Perioperative Blood Flow Restriction Rehabilitation in Patients Undergoing ACL Reconstruction

A Systematic Review

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Background: Low-load blood flow restriction (BFR) training has attracted attention as a potentially effective method of perioperative clinical rehabilitation for patients undergoing orthopaedic procedures.

Purpose: To (1) compare the effectiveness of low-load BFR training in conjunction with a standard rehabilitation protocol, pre- and postoperatively, and non-BFR interventions in patients undergoing anterior cruciate ligament reconstruction (ACLR) and (2) evaluate protocols for implementing BFR perioperatively for patients undergoing ACLR.

Study Design: Systematic review; Level of evidence, 2.

Methods: A systematic review of the 3 medical literature databases was conducted to identify all level 1 and 2 clinical trials published since 1990 on BFR in patients undergoing ACLR. Patient demographics from included studies were pooled. Outcome data were documented, including muscle strength and size, and perceived pain and exertion. A descriptive analysis of outcomes from BFR and non-BFR interventions was performed.

Results: A total of 6 studies (154 patients; 66.2% male; mean ± SD age, 24.2 ± 3.68 years) were included. Of these, 2 studies examined low-load BFR as a preoperative intervention, 1 of which observed a significant increase in muscle isometric endurance ($P = .014$), surface electromyography of the vastus medialis ($P < .001$), and muscle blood flow to the vastus lateralis at final follow-up ($P < .001$) as compared with patients undergoing sham BFR. Four studies investigated low-load BFR as a postoperative intervention, and they observed significant benefits in muscle hypertrophy, as measured by cross-sectional area; strength, as measured by extensor torque; and subjective outcomes, as measured by subjective knee pain during session, over traditional low-load resistance training (all $P < .05$). BFR occlusion periods ranged from 3 to 5 minutes, with rest periods ranging from 45 seconds to 3 minutes.

Conclusion: This systematic review found evidence on the topic of BFR rehabilitation after ACLR to be sparse and heterogeneous likely because of the relatively recent onset of its popularity. While a few authors have demonstrated the potential strength and hypertrophy benefits of perioperative BFR, future investigations with standardized outcomes, long-term follow-up, and more robust sample sizes are required to draw more definitive conclusions.

Keywords: blood flow restriction; anterior cruciate ligament reconstruction; clinical rehabilitation; KAATSU

High-intensity resistance training can induce limb muscle hypertrophy and strength gains, which are desired outcomes in physical rehabilitation after surgery.[2] However, patients undergoing anterior cruciate ligament reconstruction (ACLR) cannot tolerate high-intensity training, defined as 60% to 85% of the 1 repetition maximum weight, in the immediate perioperative period.

Blood flow restriction (BFR) by the application of a pneumatic cuff to the lower extremity during low-intensity resistance training (approximately 20% of 1 repetition maximum weight) has been shown to significantly increase thigh muscle cross-sectional area, as well as carotid arterial and venous compliance, in healthy volunteers.[1,61] The anaerobic conditions of BFR induce an angiogenic stimulus through upregulation of vascular endothelial growth

factor.[19,38] In addition, the hypoxic stimuli may stimulate the mobilization and recruitment of endothelial progenitor stem cells, improving the regenerative potential in healthy volunteers.[54] The muscle hypertrophy induced during low-intensity resistance training with BFR is an attractive method of postsurgical rehabilitation in ACLR in that it avoids placing high loads on the graft in the immediate postoperative period and provides rehabilitation options for the elderly and other patients with severe endurance or strength deficiency.

To date, there is a paucity of clinical data on BFR training and even fewer randomized controlled trials. The duration of the therapy, the intensity of the BFR (pressure), and that required to produce hypertrophic effects remain unclear.[31,47,60,73] Furthermore, given the recent increased awareness of this therapy, there is a myriad of new research with heterogeneous indications and results. For the aforementioned reasons, the purposes of the present systematic review are to (1) compare the effectiveness of low-load BFR (LL-BFR) training in conjunction with a rehabilitation protocol, pre- and postoperatively, versus non-BFR interventions in patients undergoing ACLR and (2) evaluate protocols for implementing BFR perioperatively for patients undergoing ACLR.

METHODS

Search Strategy

This review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A literature search was undertaken to identify studies evaluating BFR training as a prehabilitation or rehabilitation protocol after ACLR for the period between January 1, 1990, and May 14, 2019, within the MEDLINE, CINAHL, and EMBASE databases. The following search terms were used:

> (((((((((vascular occlusion) OR blood flow restriction) OR blood flow occlusion) OR kaatsu)) OR partial occlusion))) AND ((((((((anterior cruciate ligament reconstruction) OR ACLR) OR anterior cruciate ligament surgery) OR ACL surgery) OR anterior cruciate ligament)).

Resulting articles from the search underwent title and abstract screening, and studies investigating the utility of BFR before or after ACLR were selected. An additional search through the reference list of eligible articles was performed. Systematic review registration was performed in May 2019 with the PROSPERO International prospective register of systematic reviews.

Inclusion and Exclusion Criteria

Eligible studies were included after application of the following inclusion criteria: studies involving BFR as a prehabilitation or rehabilitation intervention in patients undergoing ACLR, English language in a scientific peer-reviewed journal, and level 1 or 2 evidence or qualification as a randomized controlled trial. Ongoing level 1 clinical trials without publication of complete data were not included.

Study Selection and Data Extraction

Studies eligible for inclusion were screened independently by 2 reviewers (Y.L. and C.K.). Duplicates and those not meeting the inclusion criteria were excluded. For the included studies, data extraction was inclusive of the following variables: (1) study design and population characteristics; (2) rehabilitation protocol, including device used, occlusion characteristics, exercise performed, and duration of BFR training; and (3) outcome measures, including muscle strength and size, perceived exertion and pain, and physical function. Data extraction was then performed with a custom spreadsheet. As almost all included studies evaluated different outcome measures, precluding a meta-analysis, we elected to proceed with a descriptive analysis of outcomes. Pooled demographic variables were calculated assuming independence of samples.

Study Quality and Reporting

Quality of the included studies was assessed with the Jadad score,[31] which is a criterion for the evaluation and appraisal of randomized clinical trials. It is based on a composite score calculated from the following 3 metrics, with 1 point for an answer of yes and 0 points for an answer of no: (1) Is the study self-described as randomized? (2) Is the study self-described as double-blinded? (3) Does the study provide an adequate description of dropouts and withdrawals? After this initial assessment, secondary grading was performed on the basis of the following: an additional point was given if, for question 1, the method for randomization was described and was appropriate or, for question 2, the method of double-blinding was described and was appropriate. Conversely, a point was deducted if the methods for questions 1 and 2 were described and were inappropriate. Final scores for studies assessed may range from 0 to 5.
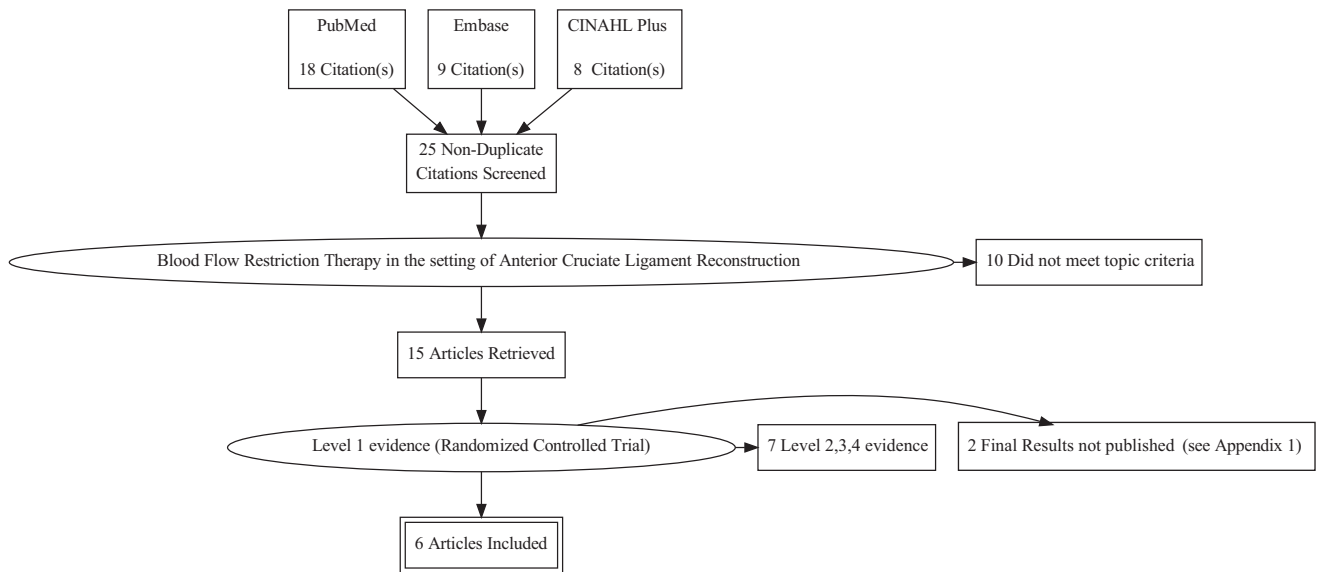
Figure 1. Flowchart of study selection process.

Additionally, an assessment of each study was performed with the modified Cochrane Risk of Bias tool,[24] a method created and validated by the Cochrane Collaboration to determine the risk of bias in randomized trials. The tool focuses on the various domains of trial design, conduct, and reporting and proposes a judgment regarding the relevant risk of bias within each domain, graded as "high risk," "low risk," or "some concern." The domains include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. If not enough information is provided in the methodology to make a judgment, the domain is listed as "not reported."

Statistical Analysis

Age and body mass index of the study participants were extracted from the included studies and pooled with weighted means. All statistical analysis was performed with RStudio software (v 1.0.143; R Foundation for Statistical Computing).

RESULTS

The database search yielded 25 articles. After initial title and abstract screening, 15 articles regarded the topic in question and were assessed for eligibility. From this selection, 6 studies were of level 1 evidence per the PRISMA statement and were included in the analysis, as illustrated by Figure 1. An overview of study characteristics is provided in Table 1. The Jadad scores for the included studies ranged from 2 to 4, indicating average to rigorous study quality based on randomization and blinding protocols. Using Cochrane risk assessment we found 1 study[26] was at high risk of bias in 1 category and 4 were at high risk in 2 categories (Table 2).

Study Populations

Of the 6 studies, 2 each were from Slovenia and Japan[23,59,73,83] and 1 each from Norway and the United Kingdom.[26,31] Two studied preoperative rehabilitation before ACLR after a chronic injury,[23,83] while 4 studied[26,31,59,73] postoperative rehabilitation. Sample sizes ranged from 16 to 44. All studies were randomized into 2 study arms with 1 exception, which was stratified into 3 study arms.[26] Control arms in the trials were sham BFR in 3 studies,[23,73,83] nonrestricted activities in 2 studies,[31,59] and, for the study with 3 arms,[26] BFR on healthy knees and nonrestricted activity. A total of 154 patients were enrolled in the 6 studies. Pooled demographics of the included studies are as follows: the mean ± SD age was 29.5 ± 7.7 years; body mass index was 24.2 ± 3.68 kg/m^2; and 66.2% of the patients were male (Table 3).

BFR Protocol

Detailed BFR protocols are provided in Table 4. BFR was used in conjunction with specifically outlined LL resistance training and/or low- to moderate-intensity postoperative rehabilitation. Training load ranged from body weight to 30% of 1 repetition maximum. Constant occlusion pressure was applied in 4 studies,[23,26,59,83] and escalating pressures were utilized in 2 studies.[31,73] Occlusive pressures ranged from 130 to 238 mm Hg, while cuff width ranged from 9 to 14 cm. BFR was achieved with occlusion cuffs in 2 studies[26,73] and tourniquets in 4 studies.[23,31,59,83] Duration of BFR exercise regimen ranged from 1 day[25] (to examine acute perceptual and hemodynamic responses) to 16 weeks, with frequency ranging from a single session over 48 hours to 6 sessions per week. One group reported on 2 daily BFR sessions.[73] Exercise volume ranged from 75 to 100 repetitions per session; in 2 studies,[23,83] volume was determined by number of

TABLE 1
Overview of Study Characteristics[a]

Author (Year)	Level of Evidence	No.	Study Design	Jadad Score	Study Arms (No.)	Surgery Description	Graft Type
Zargi[83] (2018)	2	20	Prospective single-center quasi-randomized controlled trial with sham intervention Population: chronic ACL rupture (>6 mo) Country: Slovenia	4	Pre-ACLR BFR (12) Pre-ACLR sham BFR (12)	Arthroscopic single bundle	Double-stranded ipsilateral semitendinosus-gracilis autograft
Hughes[25] (2018)	2	30	Between-participant partially randomized controlled trial Population: ACL rupture, active nonsmokers Country: United Kingdom	2	Uninjured BFR (10) Post-ACLR BFR, light resistance (10) Post-ACLR, heavy resistance (10)	—	Hamstring tendon autograft
Grapar Zargi[22] (2016)	2	20	Prospective single-center quasi-randomized controlled trial with sham intervention Population: chronic ACL rupture (>6 mo) Country: Slovenia	4	Pre-ACLR BFR (13) Pre-ACLR sham BFR (13)	Arthroscopic single bundle	Double-stranded ipsilateral semitendinosus-gracilis autograft
Iversen[30] (2016)	1	24	Randomized blinded controlled trial Population: acute ACL rupture (<6 mo) Country: Norway	4	Post-ACLR BFR (12) Post-ACLR nonrestricted activity (12)	—	Hamstring tendon autograft
Ohta[59] (2003)	1	44	Prospective randomized controlled trial Population: ACL rupture Country: Japan	3	Post-ACLR BFR (22) Post-ACLR nonrestricted activity (22)	—	Semitendinosus autograft
Takarada[73] (2000)	1	16	Controlled trial Population: ACL rupture Country: Japan	2	Post-ACLR BFR (8) Post-ACLR sham BFR (8)	—	—

[a]Dashes signify not available. ACL, anterior cruciate ligament; ACLR, anterior cruciate ligament reconstruction; BFR, blood flow restriction.

TABLE 2
Overview of Study Characteristics

	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Iversen[30] (2016)	Low risk	Low risk	Not reported	Low risk	Low risk	Low risk
Zargi[83] (2018)	High risk	High risk	Low risk	Low risk	Low risk	Low risk
Grapar Zargi[22] (2016)	High risk	High risk	Low risk	Low risk	Low risk	Low risk
Hughes[25] (2018)	Low risk	High risk	Not reported	Not reported	Low risk	Low risk
Ohta[59] (2003)	High risk	High risk	Not reported	Not reported	Low risk	Low risk
Takarada[73] (2000)	High risk	High risk	Not reported	Not reported	Low risk	Low risk

TABLE 3
Pooled Demographic Data of Included Studies

Patients, No.	154
Age, y, mean ± SD	29.5 ± 7.7
Male sex, %	66.2
Body mass index (n = 110), mean ± SD	24.2 ± 3.68

repetitions to volitional failure.[23,83] BFR occlusion periods ranged from 3 to 5 minutes, with rest periods ranging from 45 seconds to 3 minutes.

Outcome Measures

Muscle strength was assessed through measurement of maximal volitional isometric contraction torque in 2 studies[23,83] and by muscular torque ratio of the knee flexors to the knee extensors in 1 study.[23,60,83] Additional measures of muscle strength and activation included surface electromyography (EMG) of the vastus medialis, EMG amplitude, time of sustained contraction, and blood flow to the vastus lateralis.[83] Muscle size was assessed through measurement of the cross-sectional area and volume of the individual muscles, the extensor groups, and the flexor groups, as well

TABLE 4
Overview of Study Protocols[a]

Author (Year)	Device Used	Occlusion Pressure/ Cuff Width	Exercises	Volume and Frequency	Duration
Zargi[83] (2018)	Contoured pneumatic tourniquet cuff	Intervention: 150 mm Hg, 14 cm Sham: 20 mm Hg, 14 cm	Unilateral resisted knee extension in open kinetic chain on leg extension machine	Warm-up: 10-15 reps × 0.5 kg Working set: 30 s of resting occlusion, 6 sets to volitional failure. A metronome at 56 bpm is used to set rhythm/ speed of exercise: 1 beat for eccentric contraction, 1 for eccentric Rest periods: 45 s without reperfusion after first, third, and fifth sets; 90 s with reperfusion after second and fourth sets	5 sessions over 8 d preop Last session performed within 48 h of surgery
Hughes[25] (2018)	Dual-purpose easy-fit variable contour nylon cuff	Intervention ACLR: 145 mm Hg, 11.5 cm Intervention uninjured: 138, 11.5 cm	Unilateral leg press	Warm-up: 5 min, unloaded cycling; 10 reps, unilateral leg press; 5-min rest Working sets: low-load BFR ACLR and BFR uninjured: 4 sets (30, 15, 15, 15 reps with 30-s interset rest) at 30% 1RM (1RM for uninjured BFR, 161 ± 44 kg; 1RM for ACLR-BFR, 61 ± 28 kg) throughout 0°-90° range of motion and contraction cycling of 1 s concentric / 1 s eccentric with BFR continuous at 80% limb occlusive pressure High-load ACLR: unilateral leg press (3 × 10 reps with 30-s interset rest) throughout 0°-90° range of motion at 70% 1RM (57 ± 17 kg)	1 session of familiarization and 1 session of BFR intervention over 2 d, starting at 22 d postop
Grapar Zargi[22] (2016)	Contoured pneumatic tourniquet cuff	Intervention: 150 mm Hg, 14 cm Sham: 20 mg Hg, 14 cm	Unilateral resisted knee extension in open kinetic chain on leg extension machine	Warm-up: 10-15 reps × 0.5 kg Working set: 30 s of resting occlusion, 6 sets to volitional failure. A metronome at 56 bpm is used to set rhythm/speed of exercise: 1 beat for eccentric contraction, 1 for eccentric Rest periods: 45 s without reperfusion after first, third, and fifth sets. 90 s with reperfusion after second and fourth sets	5 sessions over 10 d preop Last session performed within 48 h of surgery
Iversen[30] (2016)	Contoured pneumatic tourniquet cuff	Starting pressure set to 130 mm Hg, increased by 10 mm Hg daily from postop days 2 to 14 up to maximum pressure of 180 mm Hg or highest tolerable pressure; 14 cm	Isometric quadriceps contractions Progressing to leg extension over a knee roll Straight leg raises	Warm-up: NA Working set: 20 reps during each 5-min occlusion period, totaling 100 reps per training session and 200 reps per day Rest periods: 3 min	2 sessions per day over 12 d, starting at day 2 postop, ending on day 14 postop; MRI on day 16 postop
Ohta[59] (2003)	Hand-pumped air tourniquet	180 mm Hg	Straight leg raise Hip joint abduction Half squat Elastic tube exercise (bending knee from 45° to 100°) Knee bend walking exercise (walking in half squat for 60 steps)	Warm-up: NA Working sets: Straight leg raise—performed 2 sets daily, 6 times weekly during weeks 1-8 after surgery. No load during week 1, 1-kg load for weeks 2-4, 2-kg load for weeks 5-8. Hip joint adduction—5-s maximum effort, repeated 20×,	6 sessions per week for 14 wk, starting at 2 wk postop, ending 16 wk postop

Table 4 (continued)

Author (Year)	Device Used	Occlusion Pressure/ Cuff Width	Exercises	Volume and Frequency	Duration
				performed 2 sets daily, 6×/wk during weeks 1-12. Half squat—exercise maintained for 6 s, repeated 20×, 2 sets daily, 6× weekly during weeks 5-16 (5-6 wk, no load; 7-8 wk, 4- to 6-kg load; 9-12 wk, 8- to 10-kg load; 13-16 wk, 12- to 14-kg load). Elastic tube exercise— repeated 20×, 1 set daily, 6× weekly during weeks 9-12 postop, and 2 sets daily, 6× weekly during weeks 13-16. Knee bend walking exercise—3 sets daily, 6× weekly during weeks 13-16	
Takarada[73] (2000)	Pneumatic occlusion cuff	Initially 180 mm Hg, increased at 10 mm Hg intervals, maximum pressure at 238 mm Hg; 9 cm Sham: cuff placed without inflation or occlusion	Intervention and control groups performed low-intensity exercise described as the "usual program for recovery in the hospital with their injured knee kept immobilized by means of knee brace"	Warm-up: NA Working set: 5 sets of occlusions for 5 min, twice a day at 9 AM and 2 PM Rest periods: 3 min	2 sessions per day for 11 d, starting at 3 d postop, ending 14 d postop

[a]Values are presented as mean ± SD where indicated. ACLR, anterior cruciate ligament reconstruction; bpm, beats per minute; BFR, blood flow restriction; MRI, magnetic resonance imaging; NA, not available; postop, postoperative; preop, preoperative; reps, repetitions; RM, repetition maximum; ROM, range of motion.

as the femoral muscle group en bloc; anatomic cross-sectional measurements were performed through magnetic resonance imaging.[31,60,73,83] Subjective outcomes assessed included the levels of perceived pain and exertion. Physical function assessments included the single-leg anterior reach distance and tests of anterior instability.[23,60] Two studies performed intergroup and temporal comparisons using factorial analysis of variance to assess for differences between BFR and sham, between pre- and postsurgery, and between operative and healthy legs, with post hoc Tukey test for pairwise comparisons where a significant main effect was determined.[23,83] For the purposes of this review, only significant intergroup (BFR vs sham) differences are reported in Tables 5 and 6.

Descriptive Outcomes

With respect to BFR as a preoperative intervention, 1 study[23] observed no significant differences in outcome measures, including postoperative changes in vastii or rectus volume. However, a second study by the same group observed that several outcome measures were significantly greater in the BFR group as compared with the sham BFR controls at 12-week follow-up, including muscle isometric endurance ($P = .014$), surface EMG amplitude of the vastus medialis ($P = .001$), and muscle blood flow to the vastus lateralis ($P < .001$).[83]

With respect to BFR as a postoperative intervention, 2 of 3 studies[59,73] observed significantly less muscle atrophy as measured by cross-sectional area of the knee extensor muscles when compared with controls ($P < .05$). Postoperative BFR was also associated with significantly greater cross-sectional area of the flexor and total quadriceps muscle group in 1 of 2 studies (all $P < .05$)[73] and with significantly greater strength of the operative limb in the other study (all $P < .05$), as measured by muscular torque ratio of the injured extensor and flexor to their counterparts in the healthy limb.[60] One study comparing subjective outcome measures by Hughes et al found that BFR was associated with significantly increased rates of perceived exertion and reduction of muscle pain during session but significantly decreased levels of knee pain during and after session, as compared with non-BFR ACLR rehabilitation (all $P < .05$)[26] (Table 5). One study provided data regarding complications, where 2 patients in the LL-BFR group dropped out because of lower limb "dull pain" related to the tourniquet.[60]

Study Quality and Reporting

The Jadad score was utilized to assess the quality of the trials included, with scores ranging from 2 to 4. All studies included were self-described as randomized and provided appropriate description of the randomization procedure. Four studies[23,26,31,83] were double-blinded, while 3 provided descriptions of appropriate blinding methods.[23,31,83] Only 1 study included a description of participants who dropped out or withdrew from the study.[60]

TABLE 5
Overview of Outcome Measures[a]

Author (Year)	Time Points of Follow-up	Treatment Group	Attrition, %	Outcome Measures
Zargi[83] (2018)	Preop, 4 wk postop, 12 wk postop	Control: pre-ACLR sham BFR Treatment: pre-ACLR BFR	0	MVIC torque: T:C, $P = .519$ Muscle isometric endurance (time of sustained contraction): **T > C, P = .014** Surface EMG of vastus medialis: **T > C, P = .001** Median frequency calculation of EMG amplitude: T:C, $P = .730$ Muscle blood flow in vastus lateralis: **T > C, P < .001**
Hughes[25] (2018)	Approximately 23 d after surgery for ACLR groups	Control: NI BFR and post-ACLR standard rehabilitation, heavy resistance Treatment: post-ACLR BFR, light resistance	0	Blood pressure: T:$C_{NI\text{-}BFR}$; T:$C_{ACLR\text{-}HL}$, $P > .05$ RPE: **T > $C_{NI\text{-}BFR}$, P < .01**; T:$C_{ACLR\text{-}HL}$, $P > .05$ Perceived muscle pain during session: **T > $C_{NI\text{-}BFR}$, P < .05**; **T > $C_{ACLR\text{-}HL}$, P < .01** Perceived knee pain during session: **T < $C_{ACLR\text{-}HL}$, P < .05** Perceived knee pain 24 h postexercise: **T < $C_{ACLR\text{-}HL}$, P < .01**
Grapar Zargi[22] (2016)	Preop, 4 wk postop, 12 wk postop	Control: pre-ACLR sham BFR Treatment: pre-ACLR BFR	0	Vastii volume: T:C, $P > .05$ Rectus femoris volume: T:C, $P = .113$ MVIC torque: T:C, $P = .556$ Single-leg anterior reach distance functional test: T:C, $P > .05$
Iversen[30] (2016)	Preop, 16 d postop	Control: post-ACLR nonrestricted activity Treatment: post-ACLR BFR	0	CSA of quadriceps at 40% femur length: T:C, $P > .05$ CSA of quadriceps at 50% of femur length: T:C, $P > .05$ Mean change in anatomic CSA: T:C, $P = .6265$

Ohta[59] (2003)	Preop, 16 d postop	Control: post-ACLR nonrestricted activity
		Treatment: post-ACLR BFR
			4.5	Muscular torque ratio of operative knee extensor/contralateral knee extensor:
				  Measured at CC60: **T > C, P < .001**
				  Measured at CC180: **T > C, P = .004**
				  Measured at IM60: **T > C, P < .001**
				Muscular torque ratio of operative knee flexor/contralateral knee flexor:
				  Measured at CC60: **T > C, P < .05**
				  Measured at CC180: **T > C, P = .04**
				  Measured at IM60: **T > C, P < .02**
				CSA ratio of operative knee extensor muscle group/contralateral knee extensor muscle group: **T > C, P = .04**
				Single-fiber diameter ratio for type 1 and 2 fibers: **T:C, P < .05**
				Range of motion (extension limit and flexion): **T:C, P < .05**
				Anterior instability: **T:C, P < .05**

Takarada[73] (2000)	Postop days 3 and 14	Control: post-ACLR nonrestricted activity Treatment: post-ACLR BFR	0	Total CSA (cm^2) of the quadriceps femoris: **T > C, P < .05** Extensor CSA: **T > C, P < .05** Flexor CSA: **T > C, P < .05** Femur CSA: T:C, $P > .05$

[a]Bold indicates $P < .05$. ACLR, anterior cruciate ligament reconstruction; BFR, blood flow restriction; C, control; CC, concentric contraction; CSA, cross-sectional area; EMG, electromyography; HL, high load; IM, isometric; MVIC, maximal voluntary isometric contraction; NI, uninjured; postop, postoperative; preop, preoperative; RPE, rating of perceived exertion; T, treatment.

DISCUSSION

The main findings from this descriptive analysis were as follows: (1) literature surrounding the topic of BFR rehabilitation in patients with ACLR is limited and heterogeneous, and (2) some but not all of the available evidence suggests that BFR as a pre- or postoperative intervention is beneficial to muscle volume and strength/endurance, at least in the early postoperative period, when compared with nonrestricted postoperative activity. These observations are in line with existing literature that has demonstrated increases in muscle hypertrophy with BFR application in healthy[8,51,52,55,80] and injured/postoperative[22,35,74] populations. Additionally, comparison of acute subjective outcomes between LL-BFR and high-load conventional rehabilitation found increased ratings of perceived exertion

TABLE 6
Comparison of BFR and Non-BFR Outcomes[a]

Author (Year)	BFR Outcome	Non-BFR Outcome	P Value
Zargi[83] (2018)	**Preop:** MVIC, Nm: 238 ± 83 Muscle isometric endurance, s: 145 ± 47 Surface EMG amplitude: 0.274 ± 0.16 EMG median frequency: 53.2 ± 11 Muscle blood flow: 1.26 ± 0.3 **4 wk postop:** MVIC, Nm: NA Muscle isometric endurance, s: 153 ± 54 Surface EMG amplitude: 0.391 ± 0.293 EMG median frequency: 45.7 ± 10.1 Muscle blood flow: 1.92 ± 0.81 **12 wk postop:** MVIC, Nm: 196 ± 48 Muscle isometric endurance, s: 199 ± 71 Surface EMG amplitude: 0.256 ± 0.160 EMG median frequency: 45.9 ± 4.4 Muscle blood flow: 1.49 ± 0.75	**Preop:** MVIC, Nm: 210 ± 44 Muscle isometric endurance, s: 95 ± 90 Surface EMG amplitude: 0.224 ± 0.1 EMG median frequency: 49.9 ± 5.9 Muscle blood flow: 1.53 ± 0.4 **4 wk postop:** MVIC, Nm: NA Muscle isometric endurance, s: 95 ± 90 Surface EMG amplitude: 0.187 ± 0.103 EMG median frequency: 41.7 ± 5.8 Muscle blood flow: 0.97 ± 0.20 **12 wk postop** MVIC, Nm: 181 ± 34 Muscle isometric endurance, s: 187 ± 94 Surface EMG amplitude: 0.210 ± 0.086 EMG median frequency: 44.1 ± 3.7 Muscle blood flow: 1.36 ± 0.32	**Time-group interaction:** MVIC, Nm: $P = .519$ Muscle isometric endurance: $\boldsymbol{P = .014}$ Surface EMG amplitude: $\boldsymbol{P = .001}$ EMG median frequency: $P = .730$ Muscle blood flow: $\boldsymbol{P < .001}$
Hughes[25] (2018)	**ACLR group with BFR rehabilitation, 22 d postop:** Perceived exertion, au: 18 Perceived muscle pain, au: 8 Perceived knee pain, au: 1.5 **NI control with BFR rehabilitation, 23 d postop:** Perceived exertion, au: 14.5 Perceived muscle pain, au: 5.5 Perceived knee pain, au: NA	**ACLR group with non-BFR high-load rehabilitation, 22 d postop:** Perceived exertion, au: 15.5 Perceived muscle pain, au: 3 Perceived knee pain, au: 2.5	**Between groups analysis at 22 d postop:** Perceived exertion, ACLR-BFR vs NI-BFR: $\boldsymbol{P < .01}$ Perceived exertion, ACLR-BFR vs ACLR-HL: $P > .05$ Perceived exertion, NI-BFR vs ACLR-HL: $P > .05$ Perceived muscle pain, ACLR-BFR vs NI-BFR: $\boldsymbol{P < .05}$ Perceived muscle pain, ACLR-BFR vs ACLR-HL: $\boldsymbol{P < .01}$ Perceived muscle pain, NI-BFR vs ACLR-HL: $\boldsymbol{P < .05}$ Perceived knee pain, ACLR-BFR vs NI-BFR: $P > .05$ Perceived knee pain, ACLR-BFR vs ACLR-HL: $\boldsymbol{P < .01}$ Perceived knee pain, NI-BFR vs ACLR-HL: $P > .05$ **Time-group interactions** Perceived exertion: $\boldsymbol{P < .01}$ Perceived muscle pain: $\boldsymbol{P < .01}$ Perceived knee pain: $P > .05$
Grapar Zargi[22] (2016)	**Preop:** MVIC, Nm: 241 ± 74 Vastii muscle volume, cm³: 1670 ± 362 Rectus femoris muscle volume, cm³: 225.4 ± 53.9 Anterior reach distance, cm: –0.5 **4 wk postop:** MVIC, Nm: NA Vastii muscle volume, cm³: 1325.9 ± 302.3 Rectus femoris muscle volume, cm³: 215.6 ± 45.4 Anterior reach distance, cm: NA **12 wk postop:** MVIC, Nm: 201 ± 47 Vastii muscle volume, cm³: 1444.3 ± 265.6 Rectus femoris muscle volume, cm³: 216.3 ± 56.3 Anterior reach distance, cm: –3.75	**Preop:** MVIC, Nm: 191 ± 59 Vastii muscle volume, cm³: 1462.7 ± 382 Rectus femoris muscle volume, cm³: 170 ± 43.7 Anterior reach distance, cm: –4.0 **4 wk postop:** MVIC, Nm: NA Vastii muscle volume, cm³: 1210.3 ± 285.9 Rectus femoris muscle volume, cm³: 164.1 ± 46.6 Anterior reach distance, cm: NA **12 wk postop:** MVIC, Nm: 172 ± 47 Vastii muscle volume, cm³: 1334.2 ± 337.2 Rectus femoris muscle volume, cm³: 171.4 ± 45.6 Anterior reach distance, cm: –4.5	**Difference between time points:** MVIC, Nm: $P = .025$ Vastii muscle volume, cm³: $\boldsymbol{P = .00}$ Rectus femoris muscle volume, cm³: $\boldsymbol{P = .00}$ Anterior reach distance, cm: $P > .05$ **Difference between BFR and non-BFR:** MVIC, Nm: $P > .05$ Vastii muscle volume, cm³: $P > .05$ Rectus femoris muscle volume, cm³: $P > .05$ Anterior reach distance, cm: $P > .05$

TABLE 6 (continued)

Author (Year)	BFR Outcome	Non-BFR Outcome	P Value
Iversen[30] (2016)	**Preop:** CSA quadriceps at 40% femur length, cm^2: 77.5 ± 2.5 CSA quadriceps at 50% femur length, cm^2: 87.0 ± 3.6 **16 d postop:** CSA quadriceps at 40% femur length, cm^2: 67.7 ± 2.7 CSA quadriceps at 50% femur length, cm^2: 73.9 ± 3.5 Reduction in CSA quadriceps at 40% femur length, cm^2: –9.7 ± 1.0 Reduction in CSA quadriceps at 50% femur length, cm^2: –13.7 ± 0.9 Mean change in CSA quadriceps from baseline to 16 d, cm^2: –13.8 ± 1.1	**Preop:** CSA quadriceps at 40% femur length, cm^2: 75.4 ± 3.2 CSA quadriceps at 50% femur length, cm^2: 82.8 ± 3.4 **16 d postop:** CSA quadriceps at 40% femur length, cm^2: 66.1 ± 3.3 CSA quadriceps at 50% femur length, cm^2: 71.3 ± 3.2 Reduction in CSA quadriceps at 40% femur length, cm^2: –9.2 ± 0.8 Reduction in CSA quadriceps at 50% femur length, cm^2: –11.5 ± 0.7 Mean change in CSA quadriceps from baseline to 16 d, cm^2: –13.1 ± 1	**Time point analysis between preop and postop:** CSA quadriceps at 40% femur length, cm^2: ***P*** < **.0001** CSA quadriceps at 50% femur length, cm^2: ***P*** < **.0001** **Between groups analysis at 16 d postop:** Mean change in CSA quadriceps from baseline to 16 d, cm^2: P = .6265
Ohta[59] (2003)	**Preop:** Extensor torque, CC60[b]: 84 ± 13 Extensor torque, CC180[c]: 84 ± 14 Extensor torque, IM60[d]: 92 ± 19 Flexor torque, CC60[b]: 96 ± 21 Flexor torque, CC180[c]: 96 ± 19 Flexor torque, IM60[d]: 91 ± 18 Extensor CSA,[e] injured:healthy: 91 ± 7 Flexor + adductor CSA,[e] injured:healthy: 99 ± 3 Range of motion, extension (deg): 3.1 ± 5.8 Range of motion, flexion (deg): 144 ± 15 Anterior instability, mm[f]: 5.3 ± 5.3 **16 wk postop:** Extensor torque, CC60[b]: 76 ± 16 Extensor torque, CC180[c]: 77 ± 13 Extensor torque, IM60[d]: 84 ± 19 Flexor torque, CC60[b]: 81 ± 14 Flexor torque, CC180[c]: 84 ± 18 Flexor torque, IM60[d]: 72 ± 11 Extensor CSA,[e] preop:postop: 101 ± 11 Flexor + adductor CSA,[e] preop:postop: 105 ± 19 Type 1 muscle fiber diameter (μm), preop:postop: 103 ± 10 Type 2 muscle fiber diameter (μm), preop:postop: 102 ± 8 Range of motion, extension (deg): 1.9 ± 3.7 Range of motion, flexion (deg): 140 ± 5.9	**Preop:** Extensor torque, CC60[b]: 86 ± 14 Extensor torque, CC180[c]: 90 ± 9 Extensor torque, IM60[d]: 94 ± 21 Flexor torque, CC60[b]: 90 ± 16 Flexor torque, CC180[c]: 99 ± 16 Flexor torque, IM60[d]: 94 ± 17 Extensor CSA,[e] injured:healthy: 92 ± 11 Flexor + adductor CSA,[e] injured:healthy: 97 ± 11 Range of motion, extension (deg): 0.7 ± 2.4 Range of motion, flexion (deg): 146 ± 7.7 Anterior instability, mm[f]: 5.3 ± 1.6 **16 wk postop:** Extensor torque, CC60[b]: 55 ± 17 Extensor torque, CC180[c]: 65 ± 13 Extensor torque, IM60[d]: 63 ± 19 Flexor torque, CC60[b]: 72 ± 15 Flexor torque, CC180[c]: 74 ± 12 Flexor torque, IM60[d]: 62 ± 14 Extensor CSA,[e] preop:postop: 92 ± 12 Flexor + adductor CSA,[e] preop:postop: 102 ± 23 Type 1 muscle fiber diameter (μm), preop:postop: 95 ± 11 Type 2 muscle fiber diameter (μm), preop:postop: 97 ± 7 Range of motion, extension (deg): 3.1 ± 3.6 Range of motion, flexion (deg): 143 ± 8.7	**Between group analysis at 16 wk:** Extensor torque, CC60[b]: ***P*** < **.001** Extensor torque, CC180[c]: ***P*** = **.004** Extensor torque, IM60[d]: ***P*** < **.001** Flexor torque, CC60[b]: P = .05 Flexor torque, CC180[c]: ***P*** = **.04** Flexor torque, IM60[d]: ***P*** = **.02** Extensor CSA,[e] preop:postop: ***P*** = **.04** Flexor + adductor CSA,[e] preop:postop: P > .05 Type 1 muscle fiber diameter (μm), preop:postop: P > .05 Type 2 muscle fiber diameter (μm), preop:postop: P > .05 Range of motion, extension (deg): P > .05 Range of motion, flexion (deg): P > .05
Takarada[73] (2000)	**3 d postop:** Total CSA of thigh, cm^2: 167.5 ± 5.1 Extensor CSA, cm^2: 54 ± 3 Flexor CSA, cm^2: 46.2 ± 2.6 Femur CSA, cm^2: 7 ± 0.3 **14 d postop:** Total CSA of thigh, cm^2: 156.3 ± 6.5 Extensor CSA, cm^2: 48.5 ± 2.6 Flexor CSA, cm^2: 41.7 ± 2.2 Femur CSA, cm^2: 7 ± 0.2	**3 d postop:** Total CSA of thigh, cm^2: 161 ± 4.7 Extensor CSA, cm^2: 52.8 ± 3.3 Flexor CSA, cm^2: 49.1 ± 4.7 Femur CSA, cm^2: 6.4 ± 0.5 **14 d postop:** Total CSA of thigh, cm^2: 137.5 ± 6.4 Extensor CSA, cm^2: 42.1 ± 3.4 Flexor CSA, cm^2: 44.8 ± 5.4 Femur CSA, cm^2: 6.5 ± 0.5	**Between-group analysis at 3 d:** All P > .05 **Between-group analysis at 14 d:** Total CSA of thigh, cm^2: ***P*** < **.05** Extensor CSA, cm^2: ***P*** < **.05** Flexor CSA, cm^2: ***P*** < **.05** Femur CSA, cm^2: ***P*** > **.05**

[a]Values are presented as mean ± SD where indicated. Bold P values indicate $P < .05$. ACLR, anterior cruciate ligament reconstruction; BFR, blood flow restriction; CC, concentric contraction; CSA, cross-sectional area; EMG, electromyography; HL, high load; IM, isometric; MVIC, maximal voluntary isometric contraction; NA, not available; NI, uninjured; postop, postoperative; preop, preoperative; RPE, rating of perceived exertion.
[b]Muscular torque, concentric contraction at 60 deg/s, expressed as operated:healthy ratio.
[c]Muscular torque, concentric contraction at 180 deg/s, expressed as operated:healthy ratio.
[d]Muscular torque, isometric contraction at 60° of knee flexion, expressed as operated:healthy ratio.
[e]CSA expressed as ratio to femur on same image.
[f]Anterior instability measured with knee ligament arthrometer KT2000 at 133 N.

and reduced in- and postsession knee pain with LL-BFR. With comparable increases in muscle cross-sectional area between LL-BFR and heavy-load training,[60-62,73] this new observation highlights the appeal of LL-BFR as a potentially effective alternative that can lead to reduced residual knee pain. Ultimately, definitive assessment of the effects of BFR in this population remains uncertain because of the quality of the present literature.

Of the 3 studies assessing strength as an outcome, the 1 with the longest training duration found a difference in muscular torque ratio between the operative knee extensor and the contralateral extensor in patients who underwent 84 sessions of LL-BFR, as opposed to unrestricted low-load training.[60] This was likely due to the presence of a dose-dependent relationship between training and strength gain such that more sessions lead to greater differences.[71] Evidence on other populations in the literature supports a difference in strength gains between LL-BFR and low-resistance training alone prescribed between 6 and 8 weeks of rehabilitation.[10,22,27,32,33] In contrast, evidence on the effect of BFR on post-ACLR muscle atrophy is conflicting. Of the 2 studies reviewed, 1 found almost a 50% reduction in muscle atrophy with BFR,[73] while the other found no difference in quadriceps cross-sectional area between the control and intervention groups.[30] However, authors of the latter study acknowledged subtherapeutic training intensity as a possible reason for this difference and suggested the incorporation of neuromuscular electrostimulation into future research models to detect the effects of BFR on a more granular level.[30]

The implementation of BFR has generally been indicated for patients with debilitation undergoing clinical rehabilitation, such as the elderly or surgical candidates[5,11,34,35,68,75,76] or athletes involved in sports at a competitive level.[2,21,30,68,78] While these 2 populations may ostensibly have distinct needs, their goals of rehabilitation or training make BFR an optimal intervention. Initial studies applied hemodynamic occlusion to low-resistance strength training in healthy and active athletes. Since then, several randomized trials and systematic reviews have established its effectiveness in improving muscle hypertrophy, strength, and fiber-type distribution, independently and as a complement to conventional training, while minimizing joint stress and risk of adverse effects.[‡]

For this reason, low-intensity resistance training with occlusion can be an effective and safe alternative in patients with sufficient extent of frailty or debility.[41,43,76] BFR also has appeal in rehabilitation of active patients after sports-related injuries, for maintenance of muscle mass and function while injuries heal, to facilitate a more rapid return to preinjury competition.[27,35,74]

Isolated incidents of adverse events have been documented in the literature, including 3 cases of syncope,[53] 1 case of rhabdomyolysis,[72] 1 case of vision loss secondary to central retinal vein occlusion,[4] and 1 case of thoracic venous outflow obstruction in a patient with thoracic outlet syndrome.[59] However, multiple trials and several systematic

reviews have supported the safety of BFR rehabilitation with regard to ischemic and hemostatic risks.[§] With the heterogeneity in quality of evidence, firm recommendations have been difficult to produce,[7,48] but a consensus among clinicians has pointed toward individualizing occlusion pressures, which has important implications for safety and effectiveness.[3,17,27,37,46,48,79]

Currently, it is recommended that individual occlusion pressures be calculated as a percentage of the total arterial occlusion pressure (AOP), with individual protocols ranging from 60% to 80%.[35,40,69,84] The gold standard method of measuring AOP and true occlusion is Doppler ultrasound,[6,9,29,56,66] although recent investigations have begun to assess the feasibility of pulse oximetry as a lower maintenance alternative.[77,84] A previous method in the literature attempted to predict the AOP as a percentage of the brachial systolic blood pressure.[48] However, a more recent investigation identified thigh circumference as the greatest predictor of AOP.[44] Therefore, limb circumference is being investigated as a highly effective nonmodifiable factor that can predict pressures applied for complete to partial occlusion.[17,28,44,81] Additionally, considerations for setting initial pressures according to tourniquet material (nylon vs elastic) has been highlighted.[46] Of note, none of the studies included in this systematic review completely employed these guidelines in their methods.

The current paradigm in training protocol is experiencing a similar transition toward individualized prescriptions to maximize gains. Studies in the literature have observed a domain-specific timeline for LL-BFR to demonstrate a significant advantage over non-BFR low-resistance training. Significant hypertrophy has been noted after as short as 6 days of training[21] and can be effectively achieved by most protocols: rehabilitation trials for patients undergoing surgery typically last 2 to 6 weeks and as long as 20 weeks.[16] Those for the elderly last longer, averaging 10 to 12 weeks.[42,54,61,62,65,76] However, there is the observation that improvements in muscle strength require a longer duration of training.[63] A comparative study demonstrated that while high-load resistance training (without BFR) yielded greater strength increases initially, results were equivalent to LL-BFR at 12 weeks of training.[12] This implies that an appropriate period of familiarization may yield hormonal and neural adaptations to more effectively utilize occlusion training.[67]

A comparison of pre- and postoperative BFR training in patients undergoing ACLR in this review found the strongest evidence of significant improvements in muscle hypertrophy and strength over standard rehabilitation protocols in candidates for postoperative BFR. Of the 2 studies on preoperative BFR, only 1 found a significant improvement over sham intervention in muscular endurance, activation, and perfusion. These outcomes were likely confounded by the significantly reduced training durations of preoperative BFR (5 sessions over 10 days).[23,83] Additionally, both trials enrolled only patients with chronic ACL rupture, where there is a greater likelihood of functional adaptation after

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[‡]References 2, 10, 14, 33, 40, 45, 49-52, 60, 62, 80.

[§]References 1, 13, 15, 20, 25, 39, 48, 57, 58, 70.

injury. An ongoing trial is examining 4 weeks of BFR prehabilitation as part of an overall perioperative protocol for ACLR, providing further insight to the optimal timing of BFR intervention[16] (Appendix Table A1). The strong evidence for the increased benefit of combined pre- and postoperative BFR rehabilitation after orthopaedic surgery[18,64] makes it imperative to continue evaluating BFR as a prehabilitation intervention.

There are several limitations to consider while interpreting the results of this study. While significant differences in short-term muscle strength and hypertrophy were demonstrated in some of the studies, none provided follow-up data with regard to changes in primary clinical outcomes or return to sports. The heterogeneity in outcome variables precluded a meta-analysis. Torque and cross-sectional areas are common outcome measurements, are readily obtained,[2,5,8,10,11,73,81-83] and warrant inclusion in the design of future trials. The study by Hughes et al[26] examining immediate subjective perspectives during and after BFR performed only a single session. Their results may not be generalizable to patients who are well-adapted to the volume and intensity of BFR protocols. Overall, there was a small number of patients in the collective cohort of studies reviewed and poor reporting of adverse events. Long-term follow-up data in these studies were sparse, and firm recommendations regarding safety cannot be made.

CONCLUSION

The evidence for the benefits of BFR rehabilitation after ACLR is sparse and heterogeneous possibly because of the novel nature of the technique. Although several studies have shown potential muscle strength and hypertrophy benefits in patients undergoing perioperative BFR in the setting of ACLR, future investigations with standardized outcomes, long-term follow-up, and more robust sample sizes are required to draw more definitive conclusions.

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APPENDIX

TABLE A1
Protocols of Ongoing Level 1 Trials on Perioperative BFR in Patients Undergoing ACLR[a]

Author (Year)	Device Used	Exercises	Volume and Frequency	Duration
Erickson[15] (2019)	Pressurized cuff to the proximal thigh that partially occludes blood flow as the patient exercises	Primary outcome measure: quadriceps strength (peak torque, rate of torque development) Secondary outcome measures: knee extensor movement, knee flexion excursion, knee flexion angle, quadriceps cross-sectional area, quadriceps muscle physiology	Not published in abstract	Presurgical blood flow restriction therapy 3×/wk for 4 wk leading up to surgery Postsurgical blood flow restriction therapy 3×/wk for 4-5 mo
Lambert[36] (2019)	Automated tourniquet around the proximal thigh outfitted with Doppler (Delfi)	Weeks 1-3: quadriceps contractions Weeks 3-12: bilateral leg press Weeks 4-6: hamstring curl Weeks 4-12: eccentric leg press Weeks 7-12: eccentric hamstring curl	All exercises preformed at 20% predicted 1 repetition maximum of contralateral leg All exercises, 4 sets of 30-15-15-15 repetitions separated by 30-s rest BFR group performed exercises with cuff at 80% arterial limb occlusion	12 wk of rehabilitation (2 sessions/wk) beginning at 10 d postsurgery Functional assessments performed at weeks 8 and 12 postsurgery DEXA scan performed pre- and postoperatively at weeks 6 and 12

[a]Occlusion pressure/cuff width was not published in either abstract. ACLR, anterior cruciate ligament reconstruction; BFR, blood flow restriction; DEXA, dual-energy x-ray absorptiometry.