TITLE

Examination of the comfort and pain experienced with blood flow restriction training during post-surgery rehabilitation of anterior cruciate ligament reconstruction patients: A UK National Health Service trial.

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Title: Examination of the comfort and pain experienced with blood flow restriction training during post-surgery rehabilitation of anterior cruciate ligament reconstruction patients: A UK National Health Service trial.

Running title: Safety and feasibility of blood flow restriction training in rehabilitation.

ABSTRACT

Objective

Examine the comfort and pain experienced with blow flow restriction resistance training (BFR-RT) compared to standard care heavy load resistance training (HL-RT) during anterior cruciate ligament reconstruction (ACLR) patient rehabilitation.

Design

Randomised controlled trial.

Setting

United Kingdom National Health Service.

Participants

Twenty eight patients undergoing unilateral ACLR surgery with hamstring autograft were recruited. Following surgery participants were block randomised to either HL-RT at 70% repetition maximum (1RM) (n=14) or BFR-RT (n=14) at 30% 1RM and completed 8 weeks of twice weekly unilateral leg press training on both limbs.

Main outcome measures

Perceived knee pain, muscle pain and rating of perceived exertion (RPE) were assessed using Borg's (1998) RPE and pain scales during training. Knee pain was also assessed 24 h post-training.

Results

There were no adverse events. Knee pain was lower with BFR-RT during ($p<0.05$) and at 24 h post-training ($p<0.05$) with BFR-RT for all sessions. Muscle pain was higher ($p<0.05$) with BFR-

RT compared to HL-RT during all sessions. RPE remained unchanged ($p>0.05$) for both BFR-RT and HL-RT.

Conclusion

ACLR patients experienced less knee joint pain and similar perceived exertion with leg press exercise with BFR-RT compared to HL-RT. BFR-RT is advantageous during the early phase post-surgery ACLR rehabilitation.

Key words: blood flow restriction, anterior cruciate ligament, pain, comfort

INTRODUCTION

Blood flow restriction (BFR) training involves exercising with partial restriction of arterial inflow to, and full restriction of venous outflow from, the working musculature during exercise (Scott, Loenneke, Slattery, & Dascombe, 2015). With BFR resistance training (BFR-RT), significant skeletal muscle hypertrophy and strength adaptations can be achieved using light external loads of 20-30% one repetition maximum (1RM) (Loenneke, Wilson, Marín, Zourdos, & Bemben, 2012). This is evidenced in several load compromised clinical populations including older adults and those with knee osteoarthritis, ligament injury and inflammatory disease (Hughes, Paton, Rosenblatt, Gissane, & Patterson, 2017). Though it seems that in non-clinical populations heavy load resistance training (HL-RT) of 65-70% 1RM may be more effective for improving strength (Lixandrão et al., 2018), in load compromised clinical populations the strength and hypertrophy adaptations are similar following BFR-RT with light loads (Bryk et al., 2016; Ferraz et al., 2017; Giles, Webster, Mcclelland, & Cook, 2017; Hughes et al., 2019; Ladlow et al., 2018).

Clinicians and practitioners report using BFR-RT for the rehabilitation of anterior cruciate ligament reconstruction (ACLR) patients (Ohta et al., 2003; Patterson & Brandner, 2017). 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 (Herrington, Myer, & Horsley, 2013), which requires re-building strength. BFR-RT can elicit greater hypertrophy and strength adaptations in ACLR patients compared to matched load training without BFR (Ohta et al., 2003), and may provide an alternative tool to HL-RT for strength rehabilitation in load compromised ACLR patients (Hughes, Rosenblatt, Paton, & Patterson, 2018). The use of BFR-RT in rehabilitation of ACLR patients was recently examined for the first time in a National Health Service (NHS) setting (Hughes et al., 2019). The effectiveness of BFR-RT on improving clinical outcomes of muscle strength, morphology and function was compared to the standard care treatment of HL-RT. Following surgery with hamstring autograft, patients underwent 8 weeks of rehabilitation training

with either BFR-RT or HL-RT. It was found that BFR-RT effectively improved muscle strength and thickness compared to HL-RT (104% vs 106% and 4% vs 3%, respectively). Importantly, clinically important and significantly greater improvements in several measures of function, knee joint swelling and pain were observed with BFR-RT (Hughes et al., 2019). BFR-RT may therefore be more favourable during the early post-surgery phases of ACLR rehabilitation.

Novel rehabilitation tools must be feasible for use in a patient population. The safety and tolerability of a rehabilitation tool, each contributing to the overall effectiveness of a rehabilitation programme, may not only be determined by physiological variables. Subjective perceptions can influence an individual's attitude toward training, and ultimately determine motivation and adherence to a rehabilitation programme, both of which are equally as important as the safety and effectiveness of training tools (Van Roie, Bautmans, Coudyzer, Boen, & Delecluse, 2015). As stressed by Martin-Hernández et al. (2016), the way in which BFR-RT programmes are perceived and psychologically tolerated is important. Therefore, to represent a truly effective and feasible alternative training tool to HL-RT in ACLR patients, BFR-RT must be well-tolerated.

The perceptual response to exercise is viewed as a potential limiting factor to the application of BFR-RT (Martín-Hernández et al., 2016; Wernbom, Järrebring, Andreasson, & Augustsson, 2009). Research in non-injured populations demonstrates amplified perception of exertion and muscle pain with BFR-RT compared to matched workloads without BFR (Loenneke *et al.*, 2011; Loenneke *et al.*, 2012). However, these responses are not necessarily high and may be lower or similar to an equivalent form of exercise at a higher intensity (Hollander et al., 2010; Neto et al., 2014). Existing evidence demonstrates that elevated perception of pain is decreased over the duration of a training programme (Fitschen et al., 2014), which may indicate a repeated bout effect (McHugh, 2003; Wernbom, Paulsen, Nilsen, Hisdal, & Raastad, 2012). Furthermore, adaptation of perceived exertion and muscle pain responses to BFR-RT and HL-RT across training have been shown to follow a similar time course (Martín-Hernández et al., 2016). The

acute perceived exertion, muscle pain and knee joint pain responses to BFR-RT and HL-RT were found to be similar in ACLR patients upon limb loading following surgery (Hughes, Paton, Haddad, Rosenblatt, et al., 2018). Importantly, less knee joint pain during and 24 hours following training was observed with BFR-RT, suggesting a pain-modulating effect with BFR-RT that may favourably influence knee joint pain throughout a rehabilitation programme. However, this acute study did not examine the perceived exertion, muscle pain and knee pain responses to BFR-RT and HL-RT across a post-surgery rehabilitation training programme. Thus, it is unclear whether there is a similar time course adaptation to each modality as observed in non-injured individuals. The adaptation of such responses in comparison to HL-RT warrants investigation if BFR-RT is to be considered a truly effective and feasible alternative to HL-RT as a training tool for the post-surgery rehabilitation of ACLR patients. Therefore, the aim of this study was two-fold: 1) to examine whether the perceived exertion, muscle pain and knee joint pain responses to BFR-RT in ACLR patients are altered after multiple training sessions; and 2) to compare whether these responses are similar to those observed with HL-RT across a rehabilitation training programme.

MATERIALS AND METHODS

Participant information

Twenty-eight patients scheduled for unilateral ACLR surgery were recruited prior to surgery for this study. Participant characteristics are detailed in Table 1. The inclusion and exclusion criteria, screening and recruitment process are detailed previously (Hughes et al. 2019). All participants were active non-smokers, had no known history of central or peripheral neurological impairment, and were free of any cardiovascular, pulmonary or metabolic conditions. 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 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).

Sample size calculation

The patients in the present study were part of a previous larger study (Hughes et al., 2019), therefore sample size was based on the primary outcome measure of muscle strength from that study using G* Power Version 3.1 (Fual, Erdfelder, Lang, & Buchner, 2007).

Experimental design

This study was a parallel group, two-arm, single assessor-blinded randomised clinical trial in a between subject's repeated measures design.

Experimental procedure

Randomisation

Following surgery, participants were block randomised to either BFR-RT (n=14) or HL-RT (n=14) by an independent member of the research team using 7 opaque envelopes each with 4

folded slips inside (2 x BFR-RT and 2 x HL-RT). 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.

Criteria-assessment and familiarisation

After surgeon approval and suture removal at approximately 2 weeks post-surgery, participants were assessed every 48 h to determine if they met the criteria for beginning leg press strength training (Herrington et al., 2013). This included the ability to: 1) unilaterally weight bear without pain; 2) demonstrate an active knee ROM of 0 to 90°, assessed using a goniometer as previously described (Norkin & White, 2003); 3) perform repeated straight leg raises without knee extension muscle lag; 4) demonstrate gluteal and knee flexor muscle activation; and 5) have minimal swelling, measured as mid-patella knee joint circumference. These criteria were assessed as described by Herrington et al. (Herrington et al., 2013).

Once these criteria were met, participants attended a familiarisation session where body mass and height were recorded to the nearest 0.1 kg and 0.01 cm, respectively; blood pressure was measured in a supine position at the brachial artery; unilateral concentric 10RM was recorded; and participants were familiarised to the BFR-RT and HL-RT protocols. As it was anticipated that post-surgery knee pain may interfere with 1RM measurements, 10RM was calculated and used to predict each individual's 1RM (Wathan, 1994) to prescribe training load for a safer approach to strength testing. This is similar to previous studies in load compromised populations (Giles, Webster, Mcclelland, & Cook, 2017). The 10RM is highly predictive of 1RM leg press (r=0.98) (Abadie & Wentworth, 2000; Reynolds, Gordon, & Robergs, 2006) and has been shown to accurately match 1RM estimates (McNair, Colvin, & Reid, 2011). To prescribe training load, 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, with 3 min of rest between each attempt to ensure full muscle recovery (Tobalina, Calleja-Gonzalez, De Santos, Fernandez-López, & Arteaga-Ayarza, 2013).

Resistance training intervention

Following the familiarisation session, participants completed 8 weeks of biweekly unilateral leg press training, totalling 16 sessions each separated by a minimum of 48 h. A trained member of the research team supervised all training sessions. 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. The HL-RT and BFR-RT protocols were designed consistent with standard recommended protocols for each type of exercise (Garber et al., 2011; Scott et al., 2015). Participants in the HL-RT group performed 3 x 10 repetitions of unilateral leg press exercise with 30 s inter-set rest periods throughout a 0 to 90° ROM at 70% 1RM, which is a recommended protocol design for improving muscle strength (Garber et al., 2011). Participants in the BFR-RT group performed 4 sets (30, 15, 15 and 15 reps, respectively) of unilateral leg press exercise with 30 s inter-set rest periods throughout a 0 to 90° ROM at 30% 1RM (Patterson, Hughes, Head, Warmington, & Brandner, 2017). BFR was applied continuously at 80% of total arterial limb occlusion pressure (LOP) (Lixandrão et al., 2015). Both limbs were trained to meet NHS ethical requirements for standard provision of care. Both limbs were trained with BFR in the BFR-RT group. The injured limb was trained first and then the non-injured limb was matched for repetitions, each at a relative percentage of its 1RM. Training load was increased by 10% if participants completed all repetitions on 2 subsequent sessions and was formally readjusted following 4 weeks of training (Cook, LaRoche, Villa, Barile, & Manini, 2017). Exercise volume (kg) was calculated as: number of repetitions x load (kg).

Standard rehabilitation programme

All participants received the standard NHS rehabilitation programme and were instructed to complete this at home on 3 days per week (Supplementary data file 1). Strength training was only completed at the scheduled intervention sessions.

Blood flow restriction

BFR was achieved using an automatic personalised tourniquet system (Delfi Medical, Vancouver, BC, Canada) designed to automatically calculate LOP with clinical acceptable accuracy and high reliability (Hughes, Jeffries, Waldron, Rosenblatt, et al., 2018; McEwen, Jeyasurya, & Owens, 2016). 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 Personalised Tourniquet system, and automatically regulates pressure within acceptable limits (Hughes, Rosenblatt, Gissane, Paton, & Patterson, 2018). 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 (Jaffray, 2015). 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 (Hughes, Jeffries, Waldron, Rosenblatt, et al., 2018). LOP was calculated for each limb individually at every training session and BFR pressure was set at 80% LOP (Fatela, Reis, Mendonca, Avela, & Mil-Homens, 2016; Lixandrão et al., 2015) for both limbs.

Perceived exertion, muscle pain and knee joint pain

Rating of perceived exertion (RPE), muscle pain and knee joint pain were assessed using Borg's (1998) RPE and pain scales immediately following each set of exercise and then averaged to obtain an overall session rating for each measure for every training session, similarly to previous research (Martín-Hernández et al., 2016). RPE and muscle pain were assessed in both the injured and non-injured limb whereas knee joint pain was assessed in the injured limb only. Participants

received verbal instructions regarding measurements during the familiarisation session and were reminded at each training session. RPE response was assessed using Borg's (1998) scale for RPE, ranging from 6 (no exertion at all) to 20 (maximal exertion) (Borg, 1998). It was explained to participants that a rating of 6 meant they felt no exertion, and 20 meant they were giving maximal effort and could not exert themselves any further (Dankel et al., 2017; Jessee et al., 2017). Perceived muscle pain response was measured using Borg's (1998) scale for pain, ranging from 0 (nothing at all, no pain) to 10 (strongest intensity pain) (Borg, 1998). Participants were informed that 10 was their reference point, and a score of 11 (absolute maximum, highest possible intensity pain) could be given if the pain was worse than they had ever felt before, similar to previous research examining discomfort with BFR-RT (Jessee et al., 2017; Dankel et al., 2017). Participants were also asked to score perceived knee joint pain and were instructed that this score represented any pain felt within the knee joint capsule. Participants were provided with a copy of the Borg (1998) pain scale and contacted 24 h after each training session to provide a post-training knee pain score.

Data analysis

All data was coded and stored on the NHS password protected and University servers. Descriptive statistics (mean ± SD) were used to describe adherence rates and exercise session attendance. All statistical analysis was performed with IBM SPSS Statistics Version 24.0 (IBM Corp, Chicago IL, United States of America) by an individual blinded to treatment group allocation. 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). Group differences in exercise session attendance, volume and load were assessed using independent-samples t-tests. Normal distribution of data was assessed using Shapiro-Wilks test ($p>0.05$), and homogeneity of variances was assessed using Levene's Test of Homogeneity of variances ($p>0.05$). Session rating of knee pain, 24 h post-exercise knee pain,

muscle pain and RPE responses were each assessed using a 2 x 16 (group x session) repeated measures ANOVA with group allocation (BFR-RT vs. HL-RT) as the between subject's independent factor, and session (1-16) as the within subject's dependent factor. For any statistically significant interaction effect determined by ANOVA, Bonferroni post-hoc analysis was performed to examine the differences. Alpha significance was set a priori $p<0.05$. Effect size descriptors were described as Cohen's d: weak <0.2, weak to moderate 0.2–0.4, moderate 0.4–0.65, moderate to strong 0.65-0.80 and strong >0.8 (Rubin, 2012).

RESULTS

Participants

Four participants were lost before completing the study protocol (2 per group), leaving 24 completed participants (86%). Reasons for non-completion included personal reasons unrelated to the study (n=2), additional unplanned ligamentous repair upon the time of surgery (n=1) and one individual who withdrew with no reasons provided (n=1). Data from non-completers was not included in the final analysis and an intention-to-treat analysis was not performed. There were no significant differences between groups for any baseline anthropometric variable (Table 1), adherence to training or training load changes (Table 2). Exercise volume was higher in the non-injured limbs compared to the injured limbs within each group, and total exercise volume was significantly greater with BFR-RT (Table 2). There were no adverse events reported.

Table 1. Participant 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
Graft type, *n*			
Hamstring autograft (%)	12 (100%)	12 (100%)	1.00
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	
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†¥	36 ± 18†¥	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.

Session knee pain

There was no statistically significant group x time interaction effect for the injured limb ($F_{(14,252)}$ = 2.174, p<0.05, d=0.1). There was a significant main effect of group ($F_{(14,252)}$ = 57.898, p<0.01, d=0.8) and time ($F_{(14,252)}$ = 15.667, p<0.01, d=0.5). Mean session knee pain was lower in the BFR-RT group compared to the HL-RT group during every session (all p<0.05, mean d=2.5 (95% CI: 2.2 to 2.8)) (Figure 1). In the BFR-RT group, mean session knee pain peaked at 1.38 ± 0.96 in session 1 and significantly decreased by session 4 (p<0.01, d=0.5 (95% CI: 0.4 to 0.7)), remaining significantly lower for all remaining sessions (all p<0.05, mean d=1.2 (95% 0.7 to 1.4)) (Figure 1). In the HL-RT group, mean session knee pain peaked at 3.43 ± 1.64 in session 1 and significantly decreased by session 6 (p<0.05, d=0.2 (95% CI: 0.1 to 0.3)), remaining significantly lower for all remaining sessions (all p<0.05, mean d=0.6 (95% CI: 0.4 to 0.7)) (Figure 1).

24 hr post-training knee pain

There was a statistically significant group x time interaction effect for the injured limb ($F_{(3.519,77.413)}$ = 26.880, p<0.01, d=0.9). There was a significant main effect of group ($F_{(3.519,77.413)}$ = 34.959, p<0.01, d=0.9) and time ($F_{(3.519,77.413)}$ = 131.628, p<0.01, d=1.0). Mean post-training knee pain was lower in the BFR-RT group compared to the HL-RT group at all timepoints (all p<0.01, mean d=3.1 (95% CI: 2.9 to 3.3)) (Figure 1). In the BFR-RT group, mean post-training knee pain

peaked at 2.98 ± 0.60 after session 1 and significantly decreased after session 3 ($p<0.05$, $d=0.7$ (95% CI: 0.6 to 0.8), remaining significantly lower after all remaining sessions (all $p<0.01$, mean $d=2.9$ (95% CI: 2.7 to 3.2)) (Figure 1). In the HL-RT group, mean post-training knee pain peaked at 4.60 ± 1.11 after session 1 and significantly decreased after session 3 ($p<0.05$, $d=0.3$ (95% CI: 0.2 to 0.4), remaining significantly lower after all remaining sessions (all $p<0.01$, mean $d=1.7$ (95% CI: 1.3 to 2.0)) (Figure 1). A greater decease relative to peak mean post-training knee pain (session 1) was observed in the BFR-RT group compared to the HL-RT group after sessions 4 to 10 (all $p<0.01$, mean $d=1.9$ (95% CI: 1.7 to 2.2)) (Figure 1).

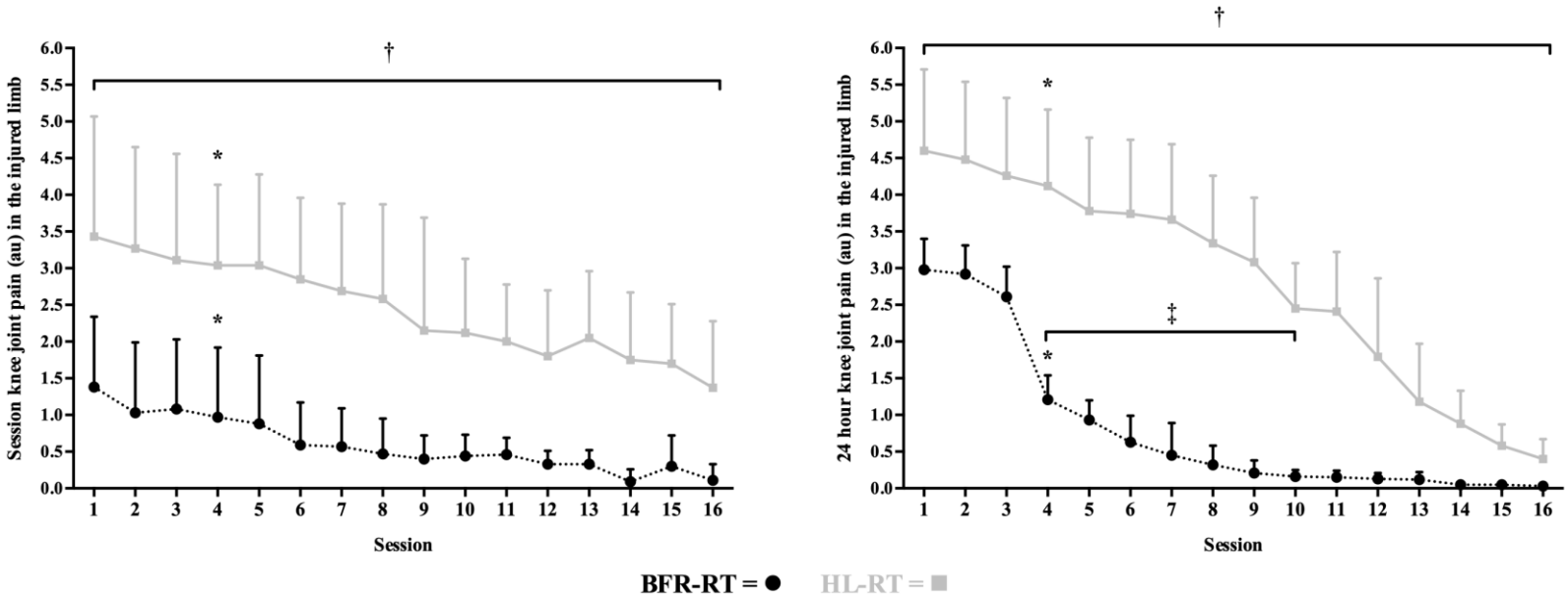

Figure 1. Mean session rating and 24 hr post-training knee pain with BFR-RT and HL-RT (Mean ± SD). * indicates the point where knee joint pain became significantly decreased compared to session 1 (time effect, $p<0.01$); † indicates a significant group effect ($p<0.01$); ‡ indicates a significant interaction effect ($p<0.01$). BFR-RT, blood flow restriction resistance training; HL-RT, heavy load resistance training.

Muscle pain

There was no statistically significant group x time interaction effect for the injured limb ($F_{(14,154)}$ = 4.047, p<0.01, d=0.2). There was a significant main effect of group ($F_{(1,11)}$ = 5.091, p<0.05, d=0.8) and time ($F_{(14,154)}$ = 17.417, p<0.01, d=0.6). Mean muscle pain was significantly higher (p<0.05) in the BFR-RT group compared to the HL-RT group during all sessions (Figure 2). In the BFR-RT group, mean muscle pain peaked at 5.5 ± 2.5 in session 1 and significantly decreased by session 15 (p<0.05, d=0.5 (95% CI: 0.3 to 0.7)) and session 16 (p<0.05, d=0.5 (95% CI: 0.4 to 0.6)) (Figure 2). In the HL-RT group, mean muscle pain peaked at 1.9 ± 1.5 in session 1 and significantly decreased by session 15 (p<0.05, d=0.7 (95% CI: 0.6 to 0.8)) and session 16 (p<0.05, d=0.8 (95% CI: 0.7 to 0.9)) (Figure 2). There was no statistically significant group x time two-way interaction effect for the non-injured limb ($F_{(14,126)}$ = 2.701, p<0.01, d=0.2). There was a significant main effect of group ($F_{(14,126)}$ = 4.790, p<0.05, d=0.3) and time ($F_{(14,126)}$ = 2.217, p<0.05, d=0.4). Muscle pain was significantly greater in the BFR-RT group (p<0.05). In the BFR-RT group, mean muscle pain peaked at 6.3 ± 2.1 in session 1 and significantly decreased by session 14 (p<0.01, d=0.8 (95% CI: 0.6 to 2.0)), session 15 (p<0.01, d=0.9 (95% CI: 0.8 to 1.0)), and session 16 (p<0.01, d=1.0 (95% CI: 0.8 to 1.2)) (Figure 2). In the HL-RT group, mean muscle pain peaked at 2.1 ± 2.1 in session 1 and significantly decreased by session 15 (p<0.05, d=0.7 (95% CI: 0.6 to 0.8)) and session 16 (p<0.05, d=0.7 (95% CI: 0.6 to 0.8)) (Figure 2).

RPE

There was no statistically significant group x time interaction effect for the injured limb ($F_{(6.944, 52.768)}$ = 0.660, p=0.704, d=0.2). There was no main effect of group ($F_{(13.465, 49.331)}$ = 0.327, p=0.872, d=0.2). There was a significant main effect of time ($F_{(7.941, 49.562)}$ = 3.752, p<0.01, d=0.4). In the BFR-RT group, mean RPE peaked at 15.8 ± 2.0 in session 1 and did not significantly change by session 16 (p>0.05) except for session 8 to 9 where there was a significant increase in RPE (p<0.05, d=0.5 (95% CI: 0.4 to 0.6)) (Figure 2). In the HL-RT group, mean RPE peaked at 16.5 ± 1.3 in session 1 and did not significantly change by session 16 (p>0.05) except for session 8 to

9 where there was a significant increase in RPE ($p<0.05$, d=0.7 (95% CI: 0.5 to 0.8)) (Figure 2). There was no statistically significant group x time interaction effect for the non-injured limb ($F_{(7.2747, 50.126)} = 0.890$ p=0.689, d=0.2). There was a significant main effect of time ($F_{(7.274, 50.126)} = 4.021$, $p<0.01$, d=0.4). In the BFR-RT group, mean RPE peaked at 16.6 ± 1.4 in session 1 and did not significantly change by session 16 ($p>0.05$) except for session 8 to 9 where there was a significant increase in RPE ($p<0.05$, d=0.4 (95% CI: 0.3 to 0.5)) (Figure 2). In the HL-RT group, mean RPE peaked at 16.5 ± 2.3 in session 1 and did not significantly change by session 16 ($p>0.05$) except for session 8 to 9 where there was a significant increase in RPE ($p<0.05$, d=0.6 (95% CI: 0.5 to 0.7)) (Figure 2).

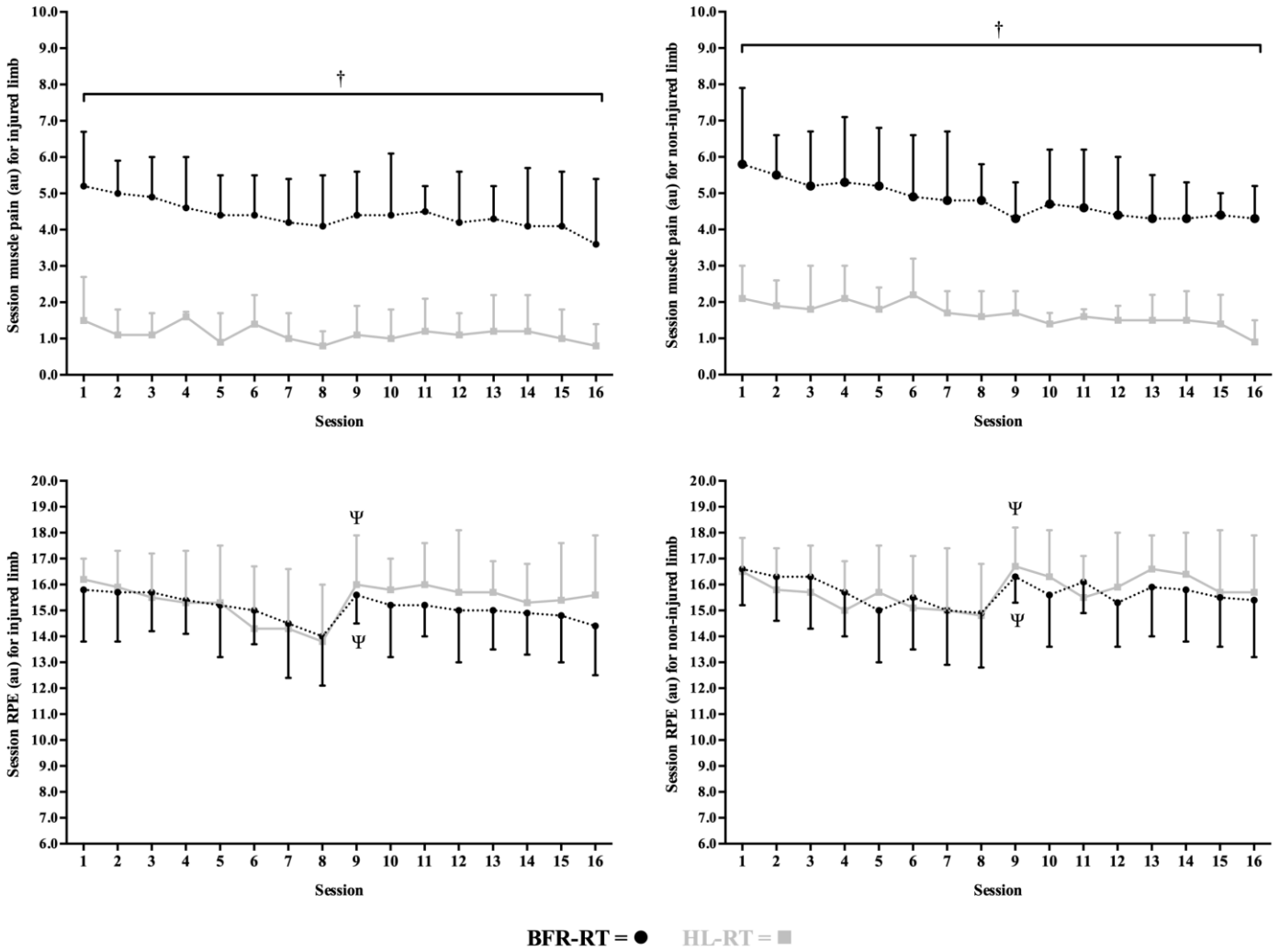

Figure 2. Mean session rating of RPE and muscle pain for the injured and non-injured limb with BFR-RT and HL-RT (Mean ± SD). † indicates a significant group effect ($p<0.01$); Ψ indicates a significant increase compared to the previous session ($p<0.01$). BFR-RT, blood flow restriction resistance training; HL-RT, heavy load resistance training.

DISCUSSION

This study was the first to examine and compare the feasibility of BFR-RT and HL-RT during post-surgery ACLR rehabilitation and the effect on knee pain. The main findings of this study were that 1) Knee pain during training was significantly lower with BFR-RT; 2) 24 h post-training knee pain was significantly lower and greater decreases relative to peak were observed with BFR-RT; 3) RPE was similar with BFR-RT and HL-RT for both limbs and did not change across training; 4) Muscle pain was higher in both limbs with BFR-RT and did not change in either group until the final few sessions.

Knee pain

There was a lack of interaction effect for knee pain during training, however a time effect was observed. Knee pain peaked in session 1 and significantly decreased by session 4 and 6 with BFR-RT and HL-RT, respectively, remaining significantly lower during the remaining training sessions. Importantly, knee pain was significantly lower during all sessions with BFR-RT, in agreement with previous findings (Hughes, Paton, Haddad, Rosenblatt, et al., 2018). This may be due to the lighter external load used with BFR-RT compared to HL-RT (30% vs. 70% 1RM) resulting in lower knee joint forces and less strain on the joint, which would support the findings of Fernandes-Bryk et al. (2016). Knee pain reported by patients 24 h following training sessions peaked in session 1 and then significantly decreased following session 3 with both BFR-RT and HL-RT, remaining significantly lower for the remaining training sessions. Importantly, knee pain was significantly lower at 24 h following BFR-RT after all training sessions, in agreement with previous findings (Hughes, Paton, Haddad, Rosenblatt, et al., 2018). Moreover, the reduction in knee pain relative to that following session 1 was significantly greater with BFR-RT following sessions 4 to 10. Previous evidence demonstrates a reduction in knee pain immediately following an acute bout of BFR-RT which remains for 45 min post-exercise (Korakakis, Whiteley, & Epameinontidis, 2018; Korakakis, Whiteley, & Giakas, 2018). A reduction in knee pain at 24 h

post-exercise with BFR-RT has been evidenced in ACLR patients (Hughes, Paton, Haddad, Rosenblatt, et al., 2018), which together with the work of Korakakis et al. suggests that BFR-RT may have a hypoalgesic effect. The results of the present study support this hypothesis. Though the phenomenon of exercise-induced hypoalgesia is well described (Koltyn, Brellenthin, Cook, Sehgal, & Hillard, 2014), the greater reduction relative to peak knee pain at 24 h with BFR-RT in the present and previous study (Hughes, Paton, Haddad, Rosenblatt, et al., 2018) suggests that BFR per se may augment any hypoalgesic effect present with resistance exercise. Though the mechanisms of this effect are not understood at present, there are several possible explanations. 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 (Leffler, Hansson, & Kosek, 2002). Conditioned pain modulation resulting from BFR cuff pressure and the high level of ischemia and exercise-induced muscle pain (Tuveson, Leffler, & Hansson, 2006) with BFR-RT may therefore contribute to an antinociceptive response. Other possible mechanisms include release of endogenous opioids and endocannabinoids with may be driven by hypoxia during exercise (Heyman et al., 2012; Koltyn et al., 2014)

Muscle pain

Previous research reports decreases in RPE and muscle pain with BFR-RT and HL-RT across 6 consecutive training sessions (Martín-Hernández et al., 2016). In contrast, no attenuation of the muscle pain response to BFR-RT or HL-RT was observed in the present study until the final few sessions. However, this is likely due to the progressive increase in external load and individualisation of pressure, as both have been shown to amplify muscle pain response (Jessee et al., 2017; Mattocks et al., 2017; Soligon et al., 2018). Muscle pain was higher in both limbs with BFR-RT throughout the training programme, in contrast to previous research (Hollander et al., 2010; Martín-Hernández et al., 2016). However, the restriction pressures used in the present study were individualised at every session and remained higher (150 and 157 mmHg for the injured and non-injured limb, respectively) than those used in the work of Hollander et al. and

Martin-Hernandez et al. (20% below systolic blood pressure and 110 mmHg, respectively) which may have increased participant's subjective perception of pain via increased metabolite production and stimulation of group III and IV afferent fibres (Suga et al., 2009; Takarada et al., 2000). The lack of significant interaction effects in the present study suggests that muscle pain responses also behaved similarly with BFR-RT and HL-RT, which is line with the findings of Martin-Hernandez et al. (2016). It is important to note that though muscle pain response appeared higher with BFR-RT, it did not prevent patients completing training or result in different adherence rates to training compared to HL-RT. As muscle pain during exercise is acute, transient and appears to be tolerated, a higher response may not limit application of BFR-RT in a post-surgery rehabilitation setting.

RPE

In the present study no attenuation of RPE response was observed, which contrasts previous findings (Martín-Hernández et al., 2016). As external training load was not adjusted in the study by Martin-Hernandez et al. (2016), the attenuation of RPE response may be due to a decrease in relative training intensity caused by an increase in muscle strength. In the present study the external load was progressively increased throughout the 8 weeks of training, which may have resulted in the steady state RPE response to exercise as RPE is typically associated with external load (Lins-Filho et al., 2012). Furthermore, RPE is influenced by BFR pressure and thus level of BFR (Jessee et al., 2017; Mattocks et al., 2017). The study by Martin-Hernandez et al. (2016) did not individualise BFR pressure and used the same pressure of 110 mmHg for all individuals for the duration of the study. Repeated individualisation of BFR pressure may have contributed to the steady-state RPE response in the present study. The lack of a significant interaction effect suggests that RPE behaved similarly during both BFR-RT and HL-RT over the rehabilitation training programme, in agreement with previous research (Martín-Hernández et al., 2016). The similar magnitude of RPE response between BFR-RT and HL-RT in the present study is consistent with previous research in ACLR patients (Hughes, Paton, Haddad, *et al.*, 2018). These

findings contrast those of Martin-Hernandez et al. (2016) where a greater RPE response to HL-RT compared to BFR-RT was observed. However, as aforementioned a higher BFR pressure was used in the present study, which may have contributed to the similar response. This would support recent research comparing RPE and muscle pain responses to BFR-RT at different percentages of LOP and HL-RT, which demonstrated a similar RPE response with HL-RT and BFR-RT at higher pressures of 60-80% LOP (Soligon et al., 2018).

Clinical implications

A patient's perception of a training intervention can influence their attitude, motivation and adherence to a rehabilitation programme. BFR-RT has been shown to be as effective at improving strength and more effective at improving function, pain and swelling compared to HL-RT in ACLR patients (Hughes et al., 2019). Importantly, the present study demonstrates that BFR is also more comfortable for patients during the early phases of post-surgery rehabilitation, which further supports its use as a rehabilitation tool. Though training with light loads (i.e <30% 1RM) alone would likely reduce pain compared to HL-RT, it would not be sufficient to stimulate adaptations in strength and function. Therefore, the ability to improve strength and function to a similar/greater extent as HL-RT but in a more comfortable, less painful manner with BFR-RT makes it an advantageous rehabilitation tool for the early post-surgery phases of rehabilitation.

Limitations

This study is not without its limitations. Other physiological variables of relevance for peripheral muscle pain and RPE were not measured, which may have helped elucidate the main determinants of perceived effort and pain and mechanisms of attenuation. 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. Finally, 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.

CONCLUSION

When undergoing post-surgery rehabilitation, ACLR patients experienced less knee joint pain and reported similar ratings of perceived exertion during and following leg press exercise with BFR-RT compared to traditional HL-RT. Greater rating of muscle pain experienced with BFR-RT did not limit adherence to the training intervention. As BFR-RT may be more comfortable for ACLR patients whilst also effective at improving strength and function compared to HL-RT, BFR-RT may be more advantageous during the early phases of post-surgery ACLR rehabilitation.

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