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Muscular adaptations to fatiguing exercise with and without blood flow restriction

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Summary

The purpose of this study was to determine the muscular adaptations to low-load resistance training performed to fatigue with and without blood flow restriction (BFR). Middle-aged (42–62 years) men ($n = 12$) and women ($n = 6$) completed 18 sessions of unilateral knee extensor resistance training to volitional fatigue over 6 weeks. One limb trained under BFR, and the contralateral limb trained without BFR [free flow (FF)]. Before and after the training, measures of anterior and lateral quadriceps muscle thickness (MTh), strength, power and endurance were assessed on each limb. The total exercise training volume was significantly greater for the FF limb compared with the BFR limb ($P<0{\cdot}001$). Anterior quadriceps thickness and muscle function increased following the training in each limb with no differences between limbs. Lateral quadriceps MTh increased significantly more ($P<0{\cdot}05$) in the limb trained under BFR (BFR: 3·50 ± 0·61 to 3·67 ± 0·62 cm; FF: 3·49 ± 0·73 to 3·56 ± 0·70 cm). Low-load resistance training to volitional fatigue both with and without BFR is viable options for improving muscle function in middle-aged individuals. However, BFR enhanced the hypertrophic effect of low-load training and reduced the volume of exercise needed to elicit increases in muscle function.

Introduction

Low-load (20–50% 1RM) resistance training with blood flow restriction (BFR) enhances muscle size and function in a variety of populations (Takarada *et al.*, 2000, 2002; Patterson & Ferguson, 2010, 2011). In contrast, low-load resistance training without BFR minimally affects muscle size and function (Loenneke *et al.*, 2012b). However, when exercise is performed to volitional fatigue, low-load (30% 1RM) knee extensor training elicits substantial increases in both quadriceps muscle size and strength, resulting in increases in muscle cross-sectional area and isometric strength comparable to high-load (80% 1RM) training (Mitchell *et al.*, 2012). Most of the literature examining the adaptations to BFR resistance training has compared BFR resistance training to volume-matched low-load resistance training or to high-load traditional training programmes. Some studies (Takarada *et al.*, 2000, 2002; Patterson & Ferguson, 2010, 2011; Kacin & Strazar, 2011) have examined the adaptations to BFR resistance training to fatigue but only in comparison with volume-matched low-load resistance training; these studies have observed greater adaptations to low-load resistance training with BFR. It is unclear whether low-load resistance exercise elicits greater muscular adaptations as does BFR resistance exercise when both are performed to volitional fatigue.

Although the effects of BFR resistance training on muscle mass and strength are well characterised, fewer studies have examined how this type of training may affect muscular power or endurance. Muscular power and endurance are two important components of muscular fitness, and considerations for these attributes are made in resistance training recommendations (Ratamess *et al.*, 2009). Maintaining muscular power with age becomes important as muscular power declines rapidly and is related to mobility and the ability to perform activities of daily living in older adults (Bean *et al.*, 2002). A minimum level of muscular endurance may also be necessary to perform activities of daily living. BFR resistance training improves muscular endurance in young athletes compared with volume-matched low-load resistance training (Takarada *et al.*, 2002). Moreover, BFR resistance training may also improve muscular power in young individuals (Abe *et al.*, 2005a). However, studies characterising the effectiveness of BFR resistance training on muscular power and endurance in middle-aged or older adults are lacking. Therefore, the purpose of this study was to determine the muscular [muscle thickness (MTh), strength, power and endurance] adaptations to low-load fatiguing resistance training with and without BFR in middle-aged individuals. We chose to study middle-aged individuals because low-load resistance training may be especially beneficial for such individuals with arthritis or orthopaedic problems who are unable to perform high-load resistance training. Additionally, we examined muscle activation during exercise and acute MTh changes after exercise as possible mechanisms to explain training induces changes in muscle size. We hypothesised that BFR training to fatigue would result in greater increases in muscular endurance and hypertrophy than low-load training to fatigue without BFR, whereas similar increases in muscular strength and power would be observed. In addition, we hypothesised that BFR exercise would elicit greater activation in the quadriceps muscle during exercise and cause greater acute changes in MTh following exercise.

Methods

Participants

Twenty-two individuals (14 men and eight women) aged 40–64 years were recruited to participate in this study. *A priori* sample size estimation indicated that 14 participants would be needed to detect a limb × time interaction for measures of MTh with an effect size of 0·25, alpha level of 0·05, and a power of 0·80. All participants provided written informed consent to participate, and this study was approved by the Institutional Review Board. Participants did not smoke, did not have any orthopaedic problems preventing strength testing or training, were not currently resistance training (or within last 6 months), had a brachial BP $\leq$140/90 mmHg, had an ankle–brachial index $\geq$0·90, had no more than one risk factor for thromboembolism (e.g. obese, Crohn's syndrome, fracture of hip, pelvis, or femur, major surgery, varicose veins, history of deep vein thrombosis), were free of overt disease as assessed by a health history questionnaire and obtained medical clearance from their primary care physician to participate. Of the 22 individuals recruited, 18 individuals (12 men, six women) completed the entire study protocol (Table 1). Two men were excluded because they could not obtain physician clearance; one woman dropped out after the initial screening visit due to an unexpected surgical procedure (unrelated to the study) and one woman dropped out during the intervention due to personal reasons.

Experimental design

Participants visited the laboratory for a screening visit and familiarisation visit followed by three testing sessions and 18 exercise training sessions. One limb was randomly assigned to exercise under BFR, while the contralateral limb performed the same exercise without BFR (free flow, FF).

Screening visit

Each participant completed a health history questionnaire which included an assessment of how frequently (hours per week) they engaged in aerobic activity during the past 6 months and a physical activity readiness questionnaire. During this visit, standing height and body mass were measured followed by measurement of the ankle–brachial index to screen for peripheral arterial disease.

Familiarisation visit

During this visit, arterial occlusion pressure (AOP) was determined on the BFR limb as previously described (Loenneke *et al.*, 2012a). The BFR cuff (5 cm wide; KaatsuMaster-mini, Sato Sports Plaza, Tokyo, Japan) was applied with an initial pressure of 25 mmHg and then inflated to 120 mmHg for 30 s and then deflated as a Doppler probe (MD6 Bidirectional Doppler; D.E. Hokanon Inc., Bellevue, WA, USA) was used to detect arterial flow in the posterior tibial artery. The cuff pressure was then incrementally increased until arterial flow was not detectable or until 300 mmHg was reached. AOP was recorded, to the nearest 10 mmHg, as the lowest cuff pressure at which arterial flow was absent. If arterial occlusion did not occur at 300 mmHg pressure, AOP was recorded as 300+ mmHg. Determination of AOP was used to prescribe

Table 1 Participant characteristics at enrolment.

	Men ***n* = 12**	**Women** ***n* = 6**	**Total** ***N* = 18**	**Range** **Min-Max**
Age (years)	54 (8)	58 (5)	55 (7)	42–62
Height (m)	1·81 (0·06)	1·65 (0·07)*	1·76 (0·10)	1·50–1·91
Body Mass (kg)	86·1 (14·1)	76·1 (20·1)	82·7 (16·5)	55·8–120·6
BMI (kg m^{-2})	26·2 (4·3)	27·6 (5·7)	26·7 (4·7)	20·4–36·1
Aerobic activity (hours per week)	2·4 (1·9)	2·2 (2·4)	2·3 (2·0)	0–6·5

Data presented as mean (SD).
BMI, body mass index; Min, minimum; Max, maximum.
*$P<0{\cdot}05$ from Men.

the cuff pressure and to ensure that the complete arterial occlusion would not occur during training. Participants were also familiarised with the knee extension machine (NT 1220; Nautilus, Louisville, CO, USA) at this time; this included familiarisation with the strength testing and power testing procedures and with the cadence of the metronome used for the exercise training.

Testing visits

Participants returned to the laboratory on three occasions for measurements of body mass, quadriceps MTh and function (strength, power and endurance). The first two testing sessions (Pre-1 and Pre-2) were separated by 3 weeks and used as a within-subject time control period to assess reliability of muscle size and function measurements. The time control period was shorter than the training intervention to help maintain participant retention in the study and for ease of scheduling. Quadriceps muscle strength was also assessed immediately before the ninth training session (mid-training, Mid). The final testing session (Post) took place between 48 and 96 h following the last training session (Post). All measurements were performed on the right side of the body first. As the BFR and FF assignment was randomized between the right and left limbs, this ensured that the testing order was randomized between the BFR and FF limbs. Participants were instructed to avoid caffeine (minimum 4 h), food (minimum 3 h) and strenuous activity (minimum 24 h) before all testing visits. All testing sessions took place at the same time of day.

Quadriceps muscle thickness

B-mode ultrasound was used to measure quadriceps MTh. Ultrasound MTh measurements of the quadriceps are highly correlated with measurement of quadriceps cross-sectional area assessed by MRI (Abe *et al.*, 1997). Measurements were obtained at six anatomical sites on each thigh: on the lateral (LT) and anterior (AT) surface of the thigh at distance of 40% (40), 50% (50) and 60% (60) between the lateral epicondyle of the femur and the greater trochanter. Distances between bony landmarks were measured with a tape measure and marked with a pen. All ultrasound measurements were made using a Fukuda Denshi UF-750XT (Tokyo, Japan) ultrasound unit and a linear probe with a frequency of 6 MHz, and the depth and gain adjusted to optimise the image. The probe was coated with transmission gel and placed perpendicular to the tissue surface at the marked sites without depressing the skin. MTh was determined as the distance from the adipose tissue–muscle interface to the muscle–bone interface and measured on-screen with electronic calipers to the nearest 0·01 cm. Two measurements of MTh at each site were obtained and averaged. All MTh measurements were taken with the participant standing relaxed with their legs fully extended. Day-to-day coefficient of variation for the MTh measurements ranged from 3·40 to 6·64% for the various measurement sites.

Muscular strength

The maximum load that could be lifted through a full range of motion with proper form during unilateral knee extension was assessed and recorded as the one repetition maximum (1RM). For each limb, the 1RM was assessed following standard 1RM procedures (Harman *et al.*, 2000). All 1RMs were determined within six attempts, and a minimum of 1 min rest was allotted between attempts.

Muscular power

Muscular power was assessed during unilateral knee extension at three relative loads (30%, 60% and 90% 1RM). The loads used to assess power were relative to the 1RM measured during that same visit. The participant was instructed to complete the concentric (CON) portion of the repetition as fast as possible. Two trials were completed at each load, in ascending order, and separated by a minimum of 1 min rest. A TENDO Fitrodyne Sports Powerlyzer unit was attached to the arm connecting the shin pad to the load which measured the mean velocity (m s^{-1}) during each trial. For each load, the greater of the two mean velocities was used for analysis. Mean power (watts) was calculated using the formula:

$$\text{Mean power (watts)} = [\text{load (kg)} \times \text{mean velocity (m/s)}]/0 \cdot 10197$$

Muscular endurance

Following the muscular power test, the participant was given a minimum of 3 min rest. The load was adjusted to 30% 1RM measured on that visit. Participants completed one set of unilateral knee extension exercise to volitional fatigue at a pace of 20 repetitions per min [1·5 s CON and 1·5 s eccentric (ECC)]. The number of repetitions completed through a full range of motion was recorded.

Quadriceps muscle soreness

Immediately prior to each training session, quadriceps muscle soreness was assessed on the vastus lateralis (VL) 20 cm distal to the lateral epicondyle of the femur with the participate seated in a chair. Up to 10 kg cm^{-2} of pressure was applied to the site using an algometer (pain diagnostic force gauge, PFK 20; Wagner Instruments, Greenwich, CT, USA). The participant was asked to verbally indicate when the pressure became ‘uncomfortable’, and this force was recorded (pressure-pain threshold; kg cm^{-2}). If no indication of discomfort was given, soreness was considered not present. Each site was tested twice and the mean pressure reading was used for analysis. If the measurements differed by more than

1 kg cm^{-2}, a third measurement was taken and the median was used as the representative value.

Blood flow restriction

With the participant in the seated position, the BFR cuff was applied to the most proximal portion of the thigh with an initial compressive force of 20–25 mmHg. The cuff was then inflated to 40% of AOP (100–120 mmHg) for 30 s and then deflated for 10 s. The cycle of cuff inflation/deflation was repeated with cuff pressure increasing in increments of 20–40 mmHg until the target inflation pressure was reached. The cuff pressure was progressively increased during the training similar to previous protocols (Abe *et al.*, 2005a). For the first week of training, target inflation pressure was 150 mmHg or 50% of AOP (whichever was lower); for the subsequent weeks (2–6) of training, target inflation pressure was 80% of AOP but no higher than 240 mmHg (Laurentino *et al.*, 2012). The cuff was inflated to the target inflation pressure for ~15 s prior to the first set of exercise, remained inflated during the exercise and rest periods, and was deflated and removed immediately following the final set of exercise. The total duration of BFR varied depending on the volume of exercise performed but on average lasted between 3 and 7·5 min per session.

Exercise training protocol

Resistance training consisted of unilateral knee extension performed to volitional fatigue using a load of 30% 1RM. If a participant had to miss a session, the session was rescheduled and the sessions proceeded sequentially. The BFR limb exercised first during the odd-numbered sessions, and the FF limb exercised first during the even numbered sessions. All sessions were carefully observed by the researches who counted each repetition with a tally counter. A metronome was used to ensure each participant performed the CON and ECC portion of each repetition in 1·5 s (20 repetitions per minute). One minute rest periods were allotted between all sets. During the first 2 weeks of training, participants completed two sets of exercise with each limb during each session. The training volume progressively increased with participants completing three sets of exercise each session for each limb during weeks 3 and 4 except the ninth exercise session during which quadriceps strength was assessed and only two sets of exercise were performed with each limb. Four sets of exercise were performed during each session for each limb during weeks 5 and 6. Following the 1RM assessment at Mid, the exercise load was readjusted for the subsequent 3 weeks of training. The number of repetitions performed during each set for each limb was recorded during each session. The exercise volume (kg) for each training session was calculated as load (kg) × total repetitions. For each limb, the training volume for all training sessions was summed to calculate total training volume (kg).

Surface electromyography

On each limb, surface electromyography (EMG) was used to record electrical activity of the VL muscle during the seventh training session. The seventh exercise training session was chosen because the participants were by this time familiar with the training regimen. The VL was chosen as a representative muscle from the quadriceps because similar changes in muscle activation of the VL and vastus medialis have been observed during BFR knee extensor exercise (Wernbom *et al.*, 2009). The muscle belly of the VL at 66% of the distance between the anterior superior iliac crest and the superior edge of the lateral side of the patella was marked, and then, the skin was shaved, abraded and cleaned with alcohol. Circular Ag/AgCl electrodes (recording area diameter 20 mm; ConMed Instatrace Electrode, ConMed) were placed in a bipolar configuration with an interelectrode distance of 20 mm. The ground electrode was placed on the 7th cervical vertebra at the neck. The electrodes were connected to an amplifier and digitized (Biopac System, Inc. Goleta, CA, USA). The signal was filtered (low-pass filter 500 Hz; high-pass filter 10 Hz), amplified (1000×) and sampled at a rate of 1 KHz. Before the exercise bout, the participant performed two 3–5 s maximal isometric voluntary contractions (MVCs) with the quadriceps of each limb at a knee joint angle of 90° with 1 min rest between MVCs. All MVCs were performed on the knee extensor machine with a supramaximal load added to the machine and the machine settings in the same configuration as used for the exercise training. The EMG signal was recorded during the MVCs and during each set of knee extensor exercise. The computer software Labview 7.1 (National Instrument Corportion, Austin, TX, USA) was used to analyse the EMG amplitude [root mean square (RMS)] from the signal. For each limb, the MVC with the higher amplitude was used for normalisation of the signal recorded during the exercise session. Normalisation was performed by dividing the EMG signal from the dynamic contractions (i.e. exercise session) by the EMG signal from the MVC and expressed as a percentage. For the dynamic contractions, 1000 ms epochs from the CON and ECC phase of the first three (first) and last three (last) repetitions of each set (S1, S2 and S3) of exercise for each limb (BFR and FF) were analysed.

Acute muscle thickness measurements

Measurements of quadriceps MTh were obtained immediately before (Pre-Acute) and within 2 min after (Post-Acute) exercise during the eighth training session as described above. On this occasion, measurements were only made at AT50 and LT50 on each thigh. The measurements taken before exercise were also included in the analysis of MTh over the course of the entire study and denoted as mid-training (Mid).

Statistical analyses

All data were analysed using PASW Statistics 18 (Chicago, IL, USA) and are expressed as mean ± standard deviation (SD).

For all statistical tests, an alpha level of 0·05 was used. Participant characteristics were compared between men and women with independent samples t-tests. All dependent variables were analysed with repeated-measures analysis of variance (ANOVA) with within-subject factors of limb and time. Analyses with a between subjects factor of sex were also conducted. However, no time × sex or limb × sex interactions were observed, and, therefore, all data were collapsed across sexes. When significant main effects were present, least significant difference pairwise comparisons were made on the marginal means. When significant interactions were present, paired samples t-tests were used to compare means within each factor. Pearson correlations used to examine the relationship between baseline strength (Pre-2 1RM) and the change in strength over the intervention (Post – Pre-2 1RM). For all muscle function measures, test–retest reliability between Pre-1 and Pre-2 was determined using the intraclass correlation coefficient ($ICC_{3,1}$). For MTh measures, % coefficient of variation (% CV) was calculated using the formula:

$$\%\mathrm{CV} = (\mathrm{SD}/[(\text{mean Pre-1} + \text{mean Pre-2})/2]) * 100$$

To compare the magnitude of each treatment effect across time, effect size (ES) was calculated using the formula:

$$\mathrm{ES} = (\text{test 2 mean} - \text{test 1 mean})/(\text{test 1 SD})$$

Results

Arterial Occlusion Pressure. For 17 of the 18 participants, AOP was 300+ mmHg (no arterial occlusion at 300 mmHg cuff pressure). Thus, for these participants, BFR training pressure was 150 mmHg during the first week and 240 mmHg during all subsequent weeks of training. The other participant had an AOP of 230 mmHg; for this individual, BFR training pressure was 120 mmHg during the first week and 180 mmHg during all subsequent weeks of training.

Training adaptations

One participant injured his back (unrelated to the study) between the final training session and the post-testing session and was unable to complete the quadriceps function tests at Post. Therefore, this participant was excluded from the analyses of muscle function tests only, and muscle function data are presented on 17 participants ($n = 17$). Quadriceps strength increased significantly over time ($P<0{\cdot}001$) with no differences between BFR and FF (Table 2). Mean power at 30% and at 60% 1RM significantly ($P = 0{\cdot}006$ and $P<0{\cdot}001$, respectively) increased over time with no statistically significant differences between BFR and FF. The change in strength over the intervention (Pre-2 to Post) was inversely related to baseline strength (1RM at Pre-2) regardless of limb (BFR limb: $r = -0{\cdot}51$, $P = 0{\cdot}037$; FF limb: $r = -0{\cdot}635$, $P = 0{\cdot}006$). Quadriceps endurance significantly increased over time ($P<0{\cdot}001$) with no differences between BFR and FF. The test–retest reliability ICCs calculated from Pre-1 to Pre-2 were relatively high for quadriceps strength (0·93–0·94), mean power (0·87–0·96) and endurance (0·74–0·89).

Muscle thickness measurements were unobtainable on one participant because of excessive adipose tissue; therefore, MTh data are presented on 17 participants ($n = 17$; Table 3). Main effects for time were observed for AT 40 ($P = 0{\cdot}002$), AT 50 ($P = 0{\cdot}015$) and AT 60 ($P = 0{\cdot}001$) with no differences between BFR and FF. AT 40, AT 50 and AT60 were significantly greater at Post compared with Pre-1 and Pre-2 with no differences between Pre-1 and Pre-2. AT 50 was also significantly greater at Mid compared with Pre-1 and Pre-2 but not different between Mid and Post. Significant interactions were observed for LT 40 ($P = 0{\cdot}029$), LT 50 ($P = 0{\cdot}044$) and LT 60 ($P = 0{\cdot}024$). LT 40, 50 and 60 were significantly greater at Post compared with Pre-1 and Pre-2 for BFR only; LT 60 was also significantly greater for BFR compared with FF at Post. LT 50 was significantly greater at Mid compared with Pre-1 and Pre-2 for BFR only; LT 50 was also significantly greater for BFR compared with FF at Mid. The ESs for all quadriceps muscle size and function variables are presented in Fig. 1.

Acute exercise responses

One participant could not complete six full repetitions during the third set of exercise with BFR. Therefore, EMG data were not available from this participant at all measurement time-points and the statistical analyses were performed on 17 participants ($n = 17$). A significant ($P = 0{\cdot}044$) limb × time interaction was observed for normalised EMG amplitude (RMS). RMS increased over time during each set and was significantly greater for FF compared with BFR at S3 last (Fig. 2).

Anterior 50 significantly (main effect for time; $P<0{\cdot}001$) increased following acute exercise for both BFR (from 5·40 ± 0·66 to 5·73 ± 0·64 cm) and FF (from 5·39 ± 0·68 to 5·81 ± 0·80 cm). A significant limb x time interaction ($P = 0{\cdot}009$) was observed for LT 50. At Pre-Acute, LT 50 was greater for BFR compared with FF (3·62 ± 0·69 versus 3·45 ± 0·72 cm); LT 50 increased following acute exercise for both BFR and FF with no differences between BFR and FF at Post-Acute (3·80 ± 0·70 versus 3·73 ± 0·72 cm).

A main effect for time ($P<0{\cdot}001$) for pressure-pain threshold was observed with values increasing over time. Pairwise comparisons between adjacent sessions indicated a significant increase in pressure-pain threshold from training session 2 to session 3 ($P<0{\cdot}05$).

Training volume

The number of repetitions completed in each session was greater for FF compared with BFR during all sessions. Total exercise volume was 8844 ± 3704 kg for BFR and 13 857 ± 7030 kg for FF ($P<0{\cdot}001$).

Table 2 Muscular function variables.

	Pre-1	Pre-2	Mid	Post
1RM (kg)*				
BFR	25·9 (8·3)	27·9 (9·1)**	29·6 (8·3)**	31·0 (8·0)**,***,†
FF	26·8 (8·8)	28·9 (9·7)**	30·4 (8·3)**	31·2 (8·1)**,***,†
Mean power 30% 1RM (watts)*				
BFR	78·5 (28·8)	80·0 (28·3)		89·0 (28·3)**,***
FF	78·5 (29·1)	81·3 (30·9)		88·6 (29·2)**,***
Mean power 60% 1RM (watts)*				
BFR	123·5 (45·9)	133·7 (53·0)**		142·7 (46·9)**
FF	124·3 (50·2)	138·0 (54·7)**		142·0 (50·7)**
Mean power 90% 1RM (watts)				
BFR	137·2 (54·9)	144·7 (59·5)		143·3 (55·2)
FF	141·7 (59·3)	141·3 (55·6)		147·6 (51·7)
Muscular endurance (repetitions)*				
BFR	32 (14)	35 (13)		44 (13)**,***
FF	31 (12)	32 (15)		45 (15)**,***

Data presented as mean (SD).
BFR, blood flow restricted limb; FF, free flow limb; 1RM, one repetition maximum.
*P<0·05 time effect; **P<0·05 from Pre-1; ***P<0·05 from Pre-2; †P<0·05 from Mid.

Table 3 Thigh circumference and quadriceps muscle thickness.

	Pre-1	Pre-2	Mid	Post
Thigh circumference (cm)				
BFR	53·3 (5·8)	53·1 (5·0)		53·8 (4·7)
FF	53·3 (6·0)	53·3 (4·9)		53·9 (5·0)
AT 40 (cm)*				
BFR	5·61 (0·78)	5·56 (0·62)		5·87 (0·70)***,†
FF	5·65 (0·67)	5·62 (0·72)		5·79 (0·78)***,†
AT 50 (cm)*				
BFR	5·10 (0·83)	5·13 (0·69)	5·40 (0·66)***,†	5·39 (0·72)***,†
FF	5·21 (0·68)	5·16 (0·72)	5·39 (0·68)***,†	5·36 (0·75)***,†
AT 60 (cm)*				
BFR	4·47 (0·83)	4·48 (0·69)		4·81 (0·78)***,†
FF	4·55 (0·69)	4·53 (0·67)		4·79 (0·70)***,†
LT 40 (cm)**				
BFR	3·56 (0·60)	3·54 (0·65)		3·71 (0·66)***,†
FF	3·53 (0·74)	3·47 (0·74)		3·43 (0·76)
LT 50 (cm)**				
BFR	3·54 (0·62)	3·50 (0·61)	3·62 (0·69)***,†,‡	3·67 (0·62)***,†
FF	3·57 (0·72)	3·49 (0·73)	3·45 (0·72)	3·56 (0·70)
LT 60 (cm)**				
BFR	3·37 (0·66)	3·38 (0·64)		3·57 (0·58)***,†,‡
FF	3·43 (0·67)	3·37 (0·71)		3·44 (0·63)

Data presented as mean (SD).
AT, anterior thigh; LT, lateral thigh; BFR, blood flow restricted limb; FF, free flow limb.
*P<0·05 time effect; **P<0·05 leg × time interaction; ***P<0·05 from Pre-1; †P<0·05 from Pre-2; ‡P<0·05 from FF.

Discussion

The main finding of this study is that low-load BFR and FF knee extensor exercise training performed to volitional fatigue resulted in similar increases in muscular strength, power and endurance. However, BFR training induced greater increases in MTh of the lateral thigh despite similar acute changes in MTh following exercise and lower levels of muscle activation during exercise compared with FF exercise. Most (Takarada *et al.*, 2000, 2002; Abe *et al.*, 2005b; Evans *et al.*, 2010; Patterson & Ferguson, 2010, 2011) but not all (Burgomaster *et al.*, 2003; Moore *et al.*, 2004; Kacin & Strazar, 2011) previous investigations have found that low-load resistance training with BFR increases muscular strength to a greater extent than volume-matched low-load exercise without BFR. To our knowledge, this is the first study to compare muscular adaptations

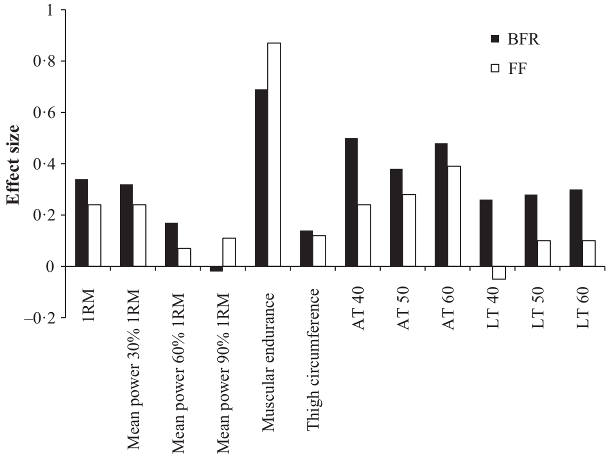

Figure 1 Effect sizes compared between limbs for muscle size and function variables.

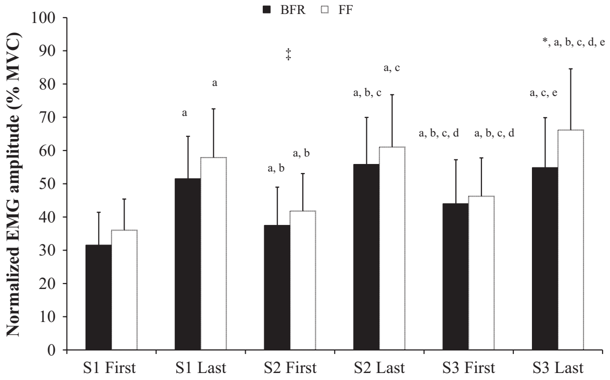

Figure 2 Normalised electromyography amplitude compared between limbs across time. Data presented as mean (SD); $^{\ddagger}P<0{\cdot}05$ limb × time interaction; $^{a}P<0{\cdot}05$ from S1 First; $^{b}P<0{\cdot}05$ from S1 Last; $^{c}P<0{\cdot}05$ from S2 First; $^{d}P<0{\cdot}05$ from S2 Last; $^{e}P<0{\cdot}05$ from S3 First; $^{*}P<0{\cdot}05$ from blood flow restricted.

to low-load resistance training with and without BFR under non-volume-matched conditions.

Although all participants were familiarised with the strength testing procedure before testing, there was still a significant increase in muscular strength over the time control period (Pre-1 to Pre-2) and it is likely that a learning effect was responsible for this increase. The calculated ES for strength over the training intervention is lower (ES = 0·34; Fig. 1) than previously reported in a meta-analysis (Loenneke *et al.*, 2012b) on the effect of BFR training on muscular strength (average ES = 0·58). In contrast, the ES for muscular strength in the FF limb over the training intervention (ES = 0·24) is larger than reported for low-load training without BFR (average ES = 0·00). The relatively small increase in dynamic strength following low-load training (regardless of limb) likely reflects the specificity of the training loads used (Mitchell *et al.*, 2012). The lack of isometric strength measures is a limitation of this study as it may have provided more insight into the adaptations in muscular strength. Overall, we did observe an inverse relationship between baseline strength and strength adaptation suggests that the increase in dynamic strength following low-load resistance training is dependent on baseline strength. Of note, increases in muscular strength did not occur until later in the training interventions which is contrary to the rapid increases in strength that may be observed with traditional resistance training (Sale, 1988) but is consistent with the time-course of BFR training adaptations reported previously (Loenneke *et al.*, 2012b).

Irrespective of limb (BFR or FF), mean power only at a low load (30% 1RM) increased following the training intervention (Pre-2 to Post). These results are in line with previous findings (Izquierdo *et al.*, 2001) which suggest that the greatest increase in power is observed at similar loads to that which is used during the resistance training (in this case 30% 1RM). Other studies have also found that resistance training with low loads (20% 1RM) is capable of increasing muscular power in older (~69 years) adults (de Vos *et al.*, 2005). It is likely that increases in muscular power from traditional, low velocity resistance training (similar to the present study), are attributable primarily to increases in muscular strength, whereas changes in muscle shortening velocity and neural recruitment would be more likely to be elicited by high velocity resistance training (Fielding *et al.*, 2002). Previously, low-load BFR resistance training has been shown to improve sprint performance in male athletes (Abe *et al.*, 2005a). Our results extend previous work and suggest that low-load training with or without BFR can increase muscular power at low loads in middle-aged individuals.

The most robust effect of the training was on muscular endurance which increased in both limbs following the training intervention. Compared with volume-matched non-BFR resistance training, BFR resistance training has been shown to augment resting levels of muscle glycogen and ATP (Burgomaster *et al.*, 2003) and enhances muscular endurance in both athletes (Takarada *et al.*, 2002) and non-athletes (Kacin & Strazar, 2011). Our results suggest that a higher volume of non-BFR resistance exercise can elicit similar increases in muscular endurance as BFR resistance exercise in middle-aged individuals. As both limbs performed exercise in a no-relaxation manner (i.e. no rest between repetitions), it is possible that the metabolic stress, and ultimately the metabolic adaptations, in the quadriceps was similar between limbs. However, the mechanisms behind the adaptations observed are beyond the scope of this study; future studies are needed to clarify these mechanisms. In comparing the ESs between the changes in muscular strength and endurance over the course of training (Fig. 1), our results are in line with previous findings that high-repetition, low-load resistance training elicits greater adaptations in muscular endurance relative to muscular strength (Campos *et al.*, 2002).

Measurements of MTh suggest hypertrophy of the AT quadriceps occurred in both limbs, whereas only BFR training induced hypertrophy of the lateral quadriceps muscles. The majority of changes in MTh that occurred over the training intervention occurred during the first 3 weeks of training (i.e. significant increase in MTh was observed from Pre-2 to Mid). This suggests that muscle hypertrophy can occur following a short duration of training and is consistent with previous observations which have shown muscle hypertrophy can occur with just 2–3 weeks of BFR resistance training (Abe *et al.*, 2005a; Fujita *et al.*, 2008; Yasuda *et al.*, 2010). Additionally, for all MTh measurement sites, the ES was greater for the BFR limb compared with the FF limb over the course of the training intervention (Fig. 1). Previous studies have observed muscle hypertrophy following low-load resistance training (Mitchell *et al.*, 2012). However, most studies comparing volume-matched low-load BFR and non-BFR resistance training have observed greater hypertrophy following BFR resistance training (Takarada *et al.*, 2000, 2002; Abe *et al.*, 2005a; Fujita *et al.*, 2008; Kacin & Strazar, 2011). Our findings extend previous work by comparing non-repetition matched BFR and non-BFR resistance training and suggest that, even with a lower volume of exercise, BFR resistance training can elicit greater increases in MTh of at least some regions of the quadriceps compared with non-BFR resistance training.

The similar increases in muscular strength over the training intervention for the BFR and FF limb may be partially due to a cross-education effect. However, although unilateral training with a high load with one limb has been shown to increase strength in the untrained, contralateral limb (Shima *et al.*, 2002), many studies (Evans *et al.*, 2010; Patterson & Ferguson, 2010, 2011; Mitchell *et al.*, 2012) have shown superior muscular strength adaptations in one limb compared with the contralateral limb using a mixed-limb study design similar to the present study. It is also unlikely that the observed increases in MTh in the FF limb are attributable to a cross-transfer effect from the BFR limb. The proposed mechanism of cross-transfer muscle hypertrophy is an exercise-induced increase in systemic anabolic hormones (Madarame *et al.*, 2008). However, unilateral lower body resistance exercise does not induce a rise in such hormones (Wilkinson *et al.*, 2006). Additionally, many resistance training studies using a mixed-limb design have shown unequal degrees of muscle hypertrophy between two limbs (Wilkinson *et al.*, 2006; Kacin & Strazar, 2011; Mitchell *et al.*, 2012).Therefore, it is likely that the increases in AT MTh observed in the FF limb are attributable to the local training stimulus and not a cross-transfer effect.

Electromyography amplitude increased over time during each of the three sets of exercise and was greater in the FF limb compared with the BFR limb at the end of the third set of exercise. The finding of greater EMG amplitude in the FF limb is in agreement with previous work which observed greater EMG amplitude of the vastus medialis and VL during the eccentric portion of low-load knee exercise without BFR compared with exercise with BFR performed to fatigue (Wernbom *et al.*, 2009). The level of activation (~55% MVC) in the VL during BFR exercise is similar to what has been previously reported during low-load BFR exercise but is lower that what may be observed during high-load exercise (Cook *et al.*, 2013). These findings suggest that other factors may be responsible for BFR exercise-induced muscle hypertrophy as activation of the VL was greater yet changes in MTh were lesser in the FF limb compared with the BFR limb.

Neither BFR nor FF low-load resistance exercise performed to volitional fatigue resulted in significant quadriceps muscle soreness. During the training, pain-pressure threshold increased in each limb which suggests that participants' lateral quadriceps became less sensitive and/or sore. In contrast to our results, previous investigations have suggested that BFR exercise, when performed to fatigue, results in muscle soreness and damage (Umbel *et al.*, 2009; Wernbom *et al.*, 2011) although other investigations have suggested otherwise (Loenneke *et al.*, 2013). One factor that may play a role on the perceptual responses to BFR exercise is the size and pressure of the restrictive cuff as well as the exercise protocol itself (Fahs *et al.*, 2012). Thus, although the exercise was performed to volitional fatigue, the exercise volume progressed slowly (starting with two sets of exercise) and the cuff pressure was individualised to ensure protocol adherence and minimise muscle soreness. It should be noted that despite the lack of muscle soreness from the protocol, the exertion level was relatively high during the exercise with each limb (as expected when exercising to volitional fatigue). Despite this, compliance to the protocol was excellent and no adverse events occurred during the training.

The results of this study are limited to short-term training and to healthy middle-aged individuals. The participants were physically active, and other lower body activities may have influenced the adaptations observed. However, the use of a within-subject design is a strength of the study as it allowed us to control for external factors (e.g. nutrition, physical activity) that could confound the effects observed in a between-group design. Moreover, we were able to assess other aspects of muscular fitness (power and endurance) that have not been previously examined in this population. The use of ultrasound to assess muscle size is a limitation as ultrasound MTh measures may be affected by other factors (e.g. fluid shifts and intramuscular fat accumulation). However, ultrasound measures of MTh are highly correlated with MRI measured muscle size (Abe *et al.*, 1997), and acute changes in MTh dissipate within 24 h of resistance exercise either with or without BFR (C. Poole, unpublished observation). Thus, as our measures of MTh were obtained at least 48 h after the last exercise session and we observed concomitant increases in muscle function, it is likely that the observed increases in MTh reflect muscle hypertrophy.

The results of this study suggest low-load resistance training either with or without BFR is a viable option to enhance muscle size and endurance for middle-aged individuals who may be unable to perform resistance training with high loads. The FF limb performed more repetitions during each exercise session, and the total exercise volume of the training intervention was substantially higher. Thus, the higher exercise volume needed to elicit muscle adaptations should be considered when comparing the changes in muscle size and function between limbs. Total exercise volume is a consideration in any resistance training programme and may be a very important concern for individuals who are limited to low-load resistance training. If exercise volume is a primary concern, then low-load BFR training may be preferable to low-load training without BFR. Low-load exercise with or without BFR performed to fatigue does not appear to induce muscle soreness. However, the magnitude of dynamic strength adaptation appears to be small with short-term low-load training performed with or without BFR. Individuals with low levels of muscular strength may see the greatest adaptation in strength following low-load resistance training.

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Conflict of interest

The authors have no conflict of interest.

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