This study investigated the hypertrophic potential of load-matched blood-flow restricted resistance training (BFR) vs free-flow traditional resistance training (low-load TRT) performed to fatigue. Ten healthy young subjects performed unilateral BFR and contralateral low-load TRT elbow flexor dumbbell curl with 40% of one repetition maximum until volitional concentric failure 3 days per week for 6 weeks. Prior to and at 3 (post-3) and 10 (post-10) days post-training, magnetic resonance imaging (MRI) was used to estimate elbow flexor muscle volume and muscle water content accumulation through training. Acute changes in muscle thickness following an early vs a late exercise bout were measured with ultrasound to determine muscle swelling during the immediate 0–48 h post-exercise. Total work was threefold lower for BFR compared with low-load TRT \( (P < 0.001) \). Both BFR and low-load TRT increased muscle volume by approximately 12% at post-3 and post-10 \( (P < 0.01) \) with no changes in MRI-determined water content. Training increased muscle thickness during the immediate 48 h post-exercise \( (P < 0.001) \) and to greater extent with BRF \( (P < 0.05) \) in the early training phase. In conclusion, BFR and low-load TRT, when performed to fatigue, produce equal muscle hypertrophy, which may partly rely on transient exercise-induced increases in muscle water content.

Strategies to stimulate skeletal muscle protein accretion are of fundamental interest to counteract pathological conditions featured by muscle wasting, such as myopathies, chronic inflammatory diseases, neurological disorders, surgical procedures and prolonged physical inactivity (Jagoe & Goldberg, 2001; Glass, 2003; Prado et al., 2008).

Mechanical loading, achieved through heavy resistance exercise, is proven to constitute one effective strategy to stimulate muscle protein accretion (American College of Sports, 2009). In accordance, > 75% of one repetition maximum (1 RM) has traditionally been recommended as optimal for inducing both muscle hypertrophy and muscle strength (American College of Sports, 2009) whereas lower intensity loading (< 50% of 1 RM) has been viewed as less efficient (Aagaard et al., 1994; Wernbom et al., 2007; Holm et al., 2008; American College of Sports, 2009). However, this contention has recently been challenged by studies, demonstrating that provided resistance exercise is performed to volitional failure (Mitchell et al., 2012) or low-load resistance exercise is combined with partial blood-flow restriction (BFR) (Abe et al., 2006; Nielsen et al., 2012; Takada et al., 2012; Yasuda et al., 2012), substantial muscle hypertrophy can be achieved. Accordingly, low-load BFR has been shown to stimulate muscle protein synthesis (1–5 h post-exercise) (Fujita et al., 2007; Fry et al., 2010) and muscle hypertrophy (Nielsen et al., 2012; Takada et al., 2012; Yasuda et al., 2012). Added to this, low-load BFR training seem to require a substantially shorter period of training to promote muscle hypertrophy (i.e., 3–6 weeks) (Abe et al., 2006; Nielsen et al., 2012; Takada et al., 2012), as compared with length of training required with high-load traditional resistance training (i.e., 8–12 weeks) (Moritani & de Vries, 1979; Folland & Williams, 2007; American College of Sports, 2009).

Additionally, a number of studies suggest that low-load BFR induce a greater myofibrillar protein synthesis and muscle hypertrophy response than free-flow low-load traditional resistance training (low-load TRT) (Fujita et al., 2007; Fry et al., 2010; Nielsen et al., 2012), when matched for load (i.e., percentage of 1 RM) and total work. These observations indicate that the partial vascular occlusion obtained with BFR constitute a time-saving, yet highly effective alternative strategy for inducing muscle hypertrophy that may be of particular relevance for clinical populations where counteracting muscle wasting is essential.

The mechanisms inherent of BFR are still largely undefined. However, when conducting load and work-matched BFR and low-load TRT, fatigue emerges much
soon with BFR than with low-load TRT (Wernbom et al., 2009). Therefore, fatigue-related mechanisms may comprise driving factors for augmenting the protein synthesis and muscle hypertrophy with BFR. In accordance, Burd et al. (Burd et al., 2010, 2012a,b) recently suggested that the degree of motor unit recruitment rather than the absolute load might constitute one such driving factor of muscle protein synthesis and muscle hypertrophy. Following this notion, during non-fatiguing exercise, a greater external load will result in recruitment of larger motor units according to Henneman’s size principle (Henneman et al., 1965). Similarly, during low-load BFR or low-load TRT performed to fatigue, a gradual increase in recruitment of larger motor units are expected to occur as type I fibers gradually fatigue (Wernbom et al., 2009; Burd et al., 2012a,b). Further support of this theory originates from a recent study by Mitchell et al. (2012), in which both heavy- (80% 1 RM) and low-load (30% 1 RM) exercise training were reported to produce equal muscle hypertrophy, when the exercise was performed to volitional failure.

It is therefore plausible that gradual recruitment of larger motor units during work performed to volitional fatigue is also driving the augmented muscle hypertrophy with BFR training. However, whether low-load TRT performed to volitional failure is an equally competent inducer of muscle hypertrophy, as compared with low-load BFR, is not yet thoroughly investigated.

In addition to motor unit recruitment, other potential mechanisms driving BFR-induced hypertrophy have been proposed to involve metabolite accumulation because of ischemia (Takada et al., 2012) and muscle cell swelling related to water retention (Yasuda et al., 2012), which may be interrelated. With regard to muscle swelling, BFR has recently been reported to promote acute post-exercise increases in muscle thickness, indicating that an increase in either intracellular or extracellular water retention has occurred (Yasuda et al., 2012). It can be speculated that increased muscle water retention will increase strain on the sarcolemma, thereby stimulating protein synthesis through mechanotransducing signaling pathways (Hornberger & Esser, 2004; Frey et al., 2009; Hornberger, 2011). Yet, the magnitude and consistency of water retention in response to BFR or low-load TRT performed to fatigue has not yet been thoroughly characterized.

The aim of the present study was to investigate if BFR vs low-load TRT exercise training performed to volitional failure could equally promote muscle water retention and muscle hypertrophy.

We hypothesized (a) that BFR and low-load TRT, when both performed to fatigue, would produce similar magnitudes of muscle hypertrophy following 6 weeks training; and (b) that BFR and low-load TRT would promote equal increases in transient post-exercise muscle swelling.

Materials and methods

Participants

Teen healthy young subjects were included in the study [male n = 8, female n = 2; age 25.5 (3) years; height 181 (6.7) cm; body mass 80 (14.5) kg]. None of the subjects had participated in any upper body resistance-type training for a minimum of 6 months prior to the inclusion in the study. Other exclusion criteria comprised (a) regular participation in any sporting activity, which contained strength-like upper arm contractions, such as rowing or climbing; (b) elbow – or shoulder joint injuries; and (c) use of prescription medicine or dietary supplements (i.e., protein and creatine supplements, Non-steroidal anti-inflammatory drugs). Each participant was informed of the risks associated with the study and a written informed consent was obtained from each subject prior to participation. The study was performed in accordance with the Declaration of Helsinki and approved by The Central Denmark Region Committees on Health Research Ethics (j. no. 37135).

Study design

Following inclusion, the participants’ left and right arms were randomly allocated to either low-intensity resistance training combined with BFR (n = 10) or low-intensity TRT (n = 10). The overall study design is outlined in Fig. 1. The subjects performed a supervised arm curl exercise three times a week for 6 weeks. Prior to and following the 6 weeks training, the subjects underwent a testing protocol to examine changes in muscle volume, water content and muscle strength (Fig. 1). Furthermore, acute changes in muscle thickness were measured following the first (i.e. the habituation bout) and the 16th training and neuromuscular activity during exercise was measured during the 3rd exercise bout (Fig. 1).

Training protocol

Before commencing the 6 weeks training protocol, all subjects completed an exercise bout to become habituated with the TRT and BFR exercise (Fig. 1). During the 6 weeks of training, the exercise intensity was set to 40% of 1 RM [estimated from 3 RM using the following equation 1 RM = (3 RM/1.0278−(3 × 0.0278)) adapted from (Brzycki, 1993)] for both groups. Subjects were randomized to perform either the BFR or TRT exercise first, with a 5-min rest period interspersed between the two exercise modalities. The exercise consisted of arm curls in a seated position with the exercise arm supported by a 45° incline bench (a preacher bench). The participants were instructed to perform repetitions from full flexion to full extension in a controlled manner and with a duty cycle of 4 s. During each exercise bout, the participants completed four sets of arm curl exercise repetitions until volitional concentric failure occurred. All sets were interspersed with a 30-s rest period.

During exercise, an 8-cm wide elastic pressure cuff (Tourniquet Cuff, VBM Medizintechnik GmbH, Sulz a.N., Germany) was attached in close proximity to the axillaris fossa on the BFR arm. The cuff was attached to a tourniquet system (Digital Tournique 9000, VBM Medizintechnik GmbH), which monitored and maintained a steady pressure throughout the entire range of motion during all repetitions. The pressure was set to 100 mmHg and kept at that level throughout the entire duration of the exercise bout (i.e., including interset rest intervals). Immediately after cessation of the fourth set, the pressure cuff was removed from the arm.

Muscle volume and muscle water determinations by magnetic resonance imaging (MRI)

The subjects were positioned in a supine position in a 3 Tesla whole-body MRI scanner (Magnetom Skyra; Siemens, Erlangen,
Germany) and an 18-element anterior receive coil was placed around the arm. Participants were positioned with the scanned arm being as close to the scanner center as possible.

After acquiring survey images in the sagittal and coronal orientations, a multislice fast spin echo scanning was acquired. It consisted of 36 slices with slice thickness of 3 mm and a slice gap of 7 mm. The following scanning parameters were used: field-of-view 190 × 190 mm, acquisition matrix 384 × 307, repetition time (TR) 837 ms, echo time (TE) 9.6 ms, echo train length 4 and pixel bandwidth 250 Hz/pixel. To standardize measurements, a fix point was used. Thus, slice 4 was placed at the base of the olecranon for all measurements.

To determine muscle cross-sectional area (CSA), slices 9 to 18 (i.e., 5–14 cm proximal to the olecranon) were used in the data analysis. Elbow flexor muscles were manually segmented and muscle CSA for each slice and muscle volume (i.e., based on CSA determinations of all included slices) were calculated using custom-made software (Siswin, S. Ringgard, Aarhus University Hospital, DK.). We have previously reported low variability with the use of this method to quantify muscle CSA (Farup et al., 2014).

To estimate muscle water content, T1 mapping was applied, i.e. T1 measurements were made in all image pixels. For the T1 measurements, a dual flip angle method was utilized, in which two sets of gradient images were obtained with a 5- and 30-degree angle, respectively. A three-dimensional spoiled gradient echo sequence with 26 slices was applied. The slices were 4 mm thick, field-of-view was 200 × 200 mm, matrix was 256 × 256, TR was 15 ms, TE was 1.68 and bandwidth was 480 Hz/pixel. Because of B1 (radio frequency magnetic field) inhomogeneity in the T1 maps, these were adjusted for the B1 fluctuations during post-processing by presuming a constant T1 value in the subcutaneous adipose tissue. Based on the adipose tissue T1 values, the real magnetization flip angle was calculated and from this the T1 maps were estimated. Muscle water content was calculated by assuming a linear association between inverse water content in percentage and inverse T1 values, as previously described (Fatouros & Marmarou, 1999). For this estimation, T1 was measured in a set of gelatine samples ranging from 65% to 100% in water content and inverse T1 values, as previously described (Fatouros & Marmarou, 1999). For this estimation, T1 was measured in a set of gelatine samples ranging from 65% to 100% in water content and a linear regression was applied to assess the T1 vs water content relation. For the water content estimation, one slide (representing the mid-arm level) was utilized in Siswin by applying an ellipse-shaped area in a representative anatomical point of the muscle.

**Ultrasound determined muscle thickness**

Acute changes in muscle thickness were measured with ultrasound technique, as described previously (Yasuda et al., 2012) following the habituation and the third-to-last exercise bout (exercise bout number 16, Fig. 1). Measurements were performed at pre- and at 0, 15, 60, 180 min and 48 h during post-exercise recovery (Fig. 1). Ultrasound measurements were carried out using a LOGIQe Book XP ultrasound scanner (GE Healthcare, Little Chalfont, United Kingdom) with the scanning head coated with a water-soluble transmission gel to provide acoustic contact without depressing the dermal surface. Participants were in a supine position on a medical bench with their elbows extended and relaxed. All measurements were performed at a fixed point (marked with a permanent marker to ensure that the same area was used for measurements), corresponding to one-third of the distance between the medial epicondyle and the coracoid process, respectively. All ultrasound measurements were performed by the same trained sonographer and with the scanning head placed perpendicular to the skin, measuring the distance from the superficial to the profound part of the muscle fascia. Three successive measurements were performed of which the average value is presented as a single data point for the statistical analysis. Initial repeatability trials indicated a low coefficient of variability (< 2%) in these data.

**Evaluation of muscle soreness**

Muscle soreness was evaluated from the BFR and TRT arms following the habituation trial (pre-exercise and at 0 and 48 h post-exercise) as well as before commencing each exercise bout. Subjects were asked to perform one eccentric muscle action with the BFR and TRT arm by lowering a submaximal load in a 3-s tempo. The subjects evaluated arm flexor muscle soreness on a visual analogue scale (VAS) of 100 mm going from no pain at all (0 mm) to worst possible pain (100 mm), previously described as a method for identification of pain (Bjur et al., 2001).

**Neuromuscular activity determinations by surface electromyography (sEMG)**

To provide an indication of muscle activity during exercise, sEMG from the m. biceps brachii was obtained during the third exercise.
bout (Fig. 1). The third exercise bout was chosen to ensure that subjects were accustomed to the exercise (i.e., avoiding potential influence of stressors related to unfamiliar exercise) in order to allow the most accurate and comparable electromyography (EMG) data. EMG recordings were conducted as previously described (Farup et al., 2014). Initially, the skin was cleansed with ethanol and then a pair of surface EMG electrodes (Blue sensor R-00-S/25, AMBU, Ballerup, Denmark) was placed at a third of the distance between the medial epicondyle and the coracoid process, medial on the thickest part of the muscle belly. The EMG electrodes were placed with a 35 mm center-to-center interelectrode distance, which was carefully replicated for within (as all subjects performed BFR with one arm and low-load TRT with the contralateral) and between participants. A wireless probe was connected to the electrodes and was placed on the skin, which pre-amplified and transmitted the signal in real time to a PC-interface receiver (TeleMyoTM 2400T DTS, Noraxon Inc., Scottsdale, Arizona, USA). All EMG sampling were recorded online at 1500 Hz, passed through a digital first-order high-pass filter with a 10 Hz cut-off, synchronized to the force signal and saved in EMG sampling software (MyoResearch XP, Noraxon Inc.). During the later off-line analysis, the raw EMG signal was fully rectified using a root mean square filter with a time constant of 50 ms. The filtered EMG signal was manually analyzed to ensure proper detection of contraction onset. The concentric contraction was defined as going from full elbow joint extension (= 0°) to full elbow joint flexion with the joint position measured using an electronic goniometer (Type SG150, Biometrics Ltd, Newport, UK) synchronized to the EMG signal. The filtered EMG signal from each concentric contraction was integrated with respect to time ($\int_{\mu} V dt$) and normalized to the peak iEMG obtained during any of the concentric contractions performed (Labview 2011, National Instruments Corporation, Austin, Texas, USA). Because the number of repetitions completed varied between subjects, the final repetition from all subjects was fixed as the last repetition.

**Determinations of dynamic and isometric muscle strength**

Three RM was measured as described previously (Farup et al., 2012), with measurements conducted prior to commencing the training period, after 2 and 4 weeks during training period to adjust the load used during exercise. After a brief warm up (consisting of 2 × 12 submaximal arm curl repetitions), the participants performed three unilateral biceps curls with loading corresponding to the estimated 3 RM. The weight was increased until the dumbbell could not be lifted three times. Subjects rested for 3 min between each trial. The test was only considered valid when the dumbbell was lifted in a controlled manner (a duty cycle of 4 s) through the entire range of motion. On average, three attempts were required to measure the true 3 RM.

Isometric maximal voluntary contraction (MVC) was obtained using an isokinetic dynamometer (Humac Norm, CSML, Stoughton, Wisconsin, USA). After a brief warm up, consisting of 2 × 12 submaximal arm curl repetitions, participants performed an isometric MVC at 30° of elbow flexion (0 equals full extension) followed by MVC at 90°. The participant was comfortably seated with a velcro band strapped across their chest and upper arm, thus, keeping the upper arm strapped down to the back rest. All participants were allowed four trials at each angle with each arm and a 2-min rest period between each trial. The participants were instructed to pull with maximal force and were verbally encouraged by the experimental assistants. The highest MVC measure was selected for further data analysis.

**Statistical analyses**

Following check for normality and equal variance, the data were expressed as mean and standard deviation (in parentheses). Differences in total training time, repetitions and VAS were determined using a paired t-test. Dependent variables (muscle volume, CSA, water content, thickness, and muscle strength) were analyzed using two-way repeated measures analysis of variance (i.e., arm × time) followed by pairwise multiple comparison procedures (Holm-Sidak). The accumulated change in acute muscle thickness, from 0 to 180 min post-exercise, was generated by integrating the change in muscle thickness with respect to time (min). Pearson’s correlation analyses were utilized to investigate the association between acute accumulated changes in muscle thickness with changes in muscle volume. Alpha level was set at 0.05. Statistical analysis was performed using SigmaPlot 12.0 (Systat Software Inc., San Jose, California, USA).

**Results**

**Training adherence, workload (repetitions), and time**

A mean of 18.6 (0.5) out of a total of 19 possible training bouts were completed. The mean number repetitions per set ($P < 0.01$, Fig. 2(a)) as well as total repetitions for the entire training period ($P < 0.001$, Fig. 2(a)) were lower for BFR compared with low-load TRT. Moreover, the time under tension per set ($P < 0.01$, Fig. 2(b)) as well as total training time (i.e., total time under tension + rest periods) for the entire training period ($P < 0.001$, Fig. 2(b)) was lower for BFR compared with low-load TRT ($P < 0.01$).

**Muscle soreness**

Following the initial habituation exercise bout, both the BFR and low-load TRT group increased muscle soreness

![Fig. 2](image-url). Repetitions and time under tension. Repetitions per set and total repetitions during the entire training period (a) and time under tension per set and total training time during the entire training period (b) for blood-flow restricted (BFR) or low-load traditional resistance training (TRT) groups. Data are presented as mean and standard deviation. Significant differences between conditions are denoted by ## ($P < 0.01$) and ### ($P < 0.001$).
immediately (0 h) and at 48 h post-exercise (P < 0.001, Fig. 3). At 0 h and 48 h, the increase was 64.1% (P < 0.05) and 88.2% (P < 0.01) greater in the BFR arm compared with the low-load TRT arm (Fig. 3), respectively. Before commencing each of the 18 exercise training bouts, the extent of muscle soreness was non-existent or very limited in both groups (Fig. 3).

Muscle hypertrophy

A representative determination of a muscle CSA is shown in Fig. 4(a). Prior to training, elbow flexor muscle volume was 208 (43) and 207 (37) cm³ for BFR and low-load TRT, respectively (Fig. 4(b)). Three days after completing training, elbow flexor volume had increased in both groups (P < 0.01) to 232 (46) cm³ and 231 (39) cm³ corresponding to an increase of 11.5% and 11.6% in BFR and low-load TRT, respectively (Fig. 4(b)). These increases were maintained at 10 days after completion of training (P < 0.01) with an elbow flexor volume of 232 (44) cm³ and 228 (38) cm³ in BFR and low-load TRT, respectively (Fig. 4(a)). No between-group differences in muscle volume gain were observed at 3 or 10 days post-training.

Muscle water content as determined before and after training by MRI

MRI technique was used to evaluate chronic changes in muscle water content. Prior to training, muscle water content was estimated to 76 (8)% and 74 (6)% with BFR and low-load TRT, respectively. After 3 days post-training, the muscle water content was 76 (6)% and 74 (6)% for BFR and low-load TRT, respectively, and 10 days post training, the muscle water content was 76 (4)% and 75 (5)% for BFR and low-load TRT, respectively. No differences were observed between pre- and post-measurements.

Ultrasound-measured muscle thickness as determined acutely after exercise

Changes in muscle thickness were determined following an initial habituation exercise bout as well as following the third last exercise bout (bout 16). Before commencing exercise at the habituation exercise bout, the muscle thickness was 34.2 (5.8) mm and 33.0 (4.8) mm for BFR and low-load TRT, respectively. Following the habituation exercise bout, muscle thickness increased at all post-exercise time points (P < 0.001, Fig. 5(a)) followed by a
gradual return towards baseline. A greater overall increase in muscle thickness was observed with BFR compared to low-load TRT ($P < 0.05$, Fig. 5(a)). At bout 16, muscle thickness was 35.4 (4.9) mm and 34.1 (4.1) mm for BFR and low-load TRT, respectively, before commencing exercise. Following exercise, muscle thickness increased at 0–60 min in both groups ($P < 0.001$, Fig. 5(b)) and returned to baseline at 180 min and 48 h post-exercise.

To further investigate the association between acute changes in muscle thickness with changes in muscle volume, we correlated the accumulated increase in muscle thickness (from 0 to 180 min) from both the early and late exercise bouts with the change in muscle volume. However, no clear and significant associations were observed when using a Pearson’s correlation analysis.

Dynamic and isometric muscle strength

Prior to commencing training, 3 RM was determined as 10.8 (3.3) kg and 11.3 (3.0) kg for BFR and low-load TRT, respectively (Fig. 6(a)). After 2 weeks of training, 3 RM increased by 10% and 7%, for BFR and low-load TRT, respectively ($P < 0.001$, Fig. 6(a)), and was further increased at week four (Fig. 6(a)). No differences were observed between BFR and low-load TRT.

Before training, isometric MVC at 30° was 76 (29) Nm and 63 (21) Nm for BFR and low-load TRT, respectively (Fig. 6(b)). No differences following training or between groups were observed. Furthermore, no changes were observed for MVC at 90° following training or between groups (data not shown).

Fig. 5. Exercise-induced changes in muscle thickness. Changes in elbow flexor thickness (in mm) following the habituation exercise bout (a) and the 16th exercise bout (b) determined at pre and at 0 min, 15 min, 60 min 180 min, and 48 h after blood-flow restricted (BFR) or low-load traditional resistance (TRT) exercise. Data are presented as mean and standard deviation. Significant differences from pre-training are denoted by *** ($P < 0.001$). Significant overall effect of group is denoted by # ($P < 0.05$).

Fig. 6. Dynamic and isometric strength. Three repetition maximum (3 RM, a) and isometric maximal voluntary contraction (MVC, b) are displayed. Three RM was determined prior to and during week two and four in the training period and MVC was determined prior to and 4 post-completion of the training period for blood-flow restricted (BFR) or low-load traditional resistance training (TRT) groups. Data are presented as mean and standard deviation. Significant difference from pre-training is denoted by *** ($P < 0.001$).
During an exercise bout, the sEMG from the m. biceps brachii was measured to provide an indication of neuromuscular activity. As illustrated in Fig. 7, normalized sEMG (normalized to peak iEMG obtained) remained at low until the last repetitions in each set, upon which the sEMG increased markedly for both BFR and low-load TRT by identical patterns, but with BFR requiring fewer repetitions (Fig. 7).

**Discussion**

The traditional strategy to increase muscle mass involves heavy load resistance training. However, recent studies have reported that low-load resistance training combined with partial vascular occlusion (BFR) may effectively induce muscle hypertrophy compared with load- and work-matched resistance exercise without occlusion (Fujita et al., 2007; Nielsen et al., 2012). This ability of BFR to promote muscle hypertrophy may partly be ascribed to fatigue-related mechanisms or through induction of water retention. A key question therefore relates to whether load-matched BFR vs low-load TRT performed to fatigue are equally capable of producing muscle water retention and hypertrophy.

In the present study, we demonstrate (a) that provided performed to volitional failure, BFR and low-load TRT training are equally capable of inducing muscle hypertrophy; (b) that transient exercise-induced increases in muscle thickness occurs with both BFR and low-load TRT; and (c) that accumulated BFR or low-load TRT training does not produce persistent changes in muscle water retention.

**Effect of exercising to volitional fatigue on muscle hypertrophy**

Earlier studies have demonstrated substantial muscle hypertrophy when combining walking (Abe et al., 2006) or low-load resistance training (Nielsen et al., 2012; Takada et al., 2012; Yasuda et al., 2012) with partial vascular occlusion (Wernbom et al., 2008). Moreover, low-load TRT produce only little or no muscle hypertrophy when load and work are matched to the BFR condition (Wernbom et al., 2008; Nielsen et al., 2012). However, as volitional fatigue is not reached during work- and load-TRT protocols that are matched to BFR protocols (Wernbom et al., 2009), it can be objected that the two conditions are not directly comparable if factors related to fatigue are strong determinants for muscle hypertrophy. In accordance, recent studies have reported that low-load resistance training can increase muscle protein synthesis and muscle growth, provided that the exercise is performed to volitional fatigue (Burd et al., 2010; Mitchell et al., 2012). The data from the present study support such findings, as we demonstrate that provided performed to volitional fatigue, both BFR and low-load TRT produce substantial and equal size muscle growth. Furthermore, with only 6 weeks of training to fatigue, the magnitude of muscle hypertrophy are comparable with previously reported magnitudes of hypertrophy achieved with upper body heavy load resistance training (approximately 15%), typically requiring 10–12 weeks of training (Erskine et al., 2012).

As BFR may induce water retention to potentially obscure interpretations of whole-muscle CSA determinations generated by MRI technique (Kristiansen et al., 2013), we also estimated water retention by...
MRI using T1 maps. From these we observed no training-induced changes in water retention and as muscle CSA changes persisted at day 10 after the final exercise bout, we are confident that the increases in muscle area and volume with both BFR and low-load TRT constitute genuine read-outs of muscle hypertrophy.

With regard to the motor unit recruitment during fatiguing exercise, our findings indirectly support the speculation by Burd et al. (2012a,b). In accordance, recruitment of larger motor units with fatiguing exercise, independent of external load, has been speculated to provide a strong stimuli for muscle protein synthesis (Burd et al., 2012a,b). Although quite descriptive, our sEMG results indicate that motor unit activity (recruitment and/or firing frequency) was similar between fatiguing BFR and low-load TRT. However, as demonstrated, low-load TRT required more than three times as many repetitions as BFR to reach the same increase in sEMG. While we cannot exclude the possibility that the differences in the total work performed between the two groups, confounded the muscle hypertrophy results, total work alone does not seem to determine the extent of muscle hypertrophy in untrained subjects (Holm et al., 2008; Mitchell et al., 2012). A second potential confounding factor of our study design relate to the premise that subjects trained BFR with one arm and low-load TRT with the contralateral arm. By using this design, we aimed to reduce variability between BFR and low-load TRT. Still, we cannot exclude that factors released in response to BFR exercise can entail a systemic effect on the low-load TRT arm – or vice versa. However, recent exercise studies have questioned if factors released to the systemic environment during exercise are in fact able to influence muscle growth (West et al., 2009, 2010a,b), so this aspect will require further investigation.

Following traditional heavy resistance training, but not low-load resistance training (Aagaard et al., 1994; Holm et al., 2008), isometric strength typically increases and is associated with changes in the central nervous system, which, in part, explains the gains in strength (Aagaard et al., 2000; Aagaard, 2003; Folland & Williams, 2007). Unexpectedly, in the present study, the increase in muscle volume and dynamic strength were not mirrored by changes in isometric MVC, in contrast to previous studies (Nielsen et al., 2012; Yasuda et al., 2012). This may relate to the minor changes in the output from the central nervous system following BFR training (and potentially also low-load TRT training) compared with heavy resistance training (Kubo et al., 2006). Additionally, we cannot exclude the possibility that fatigue (e.g., decreased adenosine triphosphate levels, altered calcium kinetics etc.) from the final training session (3 days earlier) could have influenced the MVC results.

Is muscle hypertrophy associated with muscle water retention?

It has been proposed that water retention following BFR exercise may, at least in part, drive the enhanced muscle protein synthesis and muscle hypertrophy (Yasuda et al., 2012). In accordance, muscle metabolite accumulation with BFR (Takada et al., 2012) can be speculated to promote a water flux into the muscle cell and, in consequence, increase myocellular pressure. In the present study, we observed acute transient increases in muscle thickness following the first and the 16th exercise bout with both BFR and low-load TRT. These findings indicate that the transient post-exercise increases in muscle swelling (i.e., possibly ascribed to transient water retention) are not merely a result of unaccustomed exercise stress. This acute muscle water retention likely increase the strain on the sarcolemma, thereby stimulating the myofibrillar protein synthesis through mechanosensing mechanisms possibly involving proteins such as phospholipase D or α7-β1 integrin (Hornberger & Esser, 2004; Boppart et al., 2006; Hornberger, 2011). However, as the present study did not include muscle biopsies, we cannot provide direct evidence to link water retention with protein synthesis, but this aspect invites for further investigation.

Following the early exercise bout, the increased muscle thickness with BFR was greater compared with low-load TRT, whereas after the late bout, the magnitude of muscle thickness changes was identical with BFR and low-load TRT. Thus, minor differences in acute muscle thickness may only be present during the initial exercise bouts, which suggest that acute water retention is not a phenomenon exclusively associated with BFR, but occurs with fatiguing exercise in general. This contention is supported by the findings reported by Nielsen et al. (2012) in which the authors showed similar increases in muscle fiber CSA 8 days after initiating a training period of low-load resistance training both with and without vascular occlusion. The observation that muscle soreness was higher with BFR than low-load TRT during the acute phase from the initial exercise habituation bout may partly relate to a larger degree of muscle swelling at this point. Swelling and muscle soreness during post-exercise recovery (lasting up to several days) are common features of exercise-induced muscle damage, in particular, from eccentric muscle actions (Prosk & Allen, 2005). Therefore, our data could indicate some level of muscle damage in the initial exercise bout, despite a recent review arguing that BFR exercise is not associated with muscle damage (Loenneke et al., 2014). This would also serve to explain why only the initial exercise bout was associated with a greater increase in muscle thickness with BFR compared with low-load TRT. Nonetheless, muscle soreness was virtually non-existent during the entire training period. Therefore, muscle soreness more likely relate to independent
mechanism. However, it is interesting to note that BFR training does not result in much muscle soreness after accustomization, as this justifies BFR as a strategy to counteract muscle wasting in patient groups.

In conclusion, load-matched BFR and low-load TRT conducted in arm flexor muscles are equally capable of inducing substantial muscle hypertrophy, provided that the exercise is performed to volitional failure. Utilizing the approach of fatiguing resistance exercise, substantial magnitudes of muscle hypertrophy were accomplished after only 6 weeks of training. Furthermore, the hypertrophic response may, in part, relate to transient post-exercise increases in muscle water retention, thereby providing a persistent stimulus on mechanosensory elements involved in muscle protein synthesis.

Perspectives

Our findings embody interesting perspectives in the development of strategies to counteract muscle wasting. In accordance, while high-load TRT and fatiguing low-load TRT can both stimulate muscle growth and strength, these traditional strategies may require substantial time, motivation and, in the case of high-load TRT, also comprise substantial compressive and shear loading to joints in order to obtain a hypertrophic effect. In this regard, BRF offers an alternative as it (a) is much less time consuming with respect to time per exercise bout as well as the duration of training period; (b) requires a low external load, which may prove beneficial under specific circumstances such as following acute injury/surgery or in patients suffering from rheumatoid arthritis; and finally, (c) is highly effective in stimulating muscle growth. Future studies should seek to test the feasibility and effects in clinical settings where subjects are suffering from muscle wasting. Examples of applicability comprise muscle genetic disorders, neurological disorders, inflammatory disorders and situations characterized by prolonged inactivity. Furthermore, it may also apply to rehabilitation after severe injury to the movement apparatus in athletic individuals to allow safe and fast recovery.

Key words: muscle volume, vascular occlusion, fiber recruitment, low-intensity resistance training, volitional fatigue.

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References


Fatigue and muscle hypertrophy


