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Title: Comparing the effectiveness of blood flow restriction and traditional heavy load resistance training in the post-surgery rehabilitation of anterior cruciate ligament reconstruction patients: a UK National Health Service randomised controlled trial.

Running title: Blood flow restriction training in clinical rehabilitation

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As the corresponding author, I can confirm that this revised manuscript has been read and approved by all the listed co-authors. The manuscript contains original material that has not been previously published and is not currently under consideration elsewhere until a final decision by the editorial board as to its suitability for this journal has been made.

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Abstract

Background: We implemented a blood flow restriction resistance training (BFR-RT) intervention during an 8 week rehabilitation programme in anterior cruciate ligament reconstruction (ACLR) patients within a National Health Service setting.

Objective: To compare the effectiveness of BFR-RT and standard care traditional heavy load resistance training (HL-RT) at improving skeletal muscle hypertrophy and strength, physical function, pain and effusion in ACLR patients following surgery.

Methods: Twenty eight patients scheduled for unilateral ACLR surgery with hamstring autograft were recruited for this parallel group, two-arm, single assessor blinded randomised clinical trial following appropriate power analysis. Following surgery, a criteria-driven approach to rehabilitation was utilised and participants were block randomised to either HL-RT at 70% repetition maximum (1RM) (n=14) or BFR-RT (n=14) at 30% 1RM. Participants completed 8 weeks of biweekly unilateral leg press training on both limbs, totalling 16 sessions, alongside standard hospital rehabilitation. Resistance exercise protocols were designed consistent with standard recommended protocols for each type of exercise. Scaled maximal isotonic strength (10RM), muscle morphology of the vastus lateralis of the injured limb, self-reported function, Y-balance test performance and knee joint pain, effusion and range of motion (ROM) were assessed at pre-surgery, post-surgery, mid-training and post-training. Knee joint laxity and scaled maximal isokinetic knee extension and flexion strength at 60°/s, 150°/s and 300°/s were measured at pre-surgery and post-training.

Results: Four participants were lost, with 24 participants completing the study (12 per group). There were no adverse events or differences between groups for any baseline anthropometric variable or pre-post-surgery change in any outcome measure. Scaled 10RM strength significantly increased in the injured limb (104 ± 30% and 106 ± 43%) and non-injured limb (33 ± 13% and 39 ± 17%) with BFR-RT and HL-RT, respectively, with no group differences. Significant increases in knee extension and flexion peak torque were observed at all speeds in the non-injured limb with no group differences. Significantly greater attenuation of knee extensor peak torque loss at 150°/s and 300°/s and knee flexor torque loss at all speeds was observed with BFR-RT. No group differences in knee extensor peak torque loss were found at 60°/s. Significant and comparable increases in muscle thickness (5.8 ± 0.2% and 6.7 ± 0.3%) and pennation angle (4.1 ± 0.3% and 3.4 ± 0.1%) were observed with BFR-RT and HL-RT, respectively, with no group differences. No significant changes in fascicle length were observed. Significantly greater and clinically important increases in several measures of self-reported function (50-218 ± 48% vs. 35-152 ± 56 %), Y-balance performance (18-59 ± 22% vs. 18-33 ± 19%), ROM (78 ± 22% vs. 48 ± 13%) and reductions in knee joint pain (67 ± 15% vs. 39 ± 12%) and effusion (6 ± 2% vs. 2 ± 2%) were observed with BFR-RT compared to HL-RT, respectively.

Conclusion: BFR-RT can improve skeletal muscle hypertrophy and strength to a similar extent as HL-RT with a greater reduction in knee joint pain and effusion, leading to greater overall improvements in

physical function. Therefore, BFR-RT may be more appropriate for early rehabilitation in ACLR patient populations within the National Health Service.

1. Introduction

Following anterior cruciate ligament reconstruction (ACLR) surgery patients experience significant loss of lower limb strength due to muscle atrophy and arthrogenic inhibition [1,2]. Knee extensor (KE) and flexor (KF) muscle weakness is substantial during the first 12 weeks [3] following surgery, impairing lower limb function [4] and quality of life [5]. Muscle weakness can persist for years after ACLR surgery [6] and is associated with chronic reductions in function [7,8], a high re-injury risk [9] and joint degeneration [10]. Therefore, targeting muscle weakness early in the rehabilitation process is imperative [11].

The principle goal of ACLR rehabilitation is to return a patient to their pre-injury level of function with a low risk of re-injury [12]. Rehabilitation protocols have evolved from a non-weight bearing and time dependent progression approach following surgery to early return to range of motion (ROM), full weight bearing and strength training with criteria-driven progression [12–14]. Heavy load resistance training (HL-RT) using external loads of 65-70% of an individual's one repetition maximum (1RM) are recommended to stimulate skeletal muscle hypertrophy and strength adaptations [15,16]. Whilst these loads may be required to increase strength to a satisfactory level [17], issues such as meniscal damage and bone bruising may contraindicate HL-RT in load compromised ACLR patients [11].

Blood flow restriction (BFR) resistance training (BFR-RT) can elicit muscle hypertrophy and strength adaptations in load compromised populations using light external loads of 20-30% 1RM [18,19], which may be comparable in magnitude to HL-RT [20–23]. Moreover, BFR-RT can reduce pain and improve physical function [18,20–22]. The passive application of BFR can attenuate muscle atrophy following ACLR surgery [24]. Only two studies to date have examined BFR-RT in the post-surgery rehabilitation of ACLR patients [25,26]. Although Iversen et al. reported that applying BFR during light load exercise did not reduce KE muscle cross-sectional area atrophy in the first two weeks following ACLR surgery, it is likely that the training load achieved using isometric contractions and straight leg raises was lower than the 10% of maximal strength required for muscle hypertrophy [27]. Ohta et al. showed that BFR-RT resulted in significantly greater increases in KE muscle size and KE and KF muscle strength compared to light load resistance training alone. Importantly there were no differences in knee ROM or reduction in knee laxity from pre-surgery to post-training, supporting the use of BFR-RT without compromising graft healing. The hemodynamic and perceptual responses to BFR-RT in ACLR patients may not limit its application and may reduce knee pain [28], possibly providing a useful rehabilitation tool for ACLR patients [11]. However, the effectiveness of BFR-RT for stimulating muscle strength and hypertrophy during ACLR rehabilitation has not been directed compared to HL-RT. Moreover, the effect of BFR-RT other aspects important in ACLR rehabilitation, such as physical function, pain and effusion has not been explored. Therefore, the aim of this study was to compare the effectiveness of

BFR-RT and HL-RT for improving skeletal muscle hypertrophy, strength, physical function, pain and effusion in ACLR patients during a post-surgery rehabilitation programme within a National Health Service (NHS) setting.

2. Methodology

2.1 Participants

Twenty-eight patients scheduled for unilateral ACLR surgery were recruited for this study. Eligible patients were sent the patient information sheet prior to surgery. Those willing to participate were scheduled for a pre-surgery medical health screening appointment. All participants were active non-smokers, had no known history of central or peripheral neurological impairment, and were free of any cardiac, pulmonary or metabolic conditions. Exclusion criteria included: multiple ligament ruptures or trauma; rheumatoid arthritis or other significant comorbidities; history of deep vein thrombosis or vascular pathology in any lower limb; intraarticular injections into the knee in the preceding 6 months; use of anticoagulant medications; inability to follow instructions during exercise (e.g. advanced dementia); and post-surgery leg bracing. Participants refrained from strenuous exercise, caffeine and alcohol in the 24 h prior to all experimental testing sessions and were asked to maintain normal dietary and supplement habits for the study duration. All participants provided signed informed consent, in compliance with the Declaration of Helsinki [29]. All protocols were approved by the University (SMEC-2015-16-118) and NHS Health Research Ethics Committee (REC reference: 16/YH/0066). This clinic trial was registered on clinicaltrials.gov (I.D: NCT03419169).

2.2 Sample size calculation

The primary study outcome measure of muscle strength was used for calculation of the required sample size using G* Power Version 3.1 [30]. This was based on the between group effect size for muscle strength with BFR-RT and HL-RT reported in a recent meta-analysis [19]. To achieve a power of 95% at an alpha level of 0.05 a total of 24 patients (12 per group) was required to detect meaningful between-group changes in strength improvement. Therefore, to account for up to a 10% withdrawal rate, a total of 28 patients were recruited.

2.3 Experimental design

This study was a parallel group, two-arm, single assessor-blinded randomised clinical trial in a between subject's repeated measures design. Participants were block randomised in blocks of 4 to either BFR-RT (n=14) or HL-RT (n=14) by an independent member of the research team. This was performed using 7 opaque envelopes each with 4 folded slips inside that included 2 x BFR-RT (Coded as Group 0) and 2 x HL-RT (Coded as Group 1). An independent member of the research team asked participants to pick from the envelope without looking. This was performed sequentially (i.e. the first four

participants selected from envelope 1). The groups were coded by an independent member of the research team and the principle assessor of all outcomes and data-analysis was blinded to group allocation.

2.4 Experimental procedure

Participants attended a familiarisation session followed by 4 experimental testing sessions: 1) pre-surgery; 2) post-surgery (week 0); 3) mid-training (week 4-5) and 4) post-training (week 9), alongside an 8 week resistance training intervention (weeks 1 to 8) (Figure 1). Beginning at 2 weeks following surgery after surgeon approval and suture removal, participants were assessed every 48 h to determine if they met the criteria for beginning leg press strength training [12]. This included the ability to: 1) unilaterally weight bear without pain for ≥ 5 s without support; 2) demonstrate a knee ROM of 0 to 90°, assessed using a goniometer as previously described [31]; and 3) perform repeated straight leg raises without KE muscle lag, demonstrate gluteal and KF muscle activation and have minimal effusion change with activity, each assessed as previously described [12]. Once all of these criteria were met, participants attended the post-surgery (week 0) experimental testing session.

INSERT FIGURE 1 HERE

2.5 Resistance training intervention

Each intervention included 8 weeks of unilateral leg press training 2 x per week, totalling 16 sessions each separated by a minimum of 48 h. All training sessions were supervised by a trained member of the research team. Both groups completed a warm-up consisting of 5 min of unloaded cycling at a free cadence followed by 10 repetitions of unilateral leg press exercise at a self-selected weight, with a subsequent 5 min rest. Both the HL-RT and BFR-RT protocols were designed consistent with standard recommended protocols for each type of exercise [16,32] and are detailed in Figure 1. It was ensured that participants performed the exercise throughout a 0-90° ROM. 10RM strength was measured and used to predict 1RM strength [33]. The 10RM is highly predictive of 1RM leg press (r=0.98) [34,35] and accurately matches 1RM estimates [36]. Both limbs were trained to meet NHS ethical requirements for standard provision of care. The injured limb was trained first and then the non-injured limb was matched for repetitions, each at a relative percentage of its 1RM, to match the volume and external load to attempt to control for any cross-transfer effects of training the limbs differently. BFR was applied to both limbs for this reason. Training load was increased by 10% if participants completed all repetitions on 2 subsequent sessions and was formally readjusted after the mid-training testing [37]. Exercise volume (kg) was calculated as: number of repetitions x load (kg).

2.6 Standard rehabilitation programme

All participants received the standard NHS rehabilitation programme and were instructed to complete this at home on 3 days per week. This is included as supplementary material (Supplementary material 1). Only the strength training component was different between groups and was only completed at the scheduled intervention sessions.

2.7. Blood flow restriction

BFR was achieved using an automatic personalised tourniquet system (Delfi Medical, Vancouver, BC, Canada) designed to automatically calculate limb occlusion pressure (LOP), defined as the minimum pressure required for full arterial occlusion [38], with clinical acceptable accuracy and high reliability [39–41]. The PT device increases cuff pressure itself in stepwise increments, analysing the pneumatic pressure pulsations in the cuff bladder by the arterial pressure pulsations at each cuff pressure increment, and uses these characteristics to determine LOP [41]. This system is comprised of a dual-purpose easy-fit variable contour nylon cuff (11.5 cm x 86 cm, 5 mm thick) connected by airtight hose tubing to a PT system, and automatically regulates pressure within acceptable limits [42]. Prior to exercise the cuff was placed on the most proximal portion of the limb and LOP was calculated in the body position that the BFR stimulus would be applied [40]. BFR pressure was set at 80% LOP to maximise fast twitch fibre recruitment [43] and maximise muscle adaptations [44]. LOP was calculated for each limb individually at every session.

2.7 Test-retest reliability, standard error of measurement and minimal detectable change

Intraclass correlation coefficients (ICC) assessed test-retest reliability of each outcome measure during pilot work. From this, standard error of measurement (SEM) and minimal detectable change (MDC) were calculated to establish random error. SEM was calculated using the formula: SD(pooled)*(√(1-ICC)). MDC was calculated using the formula: MDC = 1.96*SEM*√2.

2.8 Muscle strength

Unilateral 10RM strength was assessed on a leg press MED (Technogym, Bracknell, UK), following a warm-up consisting of 5 min light cycling and 10 repetitions of unilateral leg press at a self-selected weight. Beginning at 80% of estimated 10RM the maximum load that could be lifted for 10 repetitions through controlled, full ROM (0-90°) with correct form was recorded as the concentric 10RM. All 10RMs were achieved within 5 attempts with 5 kg increments in external load at each attempt and 3 min of rest between attempts to ensure full muscle recovery [45]. The ICC, SEM and MDC were 0.98, 1.96 kg and 5.46 kg, respectively. Participant's isokinetic KE and KF muscle strength was measured on a Biodex System 4 Isokinetic Dynamometer (IPRS Mediquipe, Suffolk, UK). Following 5 submaximal warm-up repetitions and 3 min of rest, participants performed 5 maximal effort repetitions of knee extension and flexion throughout full ROM at 60°/s and 150°/s and 10 maximal effort

repetitions at 300°/s with 20 s rest between speeds. The ICC, SEM and MDC ranges were 0.91-0.97, 0.02-0.03 kg/kgbm and 0.03-0.09 kg/kgbm, respectively).

2.9 Muscle morphology

Muscle thickness, pennation angle and fascicle length of the vastus lateralis on the injured limb only was assessed with B-mode ultrasonography using the LOGIQ E ultrasound device (GE Healthcare, Buckinghamshire, UK). All measurements were taken on the injured limb with participants lying supine on a portable treatment bed. Measurement was taken at 50% of the distance from the anterior superior iliac spine to the superior pole of the patella, which represents the maximum cross-sectional area of the vastus lateralis [46,47], in a lateral position at a distance of 10% of the limb circumference at this point, to account for the lateral location of the vastus lateralis [47]. A 4.2 to 13.0 MHz wide-band linear array scanning transducer head (12.7 x 47.1 mm) was lubricated with transmission gel and placed gently on the marked area without depressing the dermal surface. Any distortion of tissue due to excess compression was eliminated by observing that no movement of the tissue occurred in the real-time ultrasound image. When a clear image with visible aponeurosis and individual fascicles was displayed on the screen, the image was 'frozen' and then saved for analysis using ImageJ software (Version 1.47v, National Institutes of Health, Bethesda, MD, USA). An average was calculated from three images. Muscle thickness (cm) was defined at the distance between the superficial and deep aponeurosis at the widest point in each image [48]. Pennation angle was measured as the angle (°) between the fascicle and deep aponeurosis [48]. Fascicle length (cm) was measured as the distance between the insertions of the fascicle into the superficial and deep aponeurosis [49]. All measurements were performed by the same assessor. For muscle thickness, pennation angle and fascicle length the ICC's were 0.93, 0.89 and 0.95, SEM's were 0.01 cm, 0.05° and 0.02 cm and MDC's were 0.03 cm, 0.14° and 0.06 cm, respectively.

2.10 Physical function

Self-reported function was assessed using the following tools. The International Knee Documentation Committee subjective knee form assesses symptoms and function in activities of daily living. It is scored on a 0-100 scale with 100 representing higher knee function [50], has a test-retest reliability of 0.95 and MDC of 11.5 points [51]. The Knee Injury and Osteoarthritis Outcome Score is a tool to assess a patient's opinion of their knee and associated problems, including subscales for pain, symptoms, function in activities of daily living and knee-related quality of life. Each subscale includes questions with standardised answer options given across 5 Likert boxes, with scores ranging from 0 to 4. Each subscale was scored independently, and scores were transformed to a 0 to 100 score, with 0 representing extreme symptoms and 100 representing no symptoms. Collectively, the subscales have a test-retest reliability of 0.75-0.95 and a MDC of 5.0-8.5 points [51]. The lower extremity function scale contains 20 questions about a patient's ability to perform everyday tasks; each question has a scoring scale of 0

to 4, with a maximum possible total score of 80 that represents greatest function. It has a test-retest reliability of 0.94 and a MDC of 10.3 points [51]. Scores were interpreted as a percentage of maximal function (% of maximal function = ((score/80) x 100). The Lysholm knee scoring scale is used to evaluate the outcomes of knee ligament surgery, particularly symptoms of instability. Each item was scored, and scores were summed to give an overall total score out of a possible range of 0 to 150, where 150 indicates no symptoms or disability. It has a test-retest reliability of 0.97 and a MDC of 10.1 points [51]. Finally, the Tegner activity scale provides a standardised method of grading activity [52]. The scale ranges from 0 to 10, with 0 representing sick leave or disability pension because of knee problems, and 10 corresponding to participation in national and international elite level competitive sports. It has a test-retest reliability of 0.82 and a MDC of 1 point [53].

Dynamic postural control of the lower limb was assessed using the modified star excursion balance test (SEBT) [54] in the anterior, posteromedial and posterolateral directions [55,56]. Participants performed 6 familiarisation trials in each of the reach directions [55] following 5 min of light cycling at a free cadence prior to testing. A total of 3 attempts were performed for each direction, recorded to the nearest 0.5 cm. All distance scores were normalised to leg length (%LL) [55,57] and the mean of the 3 attempts was calculated. This method has a test-retest reliability of 0.88, 0.94 and 0.90, and MDC of 5.66 cm, 6.40 cm and 7.04 cm for the anterior, posterolateral and posteromedial reach directions, respectively [57].

2.11 Pain

Pain was assessed using the Knee Injury and Osteoarthritis Outcome Score pain scale. As 0 represents extreme pain and 100 represents no pain, an increase in pain score is indicative of a reduction in pain.

2.12 ROM

Knee ROM (°) was assessed using a goniometer with the participant lying supine with their heel elevated on a foam roller according to previous procedures [31]. Knee extension (EXT) was measured with participants maximally extending the knee joint and defined as the difference from 0° of extension [58]. Knee flexion (FE) was measured with patients bending their knee and slide their heel as far as possible toward their buttocks [58]. Side-to-side difference scores were calculated: difference (°) = (non-injured - injured) [7]. The ICC, SEM and MDC were 0.99, 0.01° and 0.03°, respectively.

2.13 Effusion

With the participant lying supine, effusion was evaluated by measurement of mid-patella knee joint circumference (cm) to the nearest 0.1 cm using a flexible tape measure [59]. The mean of 3 repeated measurements was calculated [60]. The ICC, SEM and MDC were 0.97, 0.04 cm and 0.2 cm respectively.

2.14 Knee joint laxity

With participants lying supine in 30° of knee flexion, knee ligament laxity (mm) was assessed using the KT-1000 knee ligament arthrometer (MEDmetric, San Diego, CA) at 30 lbs (130N) [25,61] and expressed as side-to-side differences scores (mm).

2.15 Data storage and analysis

All data was coded and stored on the NHS password protected and University servers in line with NHS data protection regulations. Descriptive statistics (mean ± SD) were used to describe adherence rates, exercise session attendance and any adverse events. All statistical analysis was performed with IBM SPSS Statistics Version 24.0 (IBM Corp, Chicago IL, United States of America). Data are presented as mean ± SD with 95% CIs unless stated otherwise. Differences between groups in baseline characteristics were assessed using independent samples t-tests for continuous dependent variables and Fisher's exact test for categorical data (gender, graft type and dominant/affected limb). Normal distribution of data was assessed using Shapiro-Wilks test ($p>0.05$) and homogeneity of variances (where appropriate) was assessed using Levene's Test of Homogeneity of variances ($p>0.05$). If the assumption of sphericity was violated (as assessed by Mauchly's test of sphericity) Greenhouse-Geisser corrected ANOVA tests were reported. 10RM strength, muscle morphology, self-reported function and modified SEBT data were each assessed using a 2 x 4 (group x time) repeated measures ANOVA with group allocation (BFR-RT vs. HL-RT) as the between subject's independent factor, and time (pre-surgery, post-surgery, mid-training and post-training) as the within subject's dependent factor. Isokinetic strength at each speed was assessed using a 2 x 2 (group x time) repeated measures ANOVA with the same factors. Alpha significance was set a priori $p<0.05$. Effect size descriptors were described as Cohen's d: weak <0.2, weak to moderate 0.2 to 0.4, moderate 0.4 to 0.65, moderate to strong 0.65 to 0.7 and strong >0.8 [62].

3. Results

3.1 Participants and rehabilitation programme

Four participants were lost before completing the study protocol (2 per group) due to unplanned additional surgery (n=1) and reasons unrelated to the study (n=3), leaving 24 completed participants (86%) (Figure 1). There were no significant differences between groups for any baseline anthropometric variable (Table 1), adherence or training load changes (Table 2). Total exercise volume was higher with BFR-RT (Table 2). There were no adverse events reported.

INSERT TABLES 1 AND 2

3.2 Scaled 10RM muscle strength

There was no statistically significant interaction for either limb. There were significant main effects of time for the injured limb ($p<0.01$, $d=1.0$) and non-injured limb ($p<0.01$, $d=1.0$). From pre-surgery to post-surgery, scaled 10RM strength decreased in the injured limb and was maintained in the non-injured limb with no group differences (Figure 2). Over 8 weeks of training, both groups experienced significant increases in scaled 10RM strength (BFR-RT: 104 ± 18% and 33 ± 12%, HL-RT: 106 ± 21% and 40 ± 16% for the injured and non-injured limbs, respectively) with no group differences ($p=0.22$, $d=0.3$ and $p=0.39$, $d=0.3$ for the injured and non-injured limbs, respectively) (Figure 2).

INSERT FIGURE 2

3.3 Scaled isokinetic strength

From pre-surgery to post-training, for the injured limb at 60°/s a decrease in KE peak torque was observed in both groups (Figure 3) with no group differences ($p=0.20$, $d=0.5$). At 150°/s and 300°/s, significant decreases in KE peak torque were observed with HL-RT while no significant changes were observed with BFR-RT (Figure 3). Significantly greater decreases in KF peak torque were observed at all speeds with HL-RT compared to BFR-RT (all $p<0.01$, $d=0.7$-1.2) (Figure 4). For the non-injured limb, significant increases in KE and KF peak torque were observed at all speeds with both BFR-RT and HL-RT (Figure 4) with no group differences (all $p<0.05$, d range=0.1-0.4).

INSERT FIGURES 3 & 4

3.3 Muscle morphology

There was no statistically significant interaction effect for muscle thickness, pennation angle or fascicle length. There were significant main effects of time for muscle thickness ($p<0.01$, $d=1.0$), pennation angle ($p<0.01$, $d=0.9$) and fascicle length ($p<0.01$, $d=1.0$). From pre-surgery to post-surgery, both groups experienced significant decreases in muscle thickness, pennation angle and fascicle length with no group differences (Supplementary data file 2). Over 8 weeks of training, both groups experienced significant increases in muscle thickness (5.8 ± 0.2% and 6.7 ± 0.3%) and pennation angle (4.1 ± 0.3% and 3.4 ± 0.1%) for BFR-RT and HL-RT, respectively, with no group differences ($p=0.33$ and $d=0.4$, $p=0.28$ and $d=0.5$ for muscle thickness and pennation angle, respectively). Changes in muscle thickness and pennation angle exceeded the MDC of 2.7 and 2.9, respectively. There were no changes in fascicle length over 8 weeks of training with no group differences ($p=0.94$ and $d=0.0$) (Table 3).

3.4 Physical function

There were statistically significant group x time interaction effects for IKDC, LEFS, LKSS and all KOOS sub-scale score. From pre-surgery to post-surgery, all self-report measures significantly

decreased with no group differences (all p>0.05, d=0.1-0.3) (Supplementary file 2). Over 8 weeks of training, there were significantly greater increases in all self-report measures with BFR-RT (Table 3).

3.5 Modified SEBT

There were statistically significant group x time interaction effects for anterior, posteromedial and posterolateral reach scores in the injured limb. From pre-surgery to post-surgery all reach scores significantly decreased with no group differences (all p>0.05, d=0.2-0.5) (Supplementary file 2). Over 8 weeks of training, there were significantly greater increases in all reach scores with BFR-RT (Table 3). There were no statistically significant group x time interaction effects for anterior, posteromedial or posterolateral reach scores for the non-injured limb. There were significant main effects of time for AM (p<0.01, d=0.9), posteromedial (p<0.01, d=1.0) and posterolateral (p<0.01, d=1.0) reach scores. From pre-surgery to post-surgery all reach scores significantly decreased with no group differences (all p>0.05, d=0.0-0.4) (Supplementary file 2). Over 8 weeks of training, all reach scores significantly increased with no group differences (all p>0.05, d=0.1-0.4) (Table 3).

3.6 ROM

There were no changes in EXT differences throughout the study (Table 3). There were statistically significant group x time interaction effects for FE difference and ROM difference. From pre-surgery to post-surgery, FE difference and ROM difference significantly increased with no group differences (p=0.22 and d=0.5, p=0.17 and d=0.5 for FE and ROM, respectively) (Supplementary file 2). Over 8 weeks of training there were significantly greater decreases in FE difference (-80% ± 27% vs -42 ± 13%) and ROM difference (-78 ± 22% vs -42 ± 16%) with BFR-RT compared to HL-RT (Table 3).

3.7 Pain

There was a statistically significant group x time interaction effect for KOOS-pain score. From pre-surgery to post-surgery, KOOS-pain score significantly decreased with no group differences (p=0.43, d=0.3) (Supplementary file 2). Over 8 weeks of training there was a significantly greater increase in KOOS pain score (67 ± 10% vs. 39 ± 14%) with BFR-RT (Table 3).

3.7 Effusion

There was a statistically significant group x time interaction effect for mid-patella knee joint circumference. From pre-surgery to post-surgery, mid-patella knee joint circumference scores significantly increased with no group differences (p=0.70, d=0.0) (Supplementary file 2). Over 8 weeks of training there was a significantly greater decreases in mid-patella knee joint circumference (-5.8 ± 1.2% vs -2.4 ± 1.8%) with BFR-RT (Table 3).

3.8 Laxity

From pre-surgery to post-training, side-to-side difference in laxity significantly decreased with no group differences (p=0.87, d=0.1). With BFR-RT, side-to-side difference decreased from 3.4 ± 1.3 to 1.1 ± 1.7 mm, a mean difference of 2.3 ± 1.6 mm (95% CI: 1.42 to 3.25) that was statistically significant (p<0.01, d=1.2). With HL-RT, side-to-side difference decreased from 3.5 ± 1.0 to 1.3 ± 0.8 mm, a mean difference of 2.3 ± 0.6 mm (95% CI: 1.90 to 2.60) that was statistically significant (p<0.01, d=1.4).

4. Discussion

This study was the first to examine the effect of BFR-RT and HL-RT on muscle hypertrophy, strength, physical function and knee pain and effusion during an ACLR rehabilitation programme within an NHS setting. The main findings of this clinical study were that 1) BFR-RT and HL-RT elicited comparable increases in skeletal muscle hypertrophy and strength; 2) BFR-RT resulted in greater improvements in physical function and ROM; 3) BFR-RT resulted in a greater reduction in pain and effusion; 4) There were no adverse events or effects on knee joint laxity with either intervention. These findings have important implications for post-surgery ACLR rehabilitation.

4.1 Muscle strength

Similarly to previous literature in load compromised populations, in the present study it was found that 8 weeks of BFR-RT resulted in comparable increases in 10RM strength to HL-RT while utilising a light external load (30% vs. 70% 1RM) [20–22,63]. The magnitude of skeletal muscle strength improvements in the non-injured limb (33% and 39% with BFR-RT and HL-RT, respectively) is consistent with the existing literature which collectively indicates that engaging in each type of training over 6-12 weeks increases muscle strength by 15-39% [20–22,63]. More substantial improvements in strength of 85% and 88% for the injured limb were observed with BFR-RT and HL-RT, respectively. Arthrogenic inhibition is associated with joint damage, effusion and pain [64], therefore the reductions in pain and effusion observed in the present study may have contributed to an improved capacity for strength adaptations in the injured limb. A combination of central and neural adaptations and muscle hypertrophy typically underpin strength improvements with HL-RT [65]. Corticomotor excitability has been shown to increase following an acute bout of BFR-RT, possibly due to altered sensory feedback from group II and IV afferent fibres [66]. This may indicate a neuromuscular adaptation occurring with BFR-RT alongside hypertrophy.

In contrast to these findings, decreases of -8% and -13% in KE muscle peak torque of the injured limb measured at 60°/s were observed following BFR-RT and HL-RT, respectively. This observation is similar to a previous study in ACL deficient patients undergoing either closed kinetic chain or open kinetic chain strength training [67]. Though the authors observed similar increases in 1RM strength with both types of training, improvements in KE muscle peak torque at 60°/s were observed following

open kinetic chain training only. Addition of open kinetic chain strength training to a closed kinetic chain post-surgery rehabilitation protocol for ACLR patients has been shown to improve KE muscle peak torque [68]. Therefore, patients may need open kinetic chain strength training specifically to regain good muscle torque [67,68]. At 150°/s and 300°/s deficits of -16% and -9% (respectively) in KE muscle peak torque were observed following HL-RT, whereas no differences were observed with BFR-RT at either speed. It is possible that the greater degree of knee joint pain and effusion with HL-RT observed throughout the 8 week training programme may have impacted performance during torque measurement. Experimentally induced knee pain and effusion have both been shown to cause greater KE muscle arthrogenic inhibition and torque deficit [64]. In the injured limb, decreases in KF muscle peak torque compared to pre-surgery values were observed at all speeds with both BFR-RT and HL-RT. This was expected given that all participants underwent hamstring autografts for surgical repair of the ACL, with the magnitude of decrease lower with BFR-RT at all speeds. Though the degree of activation of the KF muscles during leg press exercise appears smaller in magnitude compared to the KE muscles [69], BFR-RT may have increased activation of the fast twitch fibres within the KF muscles during leg press training and contributed to attenuation of strength loss [70,71].

4.2 Muscle hypertrophy

Following 8 weeks of training, muscle thickness increased by 5.8% and 6.7% with BFR-RT and HL-RT, respectively. This is in agreement with a recent meta-analysis concluding that BFR-RT and HL-RT are equally effective at improving muscle mass [19], and the magnitude of increase is in line with the existing literature showing improvements in muscle thickness of 6-8% over 5-12 weeks of training [21,72–74]. Greater increases in muscle thickness were observed in week 5 to 8 of training compared to 1 to 4 in both groups, suggesting that the early increases in strength were a result of neural adaptations in the absence of significant hypertrophy. A 4.1% and 3.4% increase in pennation angle was observed with BFR-RT and HL-RT, respectively, and no change in fascicle length, over 8 weeks of training. This is in line with previous research reporting a 5.4% and 6% increase in pennation angle with BFR-RT (20% 1RM) and HL-RT (80% 1RM), respectively, in the absence of changes in fascicle length [49]. The slighter smaller changes in the present study are likely due to a shorter training duration and lower volume. Interestingly, both studies did not observe a change in fascicle length, indicating that an increase in muscle thickness is primarily related to an increase in pennation angle. As changes in fascicle length are associated with high strain/velocity activities [75,76], the lack of change in fascicle length is unsurprising, suggesting that the observed architectural remodelling was specific to the imposed demand.

4.3 Physical function

The significant and clinically important improvements in all measures of patient self-reported function and SEBT performance that were observed with both BFR-RT and HL-RT is in line with recent

literature in knee osteoarthritis patients [21,22]. Similarly to the present study, both of these studies observed improvements in strength, which may contribute to improvements in physical function [77,78]. Importantly, in the present study the observed improvements in self-reported function and SEBT performance were of significantly greater magnitude with BFR-RT, which may be due to the greater reduction in pain and effusion and greater improvement in ROM. Greater reductions in KOOS-pain (-67% vs. -39%) were observed, which is in agreement with literature comparing these two training modalities in patients with knee osteoarthritis [21], patellofemoral pain [20] and military in-patients [23]. The latter study observed greater improvements in functional test performance alongside a reduction in pain [23]. Together with greater reduction in effusion (6% vs. 2%), a reduction in pain may have contributed to a greater improvement in ROM. Indeed, a study examining 3 weeks of KE muscle strengthening following total knee arthroplasty surgery reported an increase in knee flexion ROM alongside a decrease in pain and effusion [60]. Importantly, the degree of ROM improvement in the present study is similar to previous research with BFR-RT in ACLR patients [25].

The greater reduction in pain with BFR-RT may be attributed to the lighter load used (30% vs. 70% 1RM) compared to HL-RT [22]. Recent research also suggests that BFR-RT may have a hypoalgesia effect [79,80], particularly in ACLR patients where knee pain was found to be significantly reduced during, immediately after and at 24 hours following BFR-RT compared to HL-RT [28]. Although the mechanisms of this effect are not yet understood, there are a several possibilities. Ischemia and pressure-induced muscle pain are often used as a conditioning stimulus for pain modulation and have been shown to alter pain sensitivity in healthy individuals [81]. Conditioned pain modulation resulting from BFR cuff pressure and the high level of ischemia and exercise-induced muscle pain [82] with BFR-RT may therefore contribute to an antinociceptive response. Other possible mechanisms include release of endogenous opioids and endocannabinoids during exercise [83,84].

4.4 Implications for clinical ACLR rehabilitation

The end goal of ACLR rehabilitation is for patients to be able to return to heavy loading and their pre-injury strength and activity level [11]. The application of BFR passively or in combination with electrical stimulation and aerobic exercise during the early post-surgery phases of ACLR rehabilitation has been discussed previously [11]. The present study shows that during the progressive limb loading phase of rehabilitation, the advantages of BFR-RT over HL-RT is that it can be used to allow a greater reduction in pain and effusion and improve physical function to a superior extent than HL-RT, importantly without any detrimental effect on muscle hypertrophy and strength improvements. Interestingly, our results suggest that BFR-RT may offset the decline in isokinetic strength seen following surgery when training using a closed kinetic chain exercise. The effect of exercise in populations with MSK conditions can be attenuated in the presence of pain [85] via a detrimental effect on motor control and muscle function [86] resulting to modified movement patterns, which further

highlights the advantage of BFR-RT-induced pain reduction during this phase of ACLR rehabilitation. Therefore, BFR-RT may be a superior tool during the early stages of this phase of rehabilitation, particularly in patients with a high degree of pain and/or effusion. Once individuals are physically able, show no change in effusion with loading activity and pain in minimal/absent, BFR-RT should be integrated with HL-RT as combining BFR-RT and HL-RT has been shown to augment muscle strength and size adaptations observed with BFR-RT alone [87]. This will allow for reintroduction of greater mechanical loads to structures of the musculoskeletal system and stimulation of other adaptations important during ACLR rehabilitation that may not be possible with HL-RT, such as tendon stiffness [49].

4.5 Strengths and limitations

A number of aspects contribute to the strength of this clinical study. It was the first to examine and compare the effect of BFR-RT on skeletal muscle hypertrophy and strength during ACLR rehabilitation using recommended protocols for each type of resistance training. In addition, the effect of BFR-RT on physical function, knee pain and effusion has not been examined previously. This study is also the first within an NHS setting. There was a low number of withdrawals (10%) and a high compliance rate to training. Groups were similar at baseline (pre-surgery) for all anthropometric and dependent variables except scaled 10RM strength. Moreover, the degree of change in all dependent variables from pre-surgery to post-surgery was not different between groups. Both groups had a similar progressive increase in training load throughout the study, and the main outcome assessor was blinded to intervention group allocation throughout all data collection and analysis. However, this study is not without its limitations. Muscle hypertrophy was measured in single plane only. Other factors that may influence ROM and thus functional performance, such as tendon stiffness and condition of other ligaments, could not be accounted for; however, there were no observable differences in meniscal or cartilage damage between groups at the time of recruitment. The warm-up weight may have been better standardised and, though not feasible in the scope of the current study, measurement of aspects such as accelerometer-based activity and dietary intake may have been beneficial. It was not ethically possible to blind participants to intervention group allocation; nevertheless, participants were trained individually and thus were not exposed to the other intervention protocol at any time. This study included a specific subgroup of ACLR patients which limits transference of the findings to other graft types and ages (e.g. paediatric). In addition, the present manuscript focusses on a specific phase of ACLR rehabilitation only and the small sample size may limit the generalisability of the results to the broader populations.

4.6 Conclusion

The present study demonstrates that BFR-RT can improve skeletal muscle hypertrophy and strength to a similar extent as HL-RT with a greater reduction in knee joint pain and effusion, leading to greater

overall improvements in physical function. Therefore, BFR-RT may be more appropriate in the progressive limb loading phase of rehabilitation following surgery in ACLR patient populations within the NHS.

5. Data availability statement

The datasets generated and analysed during the study are not publicly available due to the nature of patient confidentiality but are available from the corresponding authors on reasonable request with permission.

Author contributions LH, BR, CG, BP and SP contributed to study conceptualisation, writing and review of the manuscript. LH and SP contributed to data analysis. LH, DM, TC, GF, JD and BP contributed to data collection.

6. Compliance with ethical standards

Funding This study was supported by Delfi Medical Innovations Inc. who provided a pneumatic variable contour cuff and PTS device for the study.

Conflicts of interest Dr. Luke Hughes, Dr. Benjamin Rosenblatt, Prof. Fares Haddad, Prof. Conor Gissane, Mr. Daniel McCarthy, Mr. Thomas Clarke, Mr. Graham Ferris, Miss. Joanna Dawes, Dr. Bruce Paton and Dr. Stephen David Patterson have no conflicts of interest that are directly relevant to the content of this article.

Ethical approval and consent to participate Ethical approval for the research was granted by the NHS Health Research Ethics Committee and University Ethics Committee. Written informed consent was obtained from each of the participants in compliance with the Declaration of Helsinki (2013).

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Table 1. Group characteristics (Mean ± SD).

	BFR-RT (n=14)	HL-RT (n=14)	p value
Age (y)	29 ± 7	29 ± 7	1.00
Gender (Male/female)	7/5	10/2	0.37
Body mass (kg)	75.8 ± 15.1	79.2 ± 15.2	0.28
Height (cm)	172.32 ± 8.06	176.72 ± 7.70	0.19
Body mass index (kg/m^2)	25.40 ± 3.86	26.41 ± 4.35	0.55
Blood pressure (mmHg)			
Systolic	127 ± 5	126 ± 4	0.41
Diastolic	81 ± 3	81 ± 3	0.31
Mean arterial pressure	97 ± 3	96 ± 2	0.25
Days from surgery to post-surgery testing	23 ± 2	24 ± 1	0.25
Affected limb, *n*			
Dominant	7	4	0.41
Left	8	6	0.68
Right	4	6	
Leg length (cm)			
Injured	92.1 ± 7.7	93.2 ± 7.6	0.72
Non-injured	92.2 ± 7.6	93.2 ± 7.7	0.75
Pre-injury activity level (Tegner)	6.83 ± 1.80	7.42 ± 1.24	0.37
BFR pressure (mmHg)			
LOP			
Injured	186 ± 6		
Non-injured	196 ± 7		
80%LOP			
Injured	150 ± 3		
Non-injured	157± 6		

BFR-RT, blood flow restriction resistance training; HL-RT, heavy load resistance training; BFR, blood flow restriction; LOP, limb occlusion pressure.

Table 2. Group comparison of exercise session attendance, volume and load (Mean ± SD).

	Limb	BFR-RT	HL-RT	p	ES (d)
Exercise attendance (%)		91.2	87.5	0.27	0.3
Total exercise volume (kg)	Injured	21142660	15403763	<0.01	0.9
	Non-injured	28567500*	18465840*	<0.01	1.2
Exercise load (kg)					
Week 1 to 4	Injured	17.96 ± 7.34	38.88 ± 13.83	<0.01	0.6
	Non-injured	34.75 ± 7.44*	78.00 ± 21.47*	<0.01	0.8
% change week 1 to 4	Injured	47 ± 29$^{\dagger ¥}$	36 ± 18$^{\dagger ¥}$	0.27	0.1
	Non-injured	10 ± 12$^{¥}$	13 ± 6$^{¥}$	0.40	0.1
Week 5 to 8	Injured	35.38 ± 8.73	71.29 ± 19.26	<0.01	0.7
	Non-injured	47.00 ± 8.41*	100.13 ± 24.12*	<0.01	0.9
% change week 5 to 8	Injured	16 ± 14$^{¥}$	13± 6$^{¥}$	0.50	0.1
	Non-injured	9 ± 10$^{¥}$	9 ± 5$^{¥}$	0.88	0.0

* = significantly greater than injured limb (p<0.01); † = significantly greater than non-injured limb (p<0.01); ¥ = significant change (p<0.05). BFR-RT, blood flow restriction resistance training; HL-RT, heavy load resistance training; ES, effect size.

Table 3. Changes in self-reported function, modified SEBT, ROM, knee joint effusion scores and muscle morphology (Mean ± SD).

Measure	Group	Mean difference week 0 to 4 (95% CIs)	ES (d)	Mean difference week 4 to 8 (95% CIs)	ES (d)	Overall mean difference week 0 to 8 (95% CIs)	ES (d)	*F*	ANOVA p	ANOVA ES (d)
IKDC	BFR-RT	22.44 ± 5.27 (19.46 to 25.42)*†	2.4	13.19 ± 4.95 (10.39 to 15.99)*§	1.6	35.63 ± 7.06 (31.64 to 39.63)*†‡	3.8	7.083	<0.01	0.8
	HL-RT	13.50 ± 7.42 (9.30 to 17.70)*	1.7	9.83 ± 5.54 (6.70 to 12.97)*	1.6	23.33 ± 8.76 (18.38 to 28.29)*‡	2.9			
LEFS	BFR-RT	21.46 ± 10.68 (15.41 to 27.50)*§	1.6	17.40 ± 10.09 (11.69 to 23.11)*	1.3	31.08 ± 12.22 (24.17 to 38.00)*†‡	2.5	14.45	<0.01	0.9
	HL-RT	14.69 ± 7.76 (10.30 to 19.08)*	1.3	12.60 ± 6.58 (8.88 to 16.33)*	1.0	21.83 ± 7.06 (17.84 to 25.83)*‡	1.7			
KOOS										
Pain	BFR-RT	30.25 ± 9.29 (24.99 to 35.51)*†	2.3	9.50 ± 5.57 (6.35 to 12.65)*	1.3	39.75 ± 11.74 (23.11 to 36.39)*†‡	3.5	3.512	<0.05	0.6
	HL-RT	11.67 ± 6.11 (8.21 to 15.12)*	0.9	10.33 ± 4.62 (7.72 to 12.95)*	0.9	22.00 ± 7.48 (17.77 to 26.23)*‡	1.8			
Symptoms	BFR-RT	22.17 ± 11.65 (15.58 to 28.76)*†	1.7	11.17 ± 5.56 (8.02 to 14.31)*	1.2	33.33 ± 13.60 (25.64 to 41.03)*†‡	1.3	3.380	<0.05	0.7
	HL-RT	12.17 ± 5.91 (8.83 to 15.51)*	1.2	12.33 ± 6.50 (8.66 to 16.01)*	1.2	24.50 ± 7.62 (20.19 to 28.81)*‡	1.0			
ADL	BFR-RT	21.83 ± 8.35 (17.11 to 26.56)*†	0.7	10.50 ± 8.57 (5.65 to 15.35)*	0.4	32.33 ± 10.37 (26.47 to 38.20)*†‡	1.3	4.030	<0.05	0.8
	HL-RT	11.17 ± 6.28 (7.61 to 4.72)*	0.4	10.58 ± 4.32 (8.14 to 13.03)*	0.4	21.75 ± 6.90 (17.84 to 25.66)*‡	0.6			
QOL	BFR-RT	15.10 ± 10.81 (8.99 to 21.22)*	1.1	14.48 ± 10.05 (8.79 to 20.16)*§	1.2	29.58 ± 14.81 (21.20 to 37.96)*†‡	2.1	3.654	<0.05	0.7
	HL-RT	12.50 ± 13.85 (4.67 to 20.33)*	0.9	7.81 ± 7.11(3.79 to 11.84)*	0.6	20.31 ± 12.82 (13.06 to 27.56)‡	1.7			
Lysholm	BFR-RT	29.75 ± 12.86 (22.48 to 37.02)*†	2.6	14.83 ± 6.06 (11.41 to 18.26)*	1.8	44.58 ± 14.75 (36.24 to 52.93)*†‡	3.9	3.529	<0.05	0.8
	HL-RT	17.25 ± 9.96 (11.61 to 22.89*	1.5	12.25 ± 4.29 (9.82 to 14.68)*	1.8	29.50 ± 12.07 (22.67 to 36.33)*‡	2.7			
SEBT (%LL)										
ANT Non-injured	BFR-RT	8.4 ± 5.1 (5.54 to 11.34)*	1.3	4.4 ± 2.4 (3.1 to 5.8)*	0.7	18.7 ± 9.3 (13.4 to 23.9)*‡	2.7	0.165	0.75	0.3
	HL-RT	7.5 ± 8.0 (3.0 to 12.1)*	0.5	3.0 ± 2.1 (1.79 to 4.21)*	0.3	10.5 ± 9.2 (5.33 to 15.73)*‡	0.8			
Injured	BFR-RT	22.3 ± 5.2 (19.35 to 25.18)*†	2.3	5.8 ± 3.1 (4.1 to 7.5)*	0.6	32.9 ± 9.7 (27.4 to 38.4)*†‡	3.8	4.818	<0.05	0.8
	HL-RT	9.0 ± 3.5 (7.0 to 10.9)*	0.7	8.5 ± 5.5 (5.42 to 11.60)*	0.7	17.5 ± 6.7 (13.69 to 21.29)*‡	1.5			
PM Non-injured	BFR-RT	11.6 ± 8.1 (7.03 to 6.21)*	0.9	4.5 ± 3.1 (2.8 to 6.3)*	0.4	22.4 ± 13.7 (14.7 to 30.1)*‡	0.9	0.374	0.69	0.4
	HL-RT	8.5 ± 7.2 (4.4 to 12.6)*	0.5	4.3 ± 4.0 (2.01 to 6.56)*	0.2	12.8 ± 9.1 (7.61 to 17.90)*‡	0.7			
Injured	BFR-RT	19.1 ± 9.2 (13.93 to 24.37)*†	1.2	7.3 ± 4.8 (4.6 to 10.1)*	0.5	32.1 ± 15.1 (23.6 to 40.7)*†‡	2.4	14.40	<0.01	0.9
	HL-RT	5.5 ± 5.2 (2.6 to 8.5)*	0.4	8.4 ± 4.4 (5.89 to 10.92)*	0.7	13.9 ± 7.7 (9.57 to 18.32)*‡	1.1			
PL Non-injured	BFR-RT	13.0 ± 15.6 (4.13 to 21.79)*	0.8	4.9 ± 3.4 (3.0 to 6.8)*	0.4	23.8 ± 17.8 (13.8 to 33.8)*‡	1.5	0.135	0.87	0.3
	HL-RT	9.8 ± 9.7 (4.3 to 15.3)*	0.4	4.7 ± 5.1 (1.80 to 7.55)*	0.2	14.5 ± 10.1 (8.78 to 20.20)*‡	0.7			
Injured	BFR-RT	23.3 ± 12.5 (16.20 to 30.34)*†	1.5	6.2 ± 4.3 (3.8 to 8.6)*	0.5	34.8 ± 15.3 (26.1 to 43.4)*†‡	2.3	13.54	<0.01	1.0
	HL-RT	5.8 ± 8.0 (1.2 to 10.3)*	0.4	7.4 ± 3.5 (5.49 to 9.40)*	0.6	13.2 ± 10.3 (7.37 to 19.02)*‡	1.0			
ROM (°)										
FE difference	BFR-RT	31.17 ± 7.17 (27.11 to 31.17)*†	5.0	5.17 ± 4.02 (2.89 to 7.44)*	1.2	36.33 ± 6.01 (32.94 to 39.73)*†‡	6.8	6.647	<0.01	0.9
	HL-RT	16.33 ± 5.66 (13.13 to 19.54)*	3.7	4.33 ± 3.14 (2.56 to 6.11)*	0.8	20.67 ± 6.85 (16.79 to 24.54)*‡	4.6			
EXT difference	BFR-RT	-0.17 ± 0.72 (-0.57 to 0.24)	0.1	0.17 ± 0.58 (-0.16 to .49)	0.1	0.00 ± 0.85 (-0.48 to 0.48)	0.0	0.585	0.59	0.6
	HL-RT	0.00 ± 0.85 (-0.48 to 0.48)	0.0	-0.08 ± 0.67 (-0.46 to 0.29)	0.1	-0.08 ± 0.67 (-0.46 to 0.29)	0.1			
ROM difference	BFR-RT	31.33 ± 7.43 (27.13 to 35.54)*†	4.5	5.00 ± 3.88 (2.80 to 7.20)*	1.0	36.33 ± 6.11 (32.88 to 39.79)*†‡	5.9	8.307	<0.01	0.9
	HL-RT	16.33 ± 5.61 (13.16 to 19.51)*	3.5	4.42 ± 3.45 (2.46 to 6.37)*	0.8	20.75 ± 6.73 (16.94 to 24.56)*‡	4.4			
Effusion (cm)	BFR-RT	-1.2 ± 1.4 (-0.45 to -2.04)*§	0.8	-1.0 ± 1.1 (-0.42 to -1.67)*	0.6	-2.3 ± 0.9 (-1.80 to -2.77)*†‡	0.8	7.038	<0.01	0.7
	HL-RT	-0.1 ± 0.8 (-0.51 to 0.41)	0.3	-0.9 ± 0.4 (-0.72 to -1.12)*	0.5	-1.0 ± 0.7 (-0.55 to -1.39)*‡	0.5			
Muscle morphology										
MT (cm)	BFR-RT	0.02 ± 0.01 (0.02 to 0.03)	0.1	0.08 ± 0.03 (0.07 to 0.10)*	0.5	0.10 ± 0.04 (0.09 to 0.13)*‡	0.6	1.543	0.23	0.4
	HL-RT	0.03 ± 0.01 (0.03 to 0.04)	0.1	0.09 ± 0.05 (0.06 to 0.12)*	0.6	0.12 ± 0.06 (0.9 to 0.16)*‡	0.7			
PA (°)	BFR-RT	0.19 ± 0.08 (0.15 to 0.24)	0.1	0.37 ± 0.15 (0.28 to 0.45)*	0.5	0.56 ± 0.23 (0.33 to 0.69)*‡	0.6	0.583	0.56	0.5
	HL-RT	0.20 ± 0.11 (0.14 to 0.26)	0.2	0.28 ± 0.19 (0.17 to 0.39)*	0.4	0.48 ± 0.20 (0.31 to 0.55)*‡	0.6			
FL (cm)	BFR-RT	0.01 ± 0.03 (-0.01 to 0.02)	0.0	0.12 ± 0.24 (-0.02 to 0.26)	0.1	0.13 ± 0.27 (0.03 to 0.28)	0.1	0.216	0.81	0.4
	HL-RT	0.02 ± 0.04 (0.00 to 0.04)	0.0	0.12 ± 0.26 (-0.03 to 0.27)	0.1	0.14 ± 0.30 (0.03 to 0.31)	0.1			

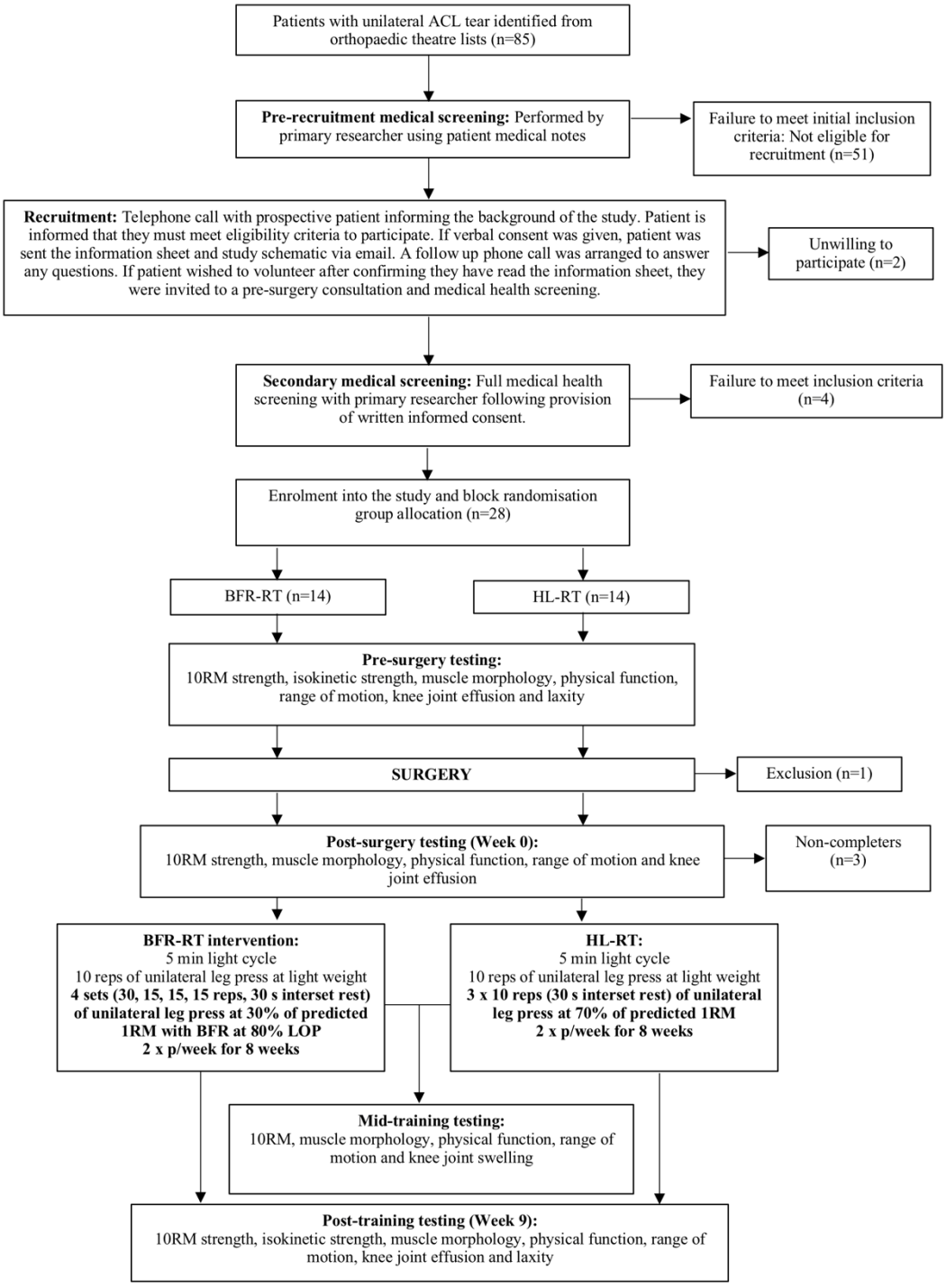

Figure 1. Flow chart of study process

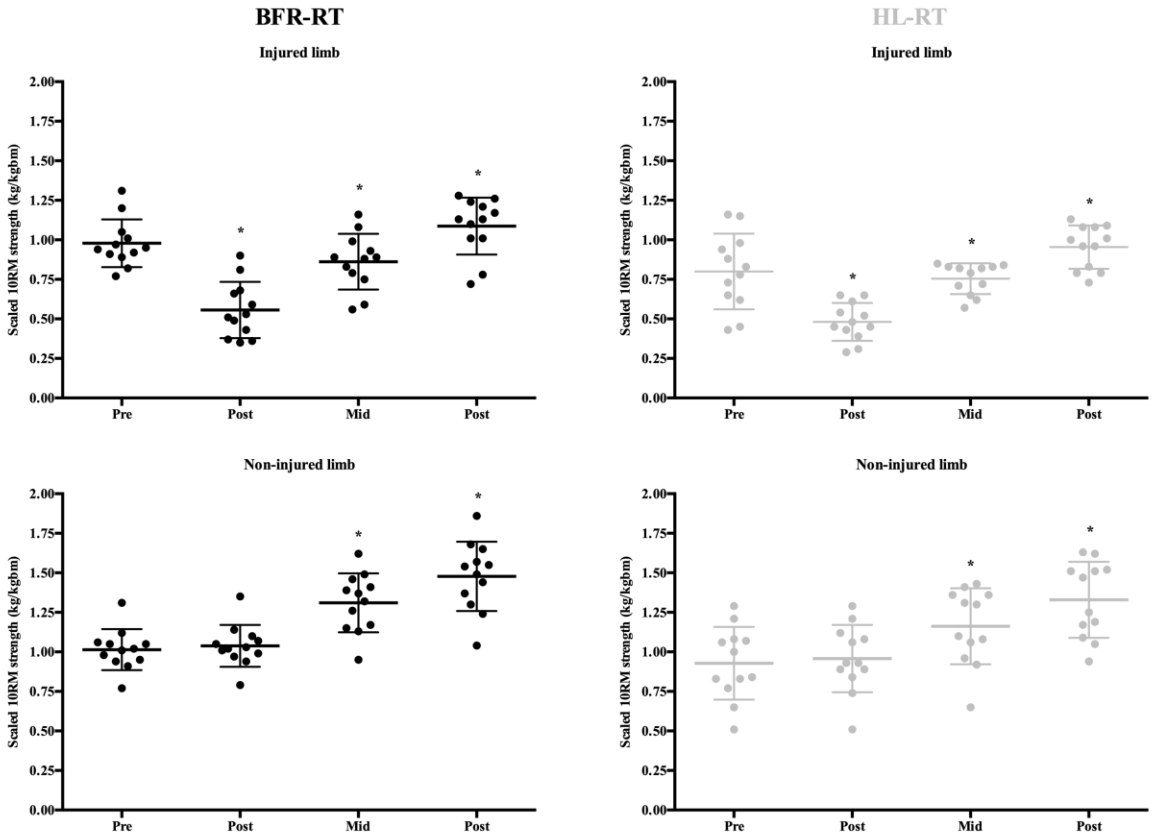

Figure 2. Change in scaled 10RM strength over the duration of the study for the injured and non-injured limb. Data are presented as mean ± SD. * indicates a significant change from previous timepoint ($p<0.01$). BFR-RT, blood flow restriction resistance training; HL-RT, heavy load resistance training.

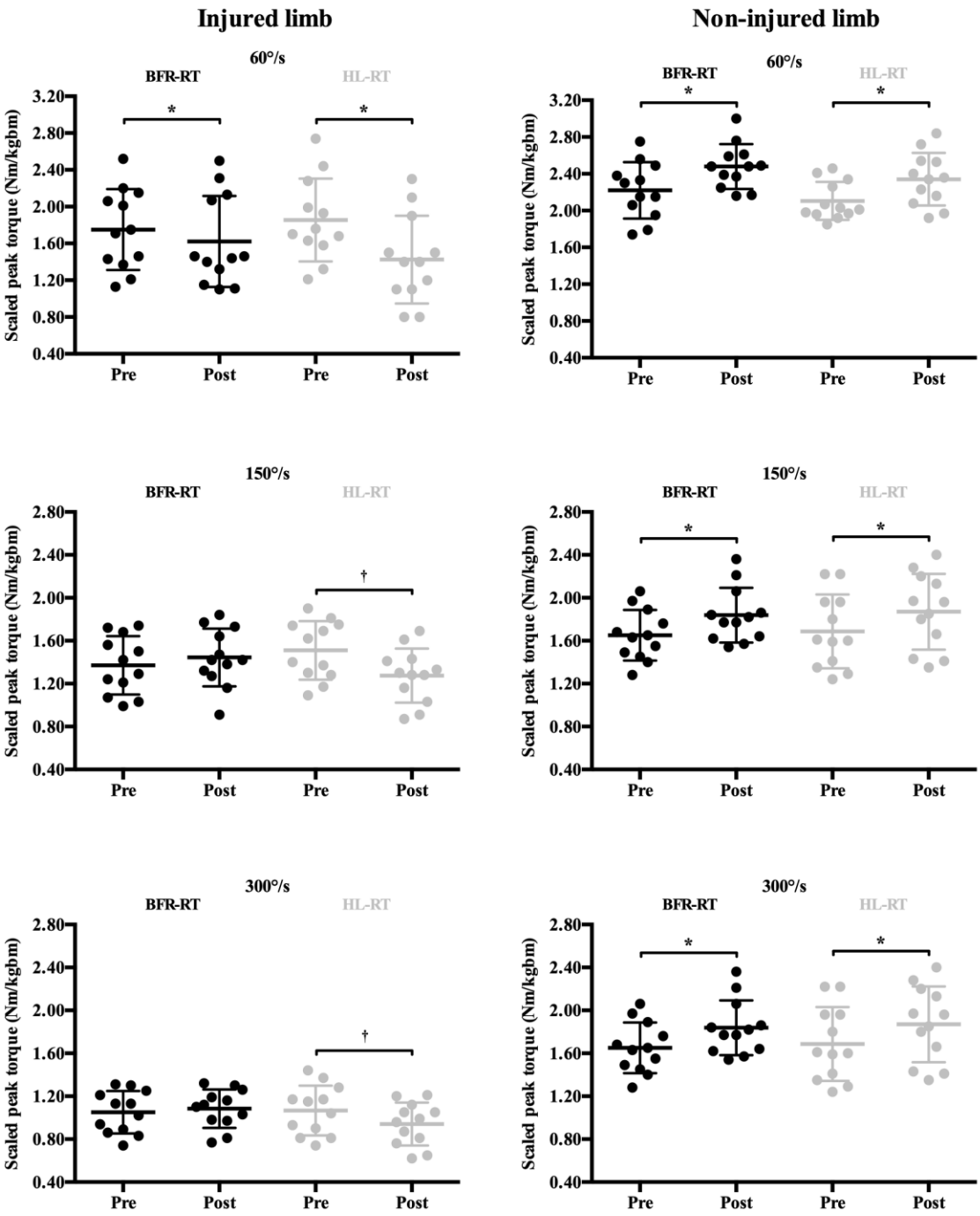

Figure 3. Change in scaled knee extensor peak torque at 60°/s, 150°s and 300°/s for the injured and non-injured limb. Data are presented as mean ± SD. * indicates a significant change ($p<0.01$); † indicates a significantly greater decrease compared to BFR-RT ($p<0.01$). BFR-RT, blood flow restriction resistance training; HL-RT, heavy load resistance training.

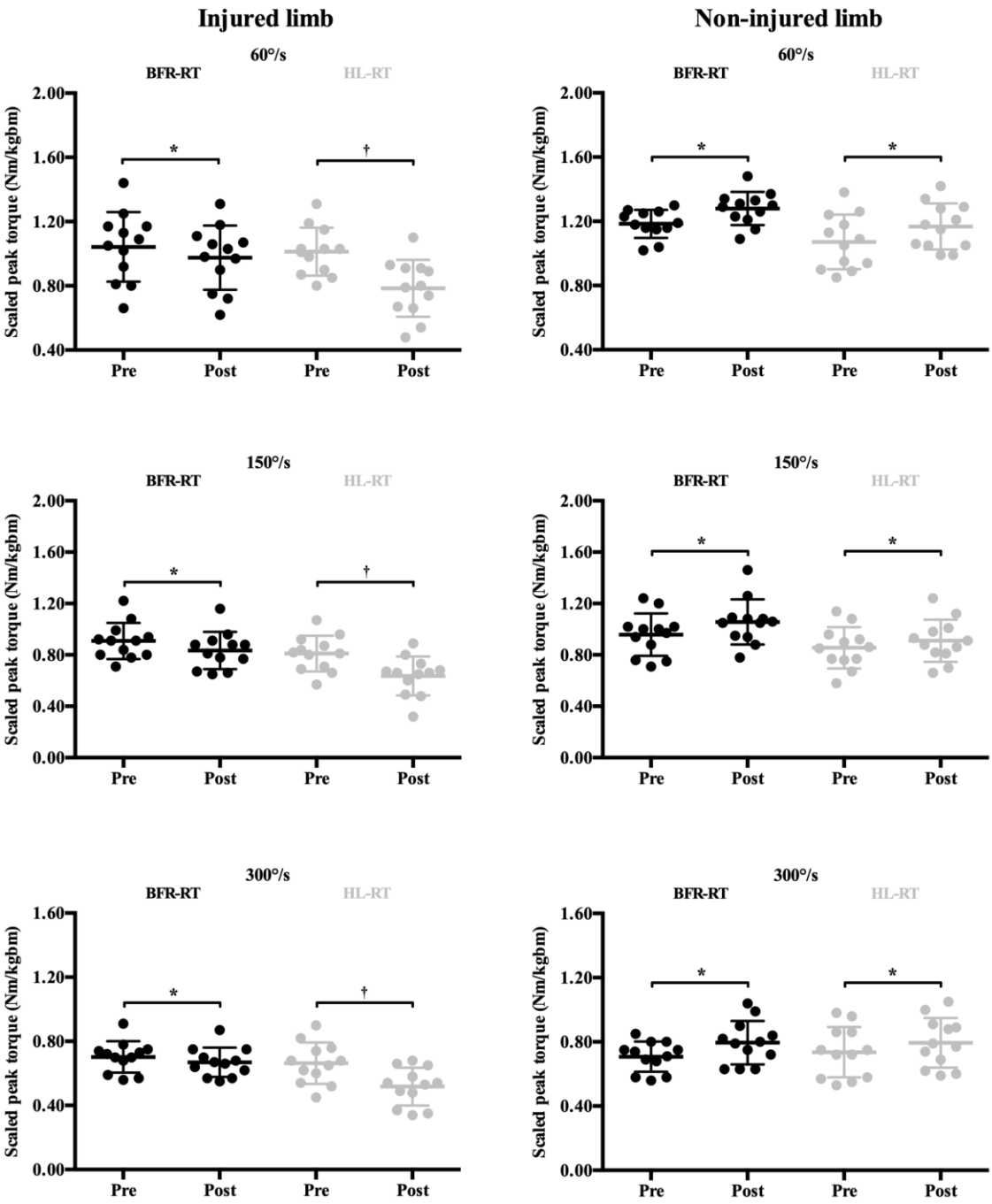

Figure 4. Change in scaled knee flexor peak torque at 60°/s, 150°s and 300°/s for the injured and non-injured limb. Data are presented as mean ± SD. * indicates a significant change ($p<0.01$); † indicates a significantly greater decrease compared to BFR-RT ($p<0.01$). BFR-RT, blood flow restriction resistance training; HL-RT, heavy load resistance training.

Supplementary data file 1

Standard post-surgery ACLR rehabilitation programme at University College London Hospital

Phase	Weight bearing	Brace	ROM	Exercise	Precaution
1 (~0-2 weeks)	Weight bearing as tolerated, working towards FWB without crutches by 10 days	No brace required if no other ligament repairs Remove compression bandage at 48 hours	Working towards full extension and flexion of 90°	KE SLR Calf raises Hip extension (standing) Gait re-education	No resisted hamstring exercise until week 6 Wounds clean, dry and covered
2 (~2-6 weeks)	FWB with no crutches	No brace	Full extension and full flexion	KE CKC: bilateral squat and leg press, progress to unilateral. Continue gait re-education Calf raises Gluteus medius work Hamstrings work (prone) Proprioception work Pool work Scar massage	No resisted hamstring exercise until week 6 Graded return to work
3 (~6-12 weeks)	FWB with non-antalgic gait	NA	Gain full pain-free ROM	Progress KE work with CKC unilateral leg press CKC hamstring work (resisted) Exercise bike work Cross trainer/stepper Incline treadmill walk in prep for running Proprioception work	No running until 3 months post operatively Phased increases in gym loads Control swelling
4 (~12-16 weeks)	FWB	NA	Full ROM	Begin running, progress time and speed Continue KE leg press Start OKC exercise Agility worth with gentle impact to gradient Progress to sport specific drills and return to training when ready	Paced increases in running
5 (~26-38 weeks)	FWB	NA	Full ROM	Phased return to sport/activity Gradual increase in training/activity	Cautious return to training, non-contact and low impact progressing to full contact and high impact)if required)

FWB = full weight bearing; KE = knee extensors; SLR = straight leg raises; CKC = closed kinetic chain; ROM = range of motion; OKC = open kinetic chain; NA = non-applicable.

Supplementary data file 2

Group comparison (indicated by p values) of outcome measures at pre-surgery and post-surgery (Mean ± SD).

	Pre-surgery			Post-surgery		
	BFR-RT	**HL-RT**	**p**	**BFR-RT**	**HL-RT**	**p**
10RM strength (kg/bm)						
Injured	0.98 ± 0.15	0.80 ± 0.24	0.64	0.57 ± 0.19*	0.48 ± 0.12*	0.21
Non-injured	1.03 ± 0.14	0.98 ± 0.34	0.08	1.12 ± 0.17	1.02 ± 0.33	0.88
Muscle morphology						
Muscle thickness (cm)	2.37 ± 0.44	2.49 ± 0.65	0.59	1.91 ± 0.39*	1.94 ± 0.44*	0.85
Pennation angle (°)	15.64 ± 1.72	16.08 ± 1.29	0.49	13.73 ± 1.93*	14.36 ± 1.12*	0.34
Fascicle length (cm)	7.60 ± 0.85	7.77 ± 0.95	0.65	6.57 ± 0.95*	6.67 ± 0.76*	0.79
IKDC	48.59 ± 16.71	48.33 ± 10.30	0.96	32.03 ± 10.34*	30.17 ± 9.31*	0.65
LEFS (%max)	68.44 ± 13.94	67.81 ± 12.39	0.91	47.50 ± 13.71*	39.17 ± 11.75*	0.12
KOOS						
KOOS-pain	76.08 ± 12.91	74.50 ± 17.09	0.80	56.42 ± 10.62*	50.08 ± 13.26*	0.21
KOOS-symptoms	71.75 ± 15.40	70.33 ± 13.90	0.82	46.83 ± 10.22*	41.58 ± 11.20*	0.24
KOOS-ADL	87.58 ± 10.61	83.75 ± 13.09	0.96	61.08 ± 9.28*	57.42 ± 10.77*	0.33
KOOS-QOL	32.19 ± 15.60	34.35 ± 12.91	0.71	25.52 ± 16.31*	21.35 ± 11.14*	0.47
Lysholm	115.42 ± 16.58	111.83 ± 14.44	0.58	93.93 ± 14.04*	91.92 ± 14.42*	0.73
SEBT (%LL)						
ANT Injured	70.4 ± 10.5	70.3 ± 17.2	0.99	57.8 ± 10.0*	58.2 ± 13.3*	0.93
Non-injured	76.9 ± 8.3	78.1 ± 14.9	0.82	72.3 ± 7.0*	72.4 ± 15.0*	0.99
PM Injured	78.1 ± 17.6	78.0 ± 14.9	0.99	67.1 ± 15.8*	65.1 ± 13.2*	0.74
Non-injured	82.6 ± 15.6	84.9 ± 16.3	0.73	78.4 ± 14.4*	78.1 ± 15.5*	0.96
PL Injured	75.2 ± 18.3	76.7 ± 16.0	0.83	64.3 ± 18.6*	64.0 ± 13.7*	0.97
Non-injured	81.0 ± 17.4	82.2 ± 19.9	0.88	75.1 ± 19.4*	74.5 ± 22.1*	0.95
Range of motion (°)						
Flexion difference	-14.58 ± 6.46	-12.25 ± 7.29	0.42	-45.67 ± 6.98*	47.67 ± 3.65*	0.39
Extension difference	2.25 ± 3.33	1.42 ± 3.78	0.57	0.83 ± 1.80	1.00 ± 1.04	0.78
Range of motion difference	-16.83 ± 8.70	-13.67 ± 7.54	0.35	-46.50 ± 7.91*	-48.67 ± 3.45*	0.39
Knee joint swelling (cm)	36.3 ± 1.2	36.9 ± 1.5	0.34	39.1 ± 1.0†	39.8 ± 1.0†	0.25
Side-to-side difference in laxity (cm)	3.4 ± 1.3	3.5 ± 1.0	0.86			
Isokinetic strength (kg/bm)						
60°/s						
Extension						
Injured	1.75 ± 0.44	1.82 ± 0.52	0.73			
Non-injured	2.22 ± 0.31	2.27 ± 0.54	0.78			
Flexion						
Injured	1.04 ± 0.22	1.01 ± 0.15	0.69			
Non-injured	1.23 ± 0.17	1.12 ± 0.2	0.26			
150°/s						
Extension						
Injured	1.37 ± 0.27	1.42 ± 0.38	0.75			
Non-injured	1.65 ± 0.24	1.73 ± 0.43	0.60			
Flexion						
Injured	0.91 ± 0.14	0.81 ± 0.14	0.41			
Non-injured	0.97 ± 0.16	0.87 ± 0.20	0.32			
300°/s						
Extension						
Injured	1.05 ± 0.20	1.07 ± 0.23	0.85			
Non-injured	1.15 ± 0.18	1.24 ± 0.30	0.37			
Flexion						
Injured	0.70 ± 0.10	0.64 ± 0.18	0.29			
Non-injured	0.71 ± 0.09	0.74 ± 0.16	0.58			

* = significant decrease from pre-surgery ($p<0.01$); † = significant increase from pre-surgery ($p<0.01$). BFR-RT, blood flow restriction resistance training; HL-RT, heavy load resistance training; 10RM, ten repetition maximum; IKDC = International Knee Documentation Committee; LEFS = Lower Extremity Function Scale; KOOS = Knee injury and osteoarthritis outcome score; KOOS-ADL = KOOS activities of daily living; KOOS-QOL = KOOS quality of life; SEBT = star excursion balance test; ANT = anterior; PM = posteromedial; PL = posterolateral.