to occlude arterial inflow than when positioned anterolaterally. If bladder positioning impacts AOP in cuffs with partial circumferential bladder designs, this may have relevancy for clinical populations where limited applied pressure may enhance acute safety and/or longitudinal training responses. As Spitz et al. (Spitz et al., 2020) did not measure acute physiological and perceptual responses during exercise, it is unknown whether the positioning of the bladder and the magnitude of applied pressure has relevancy for BFR exercise.

Keller et al. (Keller et al., 2023) sought to validate the AOP algorithm used in a commercially available partial bladder BFR cuff system (Airbands) in the upper and lower extremities in 107 healthy males and females (n = 67 males). They compared the AOP given by the Airbands system with a gold standard doppler ultrasound assessment (using a circumferential bladder medical tourniquet [Tourniquet Touch TT20, VBM Medizintechnik GmbH, Sulz am Neckar, Germany]) in the seated position (both had 8 cm-widths). Of note, they did not specify where the bladder was positioned on the limb relative to the brachial and femoral artery with the Airbands cuff, only that it was standardized at identical positions during measurement for everyone. Their results indicated that the Airbands cuff provided considerable agreement with doppler ultrasound (125 ± 17 mmHg in the Airbands vs. 131 ± 14 mmHg in the doppler ultrasound assessment; mean difference = 7 ± 13 mmHg, 95% CI: 3–11) in the upper extremities. In the lower extremities, the Airbands cuff likely significantly underestimated AOP in 38 of 55 individuals (e.g., all had AOP of 270 mmHg) possibly due to limitations in the cuff compression technology that was unable to apply pressures greater than 270 mmHg. However, in a sub-group analysis of the 17 individuals with AOPs less than 270 mmHg, there was considerable agreement with doppler ultrasound (223 ± 14 mmHg for Airbands vs. 218 ± 23 mmHg for doppler ultrasound; mean difference = −5 mmHg, 95% CI: 17—8). Thus, it appears that in individuals whose limb circumferences are small, the Airbands cuff produces similar AOP values in the upper and lower extremities compared to a gold standard doppler ultrasound assessment using a circumferential bladder cuff. Limitations in the lower extremities on accurately predicting AOP may be of importance for future research in the lower body using the Airbands cuff as it will likely be unable to determine a personalized pressure for many individuals with larger thigh circumferences. Nonetheless, it should be acknowledged that this is not necessarily a safety issue (as the device likely cannot fully occlude the lower extremities in most individuals) but moreso a technological limitation given the reduced capability to standardize a restrictive stimulus.

Both studies provide preliminary insights into the ways in which a partial bladder system influences AOP that can guide future research. First, it appears that the bladder position matters with respect to the conduit artery, particularly in those with larger limb circumferences. Future studies using partial bladder cuff systems should specify where the bladder is relative to the conduit artery. Second, the commercially available Airbands BFR device is likely safe and valid to use for both the upper and lower extremities, but caution should be made with individuals that have larger thigh circumferences as AOP is likely under-estimated. Future studies using Airbands should monitor for lower extremity AOP values of 270 mmHg, as it indicates that the limb is likely too large to have AOP accurately determined. As such, this prevents a personalized pressure and will likely impact the magnitude of acute physiological and perceptual responses and potentially chronic training responses to BFR exercise. Last, no research exists investigating the responses of a partial bladder to exercise with BFR compared with a circumferential bladder inflated to the same relative pressure. As practitioners report using partial bladder systems in practice (Cuffe et al., 2022), understanding the impact of this cuff design on BFR exercise warrants future study.

3 Discussion

As discussed above, numerous cuff features may impact BFR exercise. While features like autoregulation appear to have some ability to modulate intra-exercise responses and potentially reduce adverse events, other features like bladder type (e.g., multi-chambered bladder systems) have the capacity to impact the ability to determine a personalized pressure. Importantly, while there are numerous ways to apply the BFR exercise stimulus (e.g., arbitrary pressures or %AOP), extrapolating acute responses using non-personalized pressure applications requires caution given the current body of evidence. Other cuff features such as bladder length (e.g., circumferential *versus* partial circumferential), presence/absence of an internal stiffener, and set/interface pressure are not widely studied and require further investigations into their potential relevancy in BFR given the existing body of research. Of note, no studies currently exist investigating the impact of an internal stiffener on determination of AOP or acute- or longitudinal responses to BFR exercise.

4 Conclusion

This manuscript attempted to contextualize the potential importance of infrequently reported BFR cuff features and hypothesize their potential impact on BFR training. As BFR continues to expand into practice, researchers should be aware of not only the importance of AOP assessment and its impact on BFR exercise responses, but of the ways that physiological responses may vary between cuffs despite standardization to %AOP. Cuffs that are unable to be standardized to a %AOP (e.g., multi-chambered bladder systems) may have clinical utility, but the current body of evidence on their efficacy is lacking and should be a focal area of future research—particularly if similar beneficial results are obtained with reductions in adverse events.

Data Availability Statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Author contributions

NR wrote the initial draft of the manuscript. KK and VQ provided critical review and helped edit the manuscript for content and flow. All authors agreed to the final version of the manuscript and the statements made in the article.

Acknowledgments

We wish to acknowledge Eugen and Arsim Loki (@physeaque on Instagram) for their contributions to illustrating the different cuff design and features included within this manuscript.

Conflict of interest

NR is the founder of The BFR PROS and teaches BFR training workshops to fitness and rehabilitation practitioners using a variety of BFR training devices. KK is a clinical instructor for Owens Recovery Science, a BFR education company that also distributes the Delfi Personalized Tourniquet Device.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor [AZ] declared a past co-authorship with the author [NR].

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

AORN Recommended Practices Committee (2007). Recommended practices for the use of the pneumatic tourniquet in the perioperative practice setting. *AORN J.* 86 (4), 640–655. doi:10.1016/j.aorn.2007.09.004

Bordessa, J. M., Hearn, M. C., Reinfeldt, A. E., Smith, T. A., Baweja, H. S., Levy, S. S., et al. (2021). Comparison of blood flow restriction devices and their effect on quadriceps muscle activation. *Phys. Ther. Sport* 49, 90–97. doi:10.1016/j.ptsp.2021.02.005

Boushel, R. (2010). Muscle metaboreflex control of the circulation during exercise. *Acta Physiol. (Oxf).* 199 (4), 367–383. doi:10.1111/j.1748-1716.2010.02133.x

Buckner, S. L., Dankel, S. J., Counts, B. R., Jessee, M. B., Mouser, J. G., Mattocks, K. T., et al. (2017). Influence of cuff material on blood flow restriction stimulus in the upper body. *J. Physiol. Sci.* 67 (1), 207–215. doi:10.1007/s12576-016-0457-0

Callanan, M. C., Christensen, K. D., Plummer, H. A., Torres, J., and Anz, A. W. (2021). Elevation of peripheral blood CD34+ and platelet levels after exercise with cooling and compression. *Arthrosc. Sports Med. Rehabil.* 3 (2), e399–e410. doi:10.1016/j.asmr.2020.10.003

Callanan, M. C., Plummer, H. A., Chapman, G. L., Opitz, T. J., Rendos, N. K., and Anz, A. W. (2021). Blood flow restriction training using the Delfi system is associated with a cellular systemic response. *Arthrosc. Sports Med. Rehabil.* 3 (1), e189–e198. doi:10.1016/j.asmr.2020.09.009

Callanan, M. C., Plummer, H. A., Green, T. M., Opitz, T., Broderick, T., Rendos, N., et al. (2022). Blood flow restriction using a pneumatic tourniquet is not associated with a cellular systemic response. *Arthrosc. Sports Med. Rehabil.* 4 (3), e877–e882. doi:10.1016/j.asmr.2021.12.018

Cerqueira, M. S., Lira, M., Mendonça Barboza, J. A., Burr, J. F., Wanderley, E., Lima, T. B., et al. (2021). Repetition failure occurs earlier during low-load resistance exercise with high but not low blood flow restriction pressures: A systematic review and meta-analysis. *J. Strength Cond. Res.* doi:10.1519/JSC.0000000000004093

Chulvi-Medrano, I., Cortell-Tormo, J. M., Hernández-Sánchez, S., Picón-Martínez, M., and Rolnick, N. (2023). Blood flow restriction training in clinical rehabilitation: Occlusion pressure methods relative to the limb occlusion pressure. *J. Sport Rehabil.* 2023, 1–8. doi:10.1123/jsr.2022-0240

Citherlet, T., Willis, S. J., Chaperon, A., and Millet, G. P. (2022). Differences in the limb blood flow between two types of blood flow restriction cuffs: A pilot study. *Front. Physiol.* 13, 931270. doi:10.3389/fphys.2022.931270

Clarkson, M. J., May, A. K., and Warmington, S. A. (2019). Chronic blood flow restriction exercise improves objective physical function: A systematic review. *Front. Physiol.* 10, 1058. doi:10.3389/fphys.2019.01058

Counts, B. R., Dankel, S. J., Barnett, B. E., Kim, D., Mouser, J. G., Allen, K. M., et al. (2016). Influence of relative blood flow restriction pressure on muscle activation and muscle adaptation. *Muscle & nerve,* 53 (3), 438–445. doi:10.1002/mus.24756

Cuffe, M., Novak, J., Saithna, A., Strohmeyer, H. S., and Slaven, E. (2022). Current trends in blood flow restriction. *Front. Physiol.* 13, 882472. doi:10.3389/fphys.2022.882472

Damas, F., Phillips, S. M., Lixandrão, M. E., Vechin, F. C., Libardi, C. A., Roschel, H., et al. (2016). Early resistance training-induced increases in muscle cross-sectional area are concomitant with edema-induced muscle swelling. *Eur. J. Appl. Physiol.* 116 (1), 49–56. doi:10.1007/s00421-015-3243-4

Dankel, S. J., Buckner, S. L., Counts, B. R., Jessee, M. B., Mouser, J. G., Mattocks, K. T., et al. (2017). The acute muscular response to two distinct blood flow restriction protocols. *Physiol. Int.* 104 (1), 64–76. doi:10.1556/2060.104.2017.1.1

Dankel, S. J., Buckner, S. L., Jessee, M. B., Mattocks, K. T., Mouser, J. G., Counts, B. R., et al. (2018). Can blood flow restriction augment muscle activation during high-load training? *Clin. Physiol. Funct. Imaging* 38 (2), 291–295. doi:10.1111/cpf.12414

de Queiros, V. S., Dantas, M., Neto, G. R., da Silva, L. F., Assis, M. G., Almeida-Neto, P. F., et al. (2021). Application and side effects of blood flow restriction technique: A cross-sectional questionnaire survey of professionals. *Med. Baltim.* 100 (18), e25794. doi:10.1097/MD.0000000000025794

Domingos, E., and Polito, M. D. (2018). Blood pressure response between resistance exercise with and without blood flow restriction: A systematic review and meta-analysis. *Life Sci.* 209, 122–131. doi:10.1016/j.lfs.2018.08.006

Early, K. S., Rockhill, M., Bryan, A., Tyo, B., Buuck, D., and McGinty, J. (2020). Effect of blood flow restriction training on muscular performance, pain and vascular function. *Int. J. Sports Phys. Ther.* 15 (6), 892–900. doi:10.26603/ijspt20200892

Ellefsen, S., Hammarström, D., Strand, T. A., Zacharoff, E., Whist, J. E., Rauk, I., et al. (2015). Blood flow-restricted strength training displays high functional and biological efficacy in women: A within-subject comparison with high-load strength training. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 309 (7), R767–R779. doi:10.1152/ajpregu.00497.2014

Evin, H. A., Mahoney, S. J., Wagner, M., Bond, C. W., MacFadden, L. N., and Noonan, B. C. (2021). Limb occlusion pressure for blood flow restricted exercise: Variability and relations with participant characteristics. *Phys. Ther. Sport* 47, 78–84. doi:10.1016/j.ptsp.2020.11.026

Fahs, C. A., Loenneke, J. P., Thiebaud, R. S., Rossow, L. M., Kim, D., Abe, T., et al. (2015). Muscular adaptations to fatiguing exercise with and without blood flow restriction. *Clin. Physiol. Funct. Imaging* 35 (3), 167–176. doi:10.1111/cpf.12141

Formiga, M. F., Fay, R., Hutchinson, S., Locandro, N., Ceballos, A., Lesh, A., et al. (2020). Effect of aerobic exercise training with and without blood flow restriction on aerobic capacity in healthy young adults: A systematic review with meta-analysis. *Int. J. Sports Phys. Ther.* 15 (2), 175–187. doi:10.26603/ijspt20200175

Graham, B., Breault, M. J., McEwen, J. A., and McGraw, R. W. (1993). Occlusion of arterial flow in the extremities at subsystolic pressures through the use of wide tourniquet cuffs. *Clin. Orthop. Relat. Res.* 286 (286), 257–261. doi:10.1097/00003086-199301000-00038

Grønfeldt, B. M., Lindberg Nielsen, J., Mieritz, R. M., Lund, H., and Aagaard, P. (2020). Effect of blood-flow restricted vs heavy-load strength training on muscle strength: Systematic review and meta-analysis. *Scand. J. Med. Sci. Sports* 30, 837–848. doi:10.1111/sms.13632

Hughes, L., Rosenblatt, B., Gissane, C., Paton, B., and Patterson, S. D. (2018). Interface pressure, perceptual, and mean arterial pressure responses to different blood flow restriction systems. *Scand. J. Med. Sci. Sports* 28 (7), 1757–1765. doi:10.1111/sms.13092

Jacobs, E., Rolnick, N., Wezenbeek, E., Stroobant, L., Capelleman, R., Arnout, N., et al. (2023). Investigating the autoregulation of applied blood flow restriction training pressures in healthy, physically active adults: An intervention study evaluating acute training responses and safety. *Br. J. Sports Med.* 2023, 106069. doi:10.1136/bjsports-2022-106069

Jessee, M. B., Buckner, S. L., Mouser, J. G., Mattocks, K. T., and Loenneke, J. P. (2016). Letter to the editor: Applying the blood flow restriction pressure: The elephant in the room. *Am. J. Physiol. Heart Circ. Physiol.* 310, H132–H133. doi:10.1002/mus.24756

Jessee, M. B., Mattocks, K. T., Buckner, S. L., Dankel, S. J., Mouser, J. G., Abe, T., et al. (2018). Mechanisms of blood flow restriction: The new testament. *Tech. Orthop.* 33 (2), 72–79. doi:10.1097/bto.0000000000000252

Kacin, A., Rosenblatt, B., Žargi, T. G., and Biswas, A. (2015). Safety considerations with blood flow restricted resistance training. *Ann. kinesiol* 6, 3–26. Available from: http://ojs.zrs-kp.si/index.php/AK/article/view/96.

Kacin, A., and Strazar, K. (2011). Frequent low-load ischemic resistance exercise to failure enhances muscle oxygen delivery and endurance capacity. *Scand. J. Med. Sci. Sports* 21 (6), e231–e241. doi:10.1111/j.1600-0838.2010.01260.x

Keller, M., Faude, O., Gollhofer, A., and Centner, C. (2023). Can we make blood flow restriction training more accessible? Validity of a low-cost blood flow restriction device to estimate arterial occlusion pressure. *J. Strength Cond. Res.* doi:10.1519/JSC.0000000000004434

Królikowska, A., Kusienicka, K., Lazarek, E., Oleksy, Ł., Prill, R., Kołcz, A., et al. (2023). A randomized, double-blind placebo control study on the effect of a blood flow restriction by an inflatable cuff worn around the arm on the wrist joint position sense in healthy recreational athletes. *J. Clin. Med.* 12 (2), 602. doi:10.3390/jcm12020602

Kumar, K., Railton, C., and Tawfic, Q. (2016). Tourniquet application during anesthesia: "What we need to know?". *J. Anaesthesiol. Clin. Pharmacol.* 32 (4), 424–430. doi:10.4103/0970-9185.168174

Laurentino, G., Ugrinowitsch, C., Aihara, A. Y., Fernandes, A. R., Parcell, A. C., Ricard, M., et al. (2008). Effects of strength training and vascular occlusion. *Int. J. Sports Med.* 29 (8), 664–667. doi:10.1055/s-2007-989405

Laurentino, G. C., Loenneke, J. P., Teixeira, E. L., Nakajima, E., Iared, W., and Tricoli, V. (2016). The effect of cuff width on muscle adaptations after blood flow restriction training. *Med. Sci. Sports Exerc* 48 (5), 920–925. doi:10.1249/MSS.0000000000000833

Lixandrão, M. E., Ugrinowitsch, C., Berton, R., Vechin, F. C., Conceição, M. S., Damas, F., et al. (2018). Magnitude of muscle strength and mass adaptations between high-load resistance training versus low-load resistance training associated with blood-flow restriction: A systematic review and meta-analysis. *Sports Med.* 48, 361–378. doi:10.1007/s40279-017-0795-y

Loenneke, J. P., Allen, K. M., Mouser, J. G., Thiebaud, R. S., Kim, D., Abe, T., et al. (2015). Blood flow restriction in the upper and lower limbs is predicted by limb circumference and systolic blood pressure. *Eur. J. Appl. Physiol.* 115 (2), 397–405. doi:10.1007/s00421-014-3030-7

Loenneke, J. P., Fahs, C. A., Rossow, L. M., Sherk, V. D., Thiebaud, R. S., Abe, T., et al. (2012). Effects of cuff width on arterial occlusion: Implications for blood flow restricted exercise. *Eur. J. Appl. Physiol.* 112 (8), 2903–2912. doi:10.1007/s00421-011-2266-8

Loenneke, J. P., Thiebaud, R. S., Fahs, C. A., Rossow, L. M., Abe, T., and Bemben, M. G. (2013). Effect of cuff type on arterial occlusion. *Clin. Physiol. Funct. Imaging* 33 (4), 325–327. doi:10.1111/cpf.12035

MacDougall, J. D., Tuxen, D., Sale, D. G., Moroz, J. R., and Sutton, J. R. (1985). Arterial blood pressure response to heavy resistance exercise. *J. Appl. Physiol.* 58 (3), 785–790. doi:10.1152/jappl.1985.58.3.785

Machek, S. B., Harris, D. R., Zawieja, E. E., Heileson, J. L., Wilburn, D. T., Radziejewska, A., et al. (2022). The impacts of combined blood flow restriction training and betaine supplementation on one-leg press muscular endurance, exercise-associated lactate concentrations, serum metabolic biomarkers, and hypoxia-inducible factor-1α gene expression. *Nutrients* 14, 5040. doi:10.3390/nu14235040

McEwen, J. A. (1981). Complications of and improvements in pneumatic tourniquets used in surgery. *Med. Instrum.* 15 (4), 253–257.

McEwen, J. A., Jameson, M., and Glinz, K. L. (2015). Extendible tourniquet cuff with stabilizer for improved utility and safety. US Patent, 9011483. Available from: https://patents.google.com/patent/US9011483.

McEwen, J. A., Owens, J. G., and Jeyasurya, J. (2019). Why is it crucial to use personalized occlusion pressures in blood flow restriction (BFR) rehabilitation? *J. Med. Biol. Eng.* 39 (2), 173–177. doi:10.1007/s40846-018-0397-7

Mills, N., Elder, M., Boyce, M., Evdokas, M., and Ives, S. (2021). The knowledge and use of blood flow restriction therapy in a sample of physical therapists in the United States. *Res. Directs Health Sci.* 1 (1), 10422. doi:10.53520/rdhs2021.10422

Morehouse, H., Goble, H. M., Lambert, B. S., Cole, J., Holderread, B. M., Le, J. T., et al. (2021). Limb occlusion pressure versus standard pneumatic tourniquet pressure in open carpal tunnel surgery - a randomized trial. *Cureus* 13 (12), e20110. doi:10.7759/cureus.20110

Mouser, J. G., Dankel, S. J., Mattocks, K. T., Jessee, M. B., Buckner, S. L., Abe, T., et al. (2018). Blood flow restriction and cuff width: Effect on blood flow in the legs. *Clin. Physiol. Funct. Imaging* 38 (6), 944–948. doi:10.1111/cpf.12504

Murray, J., Bennett, H., Boyle, T., Williams, M., and Davison, K. (2021). Approaches to determining occlusion pressure for blood flow restricted exercise training: Systematic review. *J. Sports Sci.* 39 (6), 663–672. doi:10.1080/02640414.2020.1840734

Noordin, S., McEwen, J. A., Kragh, J. F., Eisen, A., and Masri, B. A. (2009). Surgical tourniquets in orthopaedics. *J. Bone Jt. Surg. Am.* 91 (12), 2958–2967. doi:10.2106/JBJS.I.00634

Patterson, S. D., Hughes, L., Warmington, S., Burr, J., Scott, B. R., Owens, J., et al. (2019). Blood flow restriction exercise position stand: Considerations of methodology, application, and safety. *Front. Physiology* 10, 533. doi:10.3389/fphys.2019.00533

Pedowitz, R. A., Gershuni, D. H., Botte, M. J., Kuiper, S., Rydevik, B. L., and Hargens, A. R. (1993). The use of lower tourniquet inflation pressures in extremity surgery facilitated by curved and wide tourniquets and an integrated cuff inflation system. *Clin. Orthop. Relat. Res.* 287 (287), 237–244. doi:10.1097/00003086-199302000-00038

Pignanelli, C., Petrick, H. L., Keyvani, F., Heigenhauser, G. J. F., Quadrilatero, J., Holloway, G. P., et al. (2020). Low-load resistance training to task failure with and without blood flow restriction: Muscular functional and structural adaptations. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 318 (2), R284–R295. doi:10.1152/ajpregu.00243.2019

Robergs, R. A., Ghiasvand, F., and Parker, D. (2004). Biochemistry of exercise-induced metabolic acidosis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 287 (3), R502–R516. doi:10.1152/ajpregu.00114.2004

Rolnick, N., Licameli, N., Moghaddam, M., Marquette, L., Walter, J., Fedorko, B., et al. (2023). Acute central stiffness and muscle morphological responses following blood flow restricted resistance exercise with autoregulated and non-autoregulated pressure application. arXiv. doi:10.51224/srxiv.253

Rossow, L. M., Fahs, C. A., Loenneke, J. P., Thiebaud, R. S., Sherk, V. D., Abe, T., et al. (2012). Cardiovascular and perceptual responses to blood-flow-restricted resistance exercise with differing restrictive cuffs. *Clin. Physiol. Funct. Imaging* 32 (5), 331–337. doi:10.1111/j.1475-097X.2012.01131.x

Sale, D. G., Moroz, D. E., McKelvie, R. S., MacDougall, J. D., and McCartney, N. (1994). Effect of training on the blood pressure response to weight lifting. *Can. J. Appl. Physiol.* 19 (1), 60–74. doi:10.1139/h94-004

Santos, W., Vieira, C. A., Bottaro, M., Nunes, V. A., Ramirez-Campillo, R., Steele, J., et al. (2021). Resistance training performed to failure or not to failure results in similar total volume, but with different fatigue and discomfort levels. *J. Strength Cond. Res.* 35 (5), 1372–1379. doi:10.1519/jsc.0000000000002915

Spitz, R. W., Bell, Z. W., Wong, V., Viana, R. B., Chatakondi, R. N., Abe, T., et al. (2020). The position of the cuff bladder has a large impact on the pressure needed for blood flow restriction. *Physiol. Meas.* 41 (1), 01NT01. doi:10.1088/1361-6579/ab64b8

Spranger, M. D., Krishnan, A. C., Levy, P. D., O'Leary, D. S., and Smith, S. A. (2015). Blood flow restriction training and the exercise pressor reflex: A call for concern. *Am. J. Physiology - Heart Circulatory Physiology* 309, H1440–H1452. doi:10.1152/ajpheart.00208.2015

Stray-Gundersen, S., Wooten, S., and Tanaka, H. (2020). Walking with leg blood flow restriction: Wide-rigid cuffs vs. Narrow-elastic bands. *Front. Physiol.* 11, 568. doi:10.3389/fphys.2020.00568

Teixeira, E. L., Barroso, R., Silva-Batista, C., Laurentino, G. C., Loenneke, J. P., Roschel, H., et al. (2018). Blood flow restriction increases metabolic stress but decreases muscle activation during high-load resistance exercise. *Muscle Nerve* 57 (1), 107–111. doi:10.1002/mus.25616

Tourniquet technology (2017). Tourniquets.org. 2017. Available from: https://tourniquets.org/tourniquet-cuff-technology/.

Wang, J., Fu, H., Qiang, Z., Zhang, M., and Fan, Y. (2022). Effect of leg half-squat training with blood flow restriction under different external loads on strength and vertical jumping performance in well-trained volleyball players. *Dose Response* 20 (3), 15593258221123673. doi:10.1177/15593258221123673

Weatherholt, A. M., Vanwye, W. R., Lohmann, J., and Owens, J. G. (2019). The effect of cuff width for determining limb occlusion pressure: A comparison of blood flow restriction devices. *Int. J. Exerc Sci.* 12 (3), 136–143.

Wilburn, D. T., Machek, S. B., Zechmann, B., and Willoughby, D. S. (2021). Comparison of skeletal muscle ultrastructural changes between normal and blood flow-restricted resistance exercise: A case report. *Exp. Physiol.* 106 (11), 2177–2184. doi:10.1113/EP089858

Wooten, S. V., Stray-Gundersen, S., and Tanaka, H. (2020). Hemodynamic and pressor responses to combination of yoga and blood flow restriction. *Int. J. Sports Med.* 41 (11), 759–765. doi:10.1055/a-1171-1620

Wooten, S. V., Wolf, J. S., Jr, Mendoza, D., Bartholomew, J. B., Stanforth, P. R., Stanforth, D., et al. (2022). The impact of a multimodal sport science-based prehabilitation program on clinical outcomes in abdominal cancer patients: A cohort study. *Am. Surg.* 88, 2302–2308. doi:10.1177/00031348221103657

Younger, A. S. E., McEwen, J. A., and Inkpen, K. (2004). Wide contoured thigh cuffs and automated limb occlusion measurement allow lower tourniquet pressures. *Clin. Orthop. Relat. Res.* 428 (428), 286–293. doi:10.1097/01.blo.0000142625.82654.b3