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Research

The Effect of Low-intensity Resistance Training Combined with Blood Flow Restriction on Triceps Brachii Muscle Volume, Strength, and Performance

Kan Akımı Kısıtlaması ile Kombine Düşük Yoğunluklu Dirençli Egzersiz Eğitiminin Triceps Brachii Kas Hacmi, Kuvveti ve Performansına Etkisi

Yunus Emre Tütüneken[1,2], Emre Serdar Atalay[3], Yasemin Buran Çırak[2], Kadriye Öneş[4], Türker Şahinkaya[5], Bülent Bayraktar[5]

[1]University of Health Sciences Türkiye, Hamidiye Institute of Health Sciences, Department of Physiotherapy and Rehabilitation, İstanbul, Türkiye
[2]İstinye University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, İstinye University, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Gülhane Faculty of Physiotherapy and Rehabilitation, Department of Orthopedic Physiotherapy and Rehabilitation, Ankara, Türkiye
[4]University of Health Sciences Türkiye, İstanbul Physical Therapy Rehabilitation Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Türkiye
[5]İstanbul University, İstanbul Faculty of Medicine, Department of Sports Medicine, İstanbul, Türkiye

ABSTRACT

Objective: To compare the effects of low-intensity resistance training with blood flow restriction (LRT-BFR) and high-intensity resistance training (HI-RT) on triceps brachii muscle thickness and muscle strength, functional performance, and delayed-onset muscle soreness (DOMS).

Methods: Thirteen sedentary women performed two unilateral exercise protocols three days a week for six weeks. Participants were randomly divided into two groups according to exercise protocols. One group of participants performed LRT-BFR while the other performed HI-RT. The LRT-BFR group performed four sets [20-30% of 1 repetition maximum (1RM)]; and the HI-RT group performed three sets, 70-80% of 1RM. The two exercise protocols were performed in different sessions on the same day. Triceps brachii muscle thickness, triceps brachii, and biceps brachii muscle strength, upper extremity functional performance, and DOMS were evaluated before and after training.

Results: A statistically similar increase was observed in muscle thickness and strength (60°xs^{-1}), after exercise in both groups ($p<0.05$) but a greater increase in muscle strength (180°xs^{-1}) was obtained in the LRT-BFR group ($p<0.05$). There is no statistical difference between the groups for the upper-quarter Y balance test score and DOMS ($p<0.05$).

Conclusion: LRT-BFR had similar effects as HI-RT on muscle thickness and strength, functional performance, and DOMS. Where HI-RT cannot be used, we LRT-BFR is a viable alternative.

Keywords: Blood flow restriction, delayed onset muscle soreness, muscle strength, resistance exercise training, sedentary

ÖZ

Amaç: Bu çalışmanın amacı, kan akımı kısıtlamalı düşük yoğunluklu direnç eğitimi (KAK-DYDE) ile yüksek yoğunluklu direnç eğitiminin (YYDE) triceps brachii kas kalınlığı ve kuvveti, fonksiyonel performans ve gecikmiş başlangıçlı kas ağrısı (GKA) üzerine etkilerini karşılaştırmaktır.

Gereç ve Yöntem: On üç sedanter kadın, 6 hafta boyunca haftada 3 gün, iki farklı egzersiz protokolünü tek taraflı olarak uyguladı. Katılımcıların kolları egzersiz protokollerine göre rastgele iki gruba ayrıldı. Katılımcılar bir kolu ile KAK-DYDE gerçekleştirirken diğer kolu YYDE gerçekleştirdi. KAK-DYDE grubu 1 maksimum tekrarın %20-30'u (1RM) olmak üzere dört set; YYDE grubu 1RM'nin %70-80'i olmak üzere üç set olarak egzersizi uyguladı. İki egzersiz protokolü aynı gün farklı seanslarda gerçekleştirildi. Triceps brachii kas kalınlığı, triceps brachii ve biceps brachii kas kuvveti, üst ekstremite fonksiyonel performansı ve GKA eğitim öncesi ve sonrası değerlendirildi.

Address for Correspondence: Yunus Emre Tütüneken MD, İstinye University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, İstanbul, Türkiye
E-mail: emre.tutuneken@gmail.com **ORCID ID:** orcid.org/0000-0003-4080-5105

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ÖZ

Bulgular: Her iki grupta da egzersiz sonrası kas kalınlığında ve kuvvetinde (60°xs^{-1}) istatistiksel olarak benzer artış gözlendi (p<0,05), ancak KAK-DYDE grubunda kas dayanıklılığında (180°xs^{-1}) daha fazla artış elde edildi (p<0,05). Üst ekstremite Y denge testi puanı ve GKA açısından gruplar arasında istatistiksel anlamlı fark yoktur (p<0,05).

Sonuç: KAK-DYDE'nin kas kalınlığı ve kuvveti, fonksiyonel performans ve GKA üzerinde YYDE ile benzer etkilere sahip olduğunu bulduk. YYDE'nin kullanılamadığı durumlarda KAK-DYDE'nin alternatif olduğuna inanıyoruz.

Anahtar Kelimeler: Kan akımı kısıtlaması, gecikmiş başlangıçlı kas ağrısı, kas kuvveti, dirençli egzersiz eğitimi, sedanter

INTRODUCTION

Resistance training (RT) increases muscle strength and hypertrophy (1). These gains can positively impact daily physical functioning and significantly improve health, wellness, and sports performance (2).

The manipulation of RT variables such as frequency, rest interval, volume, and intensity are essential strategies to maximize exercise-induced muscular adaptations (3). Relating to intensity, RT with loads equating to 60-80% of maximum dynamic strength (1RM) has been recommended to achieve the greatest strength and muscle mass improvement (4). High-intensity resistance training (HI-RT) performed without proper supervision to achieve muscle adaptations may be impractical and dangerous (5).

In physically inactive individuals, HI-RT may increase the risk of injury and cause unusual exercise-induced pain, muscle soreness, and musculoskeletal injury (6). One study showed that HI-RT decreased central arterial compliance (7). Low arterial compliance increases the risk of coronary heart disease and systolic blood pressure, while reducing arterial baroreflex sensitivity (8,9). Thus, safe and effective methods should be developed to increase muscle volume and strength. Low-intensity RT with blood flow restriction (LRT-BFR) may be an alternative to HI-RT (10). Alternatively, when high-intensity activity is not feasible for sedentary individuals to maximize hypertrophy and strength, LRT-BFR can be used.

The literature reports conflicting results in studies comparing HI-RT and LRT-BFR. Several studies have shown that HI-RT promotes greater gain in muscle strength compared with LRT-BFR (5,10), but Takarada et al. (11) found that BFR training resulted in an increase in muscle strength comparable to HI-RT and showed significant increases in muscle hypertrophy. Yasuda et al. (5) and Vechin et al. (10) demonstrated that both HI-RT and LRT-BFR training induce increased muscle size. Meanwhile, studies investigating the effect of RT-BFR on delayed onset muscle soreness (DOMS) remain scarce; and while there are studies in the literature evaluating the immediate effects of LRT-BFR on DOMS, no long-term follow-up studies have been found. Alvarez et al. (12) found higher DOMS in LRT-BFR than in HI-RT. Another study reported the opposite result (13). Finally, no study has investigated the effects of LRT-BFR on upper limb functional performance.

This study compared the effects of LRT-BFR and HRT on triceps brachii muscle thickness (MT), strength, functional performance, and DOMS in young sedentary women.

METHODS

A prospective, randomized, controlled, single-blind study was conducted. To compare the effects of LRT-BFR and traditional RT on triceps brachii muscle strength, thickness, functional performance, and DOMS, a within-participants design was adopted. One arm of each participant (dominant or non-dominant) performed the exercise with cuff occlusion, while the other arm performed the exercise without occlusion. The arm condition of participants (with or without cuff occlusion) was randomized using a table created by a web-based computer program.

Triceps brachii MT [assessed by ultrasound (US)], muscle strength (assessed by isokinetic dynamometer), and functional performance [assessed by the upper quarter Y-balance test (the UQYBT)] were evaluated before the training program (Pre) and after the 6-week training period (Post) (Figure 1). DOMS was assessed after each training session. The Physical Activity Readiness Questionnaire for Everyone suggested by the American College of Sports Medicine was used for each participant's health screening before exercise was initiated (14).

Thirteen sedentary young women (age, 25.15±1.95 years; height, 162.62±5.56 cm; weight, 55.92±11.62 kg) were divided into the LRT-BFR and HI-RT groups (Figure 2). The number of arms was 26 (13 pairs).

The inclusion criteria were as follows: Eligibility to start an exercise program, normotension (blood pressure <135/85 mmHg), no tobacco use, and normal weight (body mass index <30 kg/m^2). The exclusion criteria included: Chronic disease (e.g., diabetes mellitus and uncontrolled hypertension), deep vein thrombosis, peripheral vascular disease, congenital heart disease, thromboembolism risk

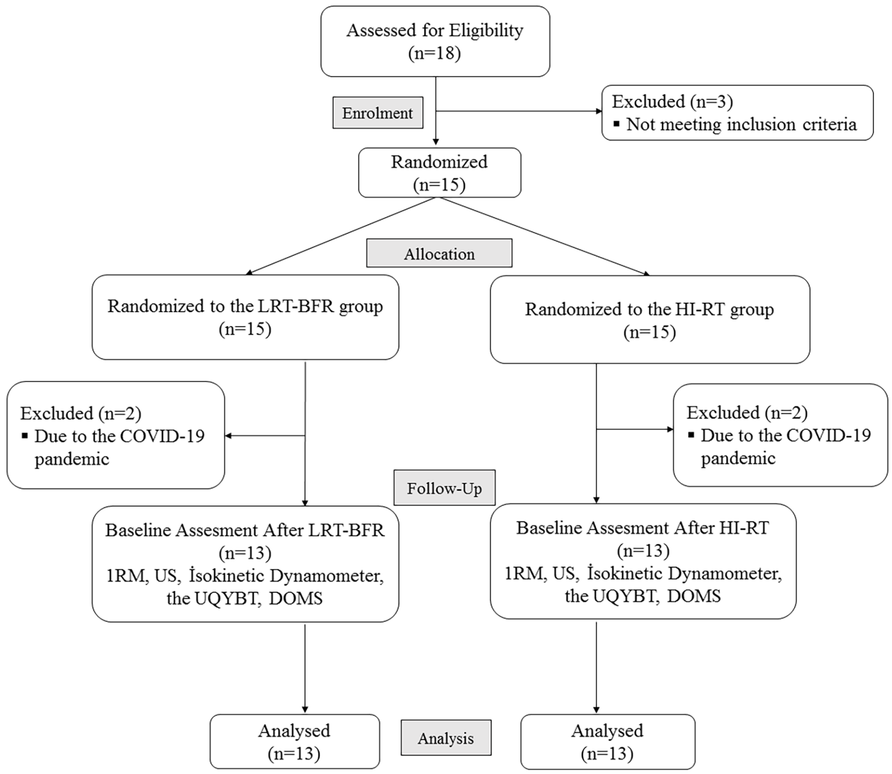

Figure 1. Study flowchart
LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training, UQYBT: Upper quarter Y-balance test, US: Ultrasound, RM: Repetition maximum, DOMS: Delayed-onset muscle soreness

factors, history of orthopedic upper extremity surgery, and medication.

Ethical approval was obtained from the University of Health Sciences Türkiye, Hamidiye Non-Interventional Research Ethics Committee (decision number: 19/138, date: 08.11.2019). Participants were informed about the benefits and risks of the study before data collection began, and informed consent was obtained. The study was performed in accordance with the Declaration of Helsinki on good clinical practice.

All participants were familiarized with the strength testing and training apparatus before the commencement of the evaluation. Following a familiarization session, the participant's medical condition was screened. Both training groups performed a supervised free-weight elbow extension exercise 3 days/week for 6 weeks, and all participants performed strengthening exercise protocols unilaterally with the dominant and nondominant arm. In the LRT-BFR group, participants performed low-intensity exercises with 20-30% of 1RM and 75 repetitions unilaterally (4 sets of 30-15-15-15 repetitions, with 30-second of rest between sets) while wearing an elastic cuff to restrict blood flow at the most proximal arm region. The HI-RT group completed the high-intensity exercise with 70-80% of 1RM and 30 repetitions

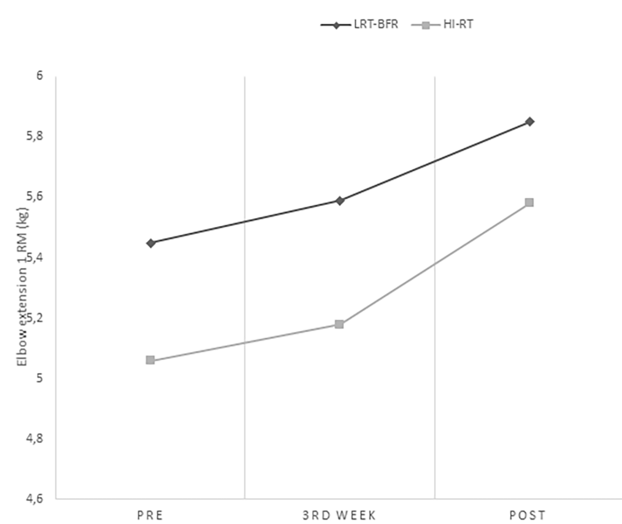

Figure 2. Muscle thickness (MT) of the triceps brachii after a 6-week training period. Data are presented as the mean ± standard deviation
LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training, RM: Repetition maximum

3 sets of 10 repetitions, with 2-3 minutes of rest between sets (5). The "triceps extension-hand behind head" exercise with a dumbbell was used as the resistance exercise in this study. Participants stood with their feet shoulder width

Figure 3. Triceps extension resistance exercise

apart. They held a dumbbell behind their necks (Figure 3). Each participant was then instructed to extend their elbow concentrically (for 2-second), and then eccentrically (for 2-second) (15).

Before the training period, the BFR pressure was determined. After 15 min of rest in the seated position, an 8-cm-wide cuff was placed at the most proximal arm region and inflated until pulse absence was observed through auscultation with a vascular Doppler probe [Sonoline B cep doppler (8 Mhz)] over the radial artery. The occlusion pressure was adjusted to 70% of the maximum radial artery pressure throughout the BFR training session. The restriction pressure was determined based on previous studies (16,17). The participants did not complain of any discomfort or pain during the training.

1RM strength of elbow extension was assessed using a free-weight. Brzycki's formula was used to predict (18). The 1RM strength was assessed before the onset of training and after the 3rd and 6th week of training to adjust the training load for the LRT-BFR and HI-RT exercise sessions.

The researcher measured the triceps brachii MT using B-mode US (Esaote mylab 70 XVISION, Genua, Italy) and a 7.5-MHz linear array transducer (Esaote MyLab™ ClassC®). The probe was placed mediolaterally and transversely on the muscle. After the US images were obtained, MT, defined as the distance from the adipose tissue-muscle interface of the triceps brachii interface, was measured. The examiner abstained from compressing the muscle during the measurements. Two measurements were performed at each region, and mean values were used. The length of the upper arm was defined as the distance between the scapula acromion and the humerus lateral epicondyle. After determining the proximal 70%, 60%, and 50% points along the upper arm length, the MT was measured in these areas (MT70, MT60, and MT50). The upper arm MT was performed while participants stood with their arms relaxed at their sides and their forearms pronated (15).

İsokinetic testing of the triceps brachii and biceps brachii muscles was conducted bilaterally at angular velocities of $60°xs^{-1}$ and $180°xs^{-1}$ using an isokinetic dynamometer (CSMI Cybex Humac Norm, USA) with standard elbow attachments. To minimize extraneous body movements, participants were positioned supine. The lateral epicondyle of the humerus was aligned to the dynamometer's lever arm's center of motion. The participant's measured arm was positioned in full extension parallel to the participant's sides, while the participant's hand on the remaining arm was placed on the chest. The forearm was pronated during the test. The elbow joint range of motion was maintained at 0°-150°. For the peak torque/body mass ($Nm \cdot kg^{-1}$) assessment, participants performed 4 repetitions at $60°xs^{-1}$. Without rest, participants performed 20 repetitions at $180°xs^{-1}$ for the measurement of total work.

The UQYBT was performed to assess the dynamic balance and stability of the upper limbs. A modified UQYBT kit produced using athletic tape was used. To determine the testing directions of the modified UQYBT kit, a line of tape was used to mark one line for the medial direction. The superolateral (SL) and inferolateral (IL) directions were determined 135° from the medial line. Participants first placed their dominant hand at the intersection of the directions and assumed a push-up position, then sequentially touched the furthest point in the medial, SL, and IL directions with their free hand. After three practice trials, the participants took 2 min to rest and completed 3 more trials for the record. The reached points were recorded and directions' average distances (measured in centimeters) were computed. There was a 15-s break between trials. The trial was renewed if the participant could not hold the position and used their free hand to touch the ground (19,20).

DOMS was assessed before exercise and 12 and 24 hours after exercise using a 10-cm visual analog scale (0 cm: No pain, 10 cm: A lot of pain) over 6 weeks. Participants marked their perceived pain on a scale after each exercise, and the researcher measured the distances between each mark (21).

Statistical Analysis

The SPSS 22.0 statistical package (SPSS Inc., USA) was used for all statistical analyses. Kolmogorov-Smirnov/Shapiro-Wilk test was used to investigate the normal distribution of the continuous variables. Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as percentage (%) and the number of patients. The chi-square test was used to determine differences in nominal variables between groups. Between-group comparison used the Student's t-test for normally distributed data. For the within-group comparisons, a paired samples t-test was used. Mann-Whitney U/Wilcoxon tests were used for data that were not normally distributed. Repeated measures analysis of covariance for the interaction effect between group and time. The effect size of the difference between the groups' means was calculated using Cohen's d and classified as small effect (0.20≤d<0.50), medium effect (0.50≤d<0.80), and large effect (d≥0.80). P<0.05 was regarded as statistically significant (22).

The G*Power 3.0.10 software was used to calculate the sample size. Based on the medium effect size (0.50) and when the bidirectional hypothesis is established for F-tests-ANOVA: Repeated measures, between factors, we estimated that a sample size of 13 upper extremity in each group would have a power of 80% to detect differences between groups with 5% error.

RESULTS

1RM values for elbow extension were increased for both the LRT-BFR group (pre: 5.45±1.06 kg, post: 5.85±1.16 kg, p<0.001) and the HI-RT group (pre: 5.06±1.05 kg, post: 5.58±1.08 kg, p<0.001). Both groups showed similar increments in 1RM values for elbow extension from the pre-training, 3rd week and post-training tests.

Both groups showed significant changes in MT after training in all regions. The LRT-BFR group exhibited a significant difference in MT50 (p<0.01), MT60 (p<0.001) and MT70 (p<0.001). The HI-RT group exhibited significant differences in MT50 (p<0.01), MT60 (p<0.001) and MT70 (p<0.01). Overall, the increment in MT was similar between the groups (p>0.05) (Table 1 and Figure 4).

The change in extension and flexion muscle strength values (60°xs^{-1}) between the groups was similar (p>0.05).

Table 1. Comparison of muscle thickness between the groups

	LRT-BFR group (n=13)			HI-RT group (n=13)				
Muscle thickness (cm)	**Pre mean±SD**	**Post mean±SD**	**Within group p-value**	**Pre mean±SD**	**Post mean±SD**	**Within group p-value**	**Treatment affect p-value**	**Cohen's d**
MT50	11.36±2.96	13.90±4.26	**<0.01***	11.73±3.19	14.08±4.02	**<0.01***	0.835	0.544
MT60	15.55±4.20	18.46±5.04	**<0.001****	15.58±3.57	18.70±4.92	**<0.001****	0.829	0.608
MT70	17.97±4.45	21.25±5.20	**<0.001****	18.65±4.24	22.06±5.30	**<0.01***	0.898	0.622

*p<0.01; **p<0.001. Statistically significant values are given by.
cm: Centimeter, LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training, MT: Muscle thickness, SD: Standard deviation

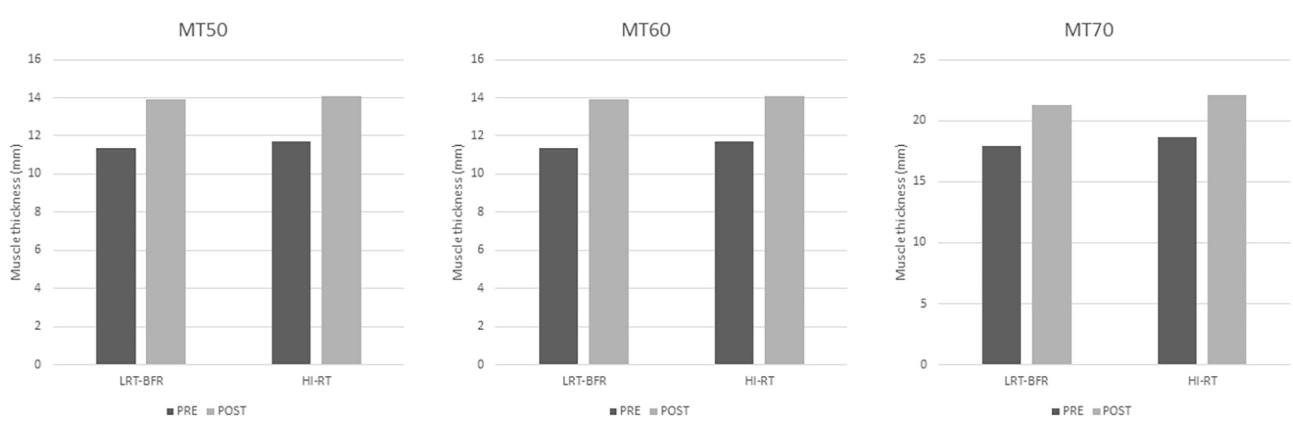

Figure 4. Muscle thickness (MT) of the triceps brachii after a 6-week training period. Data are presented as the mean ± standard deviation
LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training, MT: Muscle thickness

Table 2. Comparison of muscle strength between the groups

Peak torque ($Nm \cdot kg^{-1}$)	LRT-BFR group (n=13) Pre mean±SD	Post mean±SD	Mean difference 95% CI	Within group p-value	HI-RT Group (n=13) Pre mean±SD	Post mean±SD	Mean difference (CI) 95%	Within group p-value	Treatment affect p-value	Cohen's d
Extension										
$60°xs^{-1}$	13.53±2.90	19.53±4.96	4.01-7.99	**<0.001****	14.15±3.60	20.23±4.38	3.76-8.37	**<0.001****	0.562	0.799
$180°xs^{-1}$	185.61±104.67	367.30±159.02	128.39-234.98	**<0.001****	218.23±113.23	353.53±182.98	65.31-205.28	**<0.001****	**<0.001****	0.699
Flexion										
$60°xs^{-1}$	16.07±2.39	21.07±3.66	3.22-6.78	**<0.001****	15.53±3.38	19.38±6.30	2.71-7.88	**0.090**	0.744	0.674
$180°xs^{-1}$	190.53±102.19	350.23±134.43	110.04-209.33	**<0.001****	214.07±118.23	374.61±158.67	95.47-225.58	**<0.001****	0.956	0.638

*p<0.05, **p<0.001. Statistically significant values are given by.
LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training, CI: Confidence interval, Nm: Newton meter, SD: Standard deviation

However, the change in extension muscle strength values ($180°xs^{-1}$) was greater in the LRT-BFR group than in the HI-RT group (p<0.001) (Table 2).

Although significant differences were observed for the MR (LRT-BFR group's p<0.05; HI-RT group's p<0.01) and SLR (LRT-BFR group's p<0.01; HI-RT group's p<0.01), ILR (LRT-BFR group's p<0.01; HI-RT group's p<0.001), and composite score (LRT-BFR group's p<0.01; HI-RT group's p<0.001) on average, there were no significant differences for all directions and composite score between the groups after the training (Figure 5).

Before and after exercise, there was a significant reduction in DOMs in both groups (p<0.001). However, the changes in DOM values were not significantly different between the HI-RT and LRT-BFR group (p>0.05) (Figure 6).

DISCUSSION

Our study showed that LRT-BFR and HI-RT promoted increases in 1RM, with both protocols equally effective in inducing increases in triceps brachii muscle strength and thickness. However, differences in muscle endurance gains between the groups were associated with the LRT-BFR group. Upper limb functional performance increased in both groups. Both training protocols induced similar DOMS levels, although their magnitudes were low. Our study demonstrates LRT-BFR's effect on upper limb functional performance and, long term, DOMS. To the best of our knowledge, this is the first study to compare the effectiveness of LRT-BFR and HI-RT on upper limb functional performance and DOMS in young women.

Vechin et al. (10) found that both LRT-BFR and HI-RT were effective in increasing 1RM but stated that HI-RT training induced greater strength gains similarly. Yasuda et al. (5) reported that the change in 1RM strength was greater in the HI-RT group than in the LRT-BFR. We found that both the HI-RT and LRT-BFR groups showed improvements in elbow extension 1RM strength. Laurentino et al. (16) concluded that LRT-BFR was able to induce gains in 1RM like HI-RT. Our study showed that LRT-BFR training and HI-RT training produce similar increases in elbow extension 1RM strength.

Studies investigating the effects of BFR training on muscle hypertrophy are consistent. In a study comparing the effects of traditional RT and LRT-BFR, Korkmaz et al. (24) noted that MT increased more in the BFR group. Yasuda et al. (23) also observed BFR-induced increases in MT in a study utilizing the same intensity and duration of exercise. Another study by the same researcher reported muscle hypertrophy of similar magnitude achieved by HI-RT and LRT-BFR training

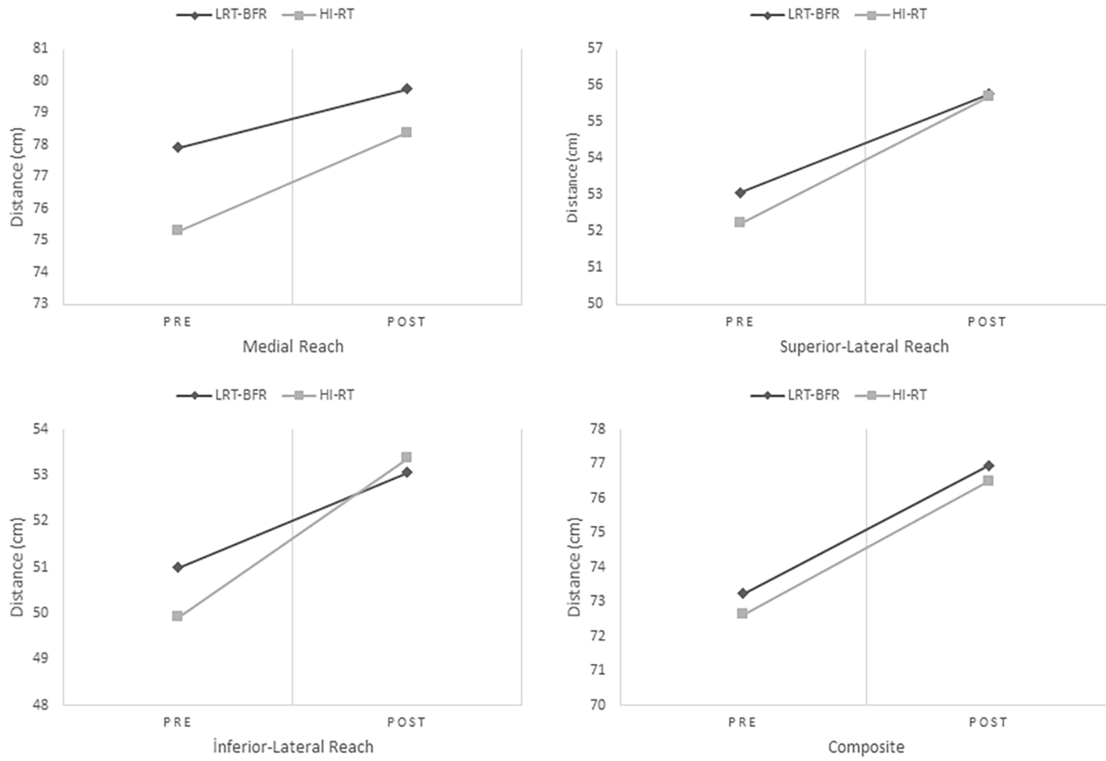

Figure 5. Comparison of the upper-quarter Y balance test (UQYBT) scores between LRT-BFR and HI-RT
LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training

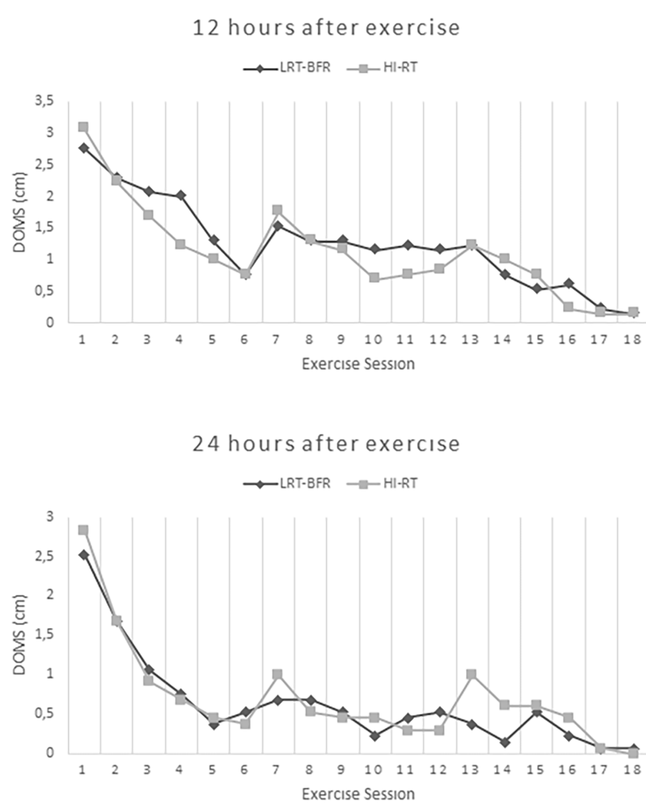

Figure 6. Delayed-onset muscle soreness (DOMS) 12 and 24 hours after resistance training
LRT-BFR: Low-intensity resistance training with blood flow restriction, HI-RT: High-intensity resistance training

(5). Our study showed that LRT-BFR produces a similar magnitude of MT increase as that reported in previous studies. Studies have reported that LRT-BFR and HI-RT muscle synthesis enhances muscle protein synthesis through the mTOR pathway (25,26). An increase in protein synthesis was detected even after a single session (5). These similar anabolic responses may induce similar increases in muscle hypertrophy in both the LI-BFR and control groups.

There are differences in the results of studies investigating the effect of BFR on strength. Most studies have reported that traditional RT causes greater increases in muscle strength. Yasuda et al. (5) demonstrated that HI-RT training induced greater improvements in elbow extension than LRT-BFR training. Another study investigating the long-term effects of LRT-BFR found that LRT-BFR was comparable to HI-RT in increasing elbow flexor muscle strength (11). Unlike several studies in the literature, Korkmaz et al. (24) found that LRT-BFR training increased muscle strength more than traditional RT. Our results showed that in the LRT-BFR group, triceps brachii muscle strength at an angular velocity of 60°xs^{-1} increase comparably to that in the HI-RT group. However, muscle strength improved more in the LRT-BFR group at an angular velocity of 180°s^{-1} than in the HI-RT group. Loads of 45-50% 1RM are required to increase the strength of untrained individuals (2). Thus, muscle strength changes due to LRT-BFR are thought to result from muscle hypertrophy, unlike HI-RT training (5).

Other than our study, no study on BFR training has investigated the effect of LI-BFR on upper extremity performance. Although BFR training is known to be an effective method for increasing muscle strength and volume, its effects on balance and postural control are unknown. Evaluating upper extremity performance using the UQYBT revealed no difference between limbs. However, there was improvement in all directions, and the total score increased for both limbs after training.

No study has investigated the effect of long-term LI-BFR on DOMS. Alvarez et al. (12) compared the effects of a single session of HI-RT and LI-BFR on muscle damage. They found that DOMS increased after LI-BFR. In their study, Wernbom et al. (13) reported that DOMS values were significantly greater in the non-occluded limb. Our results showed that both 6-week training protocols induced similar DOMS levels. DOMS values decreased as the sessions progressed in both groups. The results of DOMS studies in the literature are contradictory. The greater magnitude of DOMS in the occluded limb can be explained by the higher number of completed repetitions. Another underlying cause of the DOMS may be the ischemia-reperfusion and the formation of reactive oxygen species during exercise (27,28). In addition, the relatively high activation increase observed during eccentric phases can induce DOMS (13). The differences in the results of the studies may be due to differences in exercise volume, BFR pressure, cuff width, and limb type.

Study Limitations

That this study is controlled and randomized is one of its strengths. Another limitation of this study was that we used an individualized occlusion pressure prescription while applying BFR. Nevertheless, our study has limitations. First, our study group consists of sedentary young women; these effects should be investigated in different age groups and in women and men. Second, we did not use a pneumatic cuff system was not used, so that the occlusion pressure specific to the participant may not have been maintained during exercise.

CONCLUSION

We found that LRT-BFR had similar effects on improving muscle strength, muscle endurance, muscle volume, performance, and delayed onset muscle soreness compared to HI-RT. While muscle strength and endurance increased after both training sessions, a greater increase was obtained in the coronary artery calcification group. While similar increases were observed in muscle volume after both training sessions, this increase was similar in both groups. According to these results, we can say that RT-BFR was effective in inducing hypertrophy despite the low intensity. When we looked at the upper extremity performance evaluation results, we saw that the increase rate was similar in both training. When we compared the groups in terms of DOMS, the pain intensity after both exercise protocols was similar. In addition, the pain intensity decreased as the sessions progressed in both groups. Based on these results, we believe that LRT-BFR can be a suitable alternative in cases where HI-RT cannot be used.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Hamidiye Non-Interventional Research Ethics Committee (decision number: 19/138, date: 08.11.2019).

Informed Consent: Participants were informed about the benefits and risks of the study before data collection began, and informed consent was obtained.

FOOTNOTES

Authorship Contributions

Concept: Y.E.T., E.S.A., Y.B.Ç., Design: Y.E.T., E.S.A., Y.B.Ç., Data Collection or Processing: Y.E.T., E.S.A., K.Ö., T. Ş., Analysis or Interpretation: Y.B.Ç., Literature Search: Y.E.T., E.S.A., Writing: Y.E.T., E.S.A., Y.B.Ç., K.Ö., T. Ş., B.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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