Blood flow restriction interventions before and after anterior cruciate ligament reconstruction: A systematic review

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Introduction

Anterior cruciate ligament (ACL) rupture is a common occurrence in both recreational and professional athletes.[3-6,8-12] It is estimated that approximately 200,000 ACL reconstruction surgeries are performed annually in the United States.[9] Despite ACL reconstruction and current best practice rehabilitation, only 60% of amateur and 83% percent of elite athletes return to sport after ACL rupture.[3,9,11,12,19] Furthermore, of those whom return to sport, there is a prominent persistence of quadriceps strength deficits and limb strength asymmetry that results in decreased sports performance compared to before injury.[3-6,8,10-12] These strength and participation impairments may persist for as long as 20 years following ACL reconstruction.[5] Quadriceps strength deficits and limb strength asymmetry after ACL reconstruction has been linked to long-term consequences, such as early-onset knee osteoarthritis, despite prioritization of quadriceps strength during rehabilitation.[5,8,9,10-12,19]

Strength training is typically implemented in post-ACL reconstruction rehabilitation by progressive overload using at least 70% of an individual's 1-repetition maximum in order to trigger physiological strengthening responses.[1,2,14,17] Greater magnitudes of loading require a greater number of motor units, thus maximizing strength adaptations via higher rates of motor unit recruitment.[2] However, this magnitude of heavy loading is not practical or safe during early rehabilitation after ACL reconstruction due to high mechanical stressors placed on healing tissues.[1,14] This combination of factors has created a need for safe but effective methods of muscular strengthening after ACL reconstruction.

Blood flow restriction (BFR) training is an alternate strengthening approach to the progressive overload principle and may be appropriate during early recovery. BFR involves the application of an inflatable cuff, wrap, band, or tourniquet during therapeutic activity or exercise, in order to occlude venous return from an active muscle while still allowing arterial blood flow.[1,7] BFR training has been shown to positively affect muscle strength and hypertrophy with lower amounts of external loading, and has been successfully applied in sports training and musculoskeletal rehabilitation, the latter particularly with older adults.[1,7,13-14,16-18] BFR interventions with older adults, paired with lower loading, have resulted in strength gains comparable to those elicited with heavy loading.[1,17] It is, however, unclear if BFR is any more effective in eliciting changes in strength than usual care following ACL reconstruction. BFR interventions may be appropriate for use before, or after, ACL reconstruction for application of stimulus

mimicking heavy loading in rehabilitation while maintaining post-surgical precautions to avoid excessive stress on healing tissues.

The purpose of this systematic review was to examine the effects of BFR intervention before or after ACL reconstruction on strength, pain, range of motion (ROM), and function. Pain, ROM, and function will be addressed in addition to strength due to their intricate relationship with patient rehabilitation participation and overall outcomes.

Methods

Search strategy

The review was submitted to the PROSPERO international prospective register of systematic reviews curated by the University of York on November 15th, 2019. A search was conducted on February 5, 2020 in CINAHL, Embase, PEDRo, ProQuest Health Administration Database, PubMed, Scopus, SportDiscus, and Web of Science. Search terms and results for each database are included in Appendix A.

Inclusion and exclusion criteria

Inclusion criteria were as follows: study sample undergoing rehabilitation after ACL reconstruction, pre-habilitation prior to ACL reconstruction, or with an ACL injury; participants receive a blood flow restriction intervention; outcome measures include strength, pain, swelling, and/or function via report or performance; randomized controlled trials, non-randomized controlled trials, cohort studies, or case-control studies. Exclusion criteria were: animal studies; study sample without ACL injury; not using BFR intervention; any form of review, meta-analyses, grey literature, expert opinions, clinical commentaries, or case studies or series.

Study selection, data extraction, and risk of bias analysis

Title and abstract screening, then full text review, was performed. Each study received two independent reviewers both at the title and abstract screening stage, and full text review stage. A third independent reviewer made the final decision regarding any conflicts. Data from studies related to strength, pain, ROM, and performance were abstracted and narratively summarized by one reviewer. Studies were summarized by outcome: strength, pain, ROM, performance, and the parameters for BFR. Risk of bias for included studies was assessed used the PEDro scale for randomized controlled trials (RCTs) and the Risk of Bias Assessment for Non-Randomized Studies (RoBANS) for non-randomized studies.

Results

Three hundred and eleven articles were included for screening. Twenty-one duplicates were removed. Two hundred and ninety-three articles were screened with 11 included for final review (Figure 1). Eleven articles, encompassing 10 distinct studies, were included for analysis (Table 1). Hughes et al 2019, although published as two separate articles with different outcomes discussed, addressed the same patient cohort for the same study; thus, both studies will be referred to as Hughes et al 2019, but the respective in-text citation will match the appropriate article for reference. Five studies were partially- or quasi- randomized, in which randomization methods were not honored as truly random, such as block assignment or assignment by electronic record identification number. Four studies included data regarding the non-operative leg for comparison. Two studies included BFR intervention in a pre-habilitation program prior to ACL reconstruction surgery.[20,21] One study included BFR intervention in a rehabilitation program multiple years after ACL reconstruction surgery.[24] Iverson et al and Takarada et al intervened early after ACL reconstruction, approximately 2-3 weeks post-operatively.[22,25] Zargi et al 2016,[21] Zargi et al 2018,[20] Hughes et al 2018,[28] Hughes et al 2019,[26,27] Ohta et al,[23] Curran et al,[30] and Lambert et al[29] reported results from the intervention in the middle period of ACL reconstruction rehabilitation, approximately 12-16 weeks post-operatively. Kilgas et al reported results from long after ACL reconstruction rehabilitation.[24]

Figure 1.
PRISMA Flow Chart detailing study screening, review, and inclusion

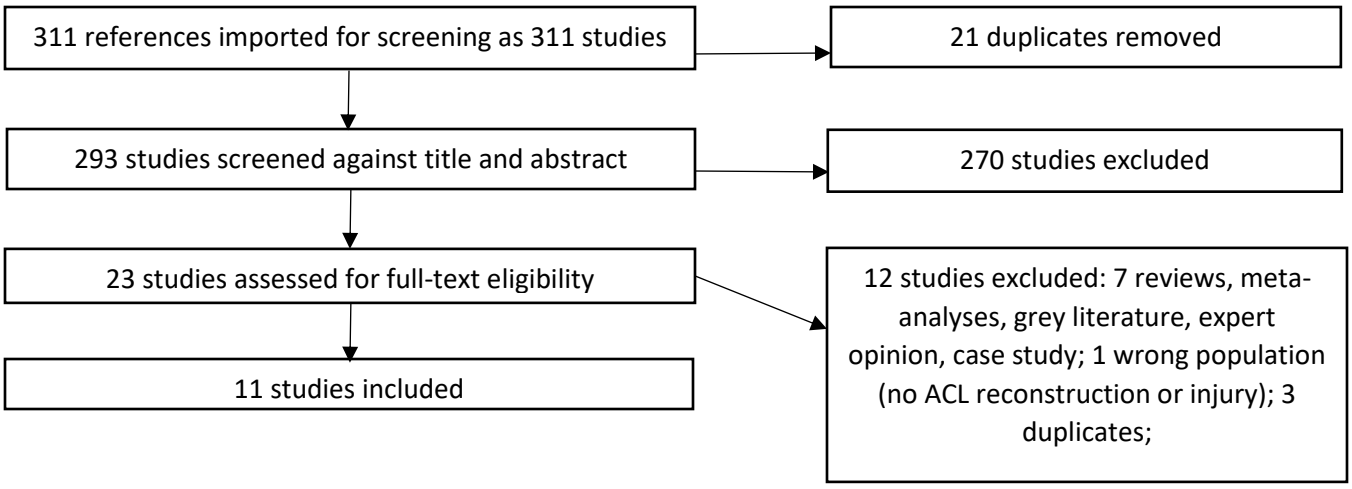

Table 1. Included Studies

	Year of publication	Study design	Timing of BFR intervention	Control/Comparison Group(s)	Non-operative leg as comparison?	N (BFR group/ control group)
BFR Intervention before ACLR						
Zargi et al 2018	2018	Quasi-randomized controlled trial	Equally distributed during the last 8 days before surgery	Same post-operative rehabilitation with sham BFR intervention with 20 mmHg	No	20 (10/10)
Zargi et al 2016	2016	Quasi-randomized controlled trial	Last 10 days before surgery	Same post-operative rehabilitation with sham BFR intervention with 20 mmHg	Yes	20 (10/10)
BFR Intervention during post-ACLR rehabilitation						
Hughes et al 2018	2018	Partially-randomized controlled trial	Approx 3 weeks after surgery (22+/-2 days for BFR group, 21+/-3 days for control), for 1 session	BFR intervention without ACL involvement, ACL reconstruction with BFR, & ACL reconstruction with heavy loading resistance exercise intervention without BFR	No	30 (10/10/10)
Hughes et al 2019	2019	Randomized controlled trial	Approx 3 weeks after surgery (23+/-2 for BFR intervention group, 24+/-1 days for control group) for 8 weeks until approx 11-12 wks post-op	Heavy load resistance training without BFR	Yes	24 (12/12)
Ohta et al	2003	Randomized controlled trial	1st week post-op to 16th week post-op	Same post-operative rehabilitation without BFR	Yes	44 (22/22)
Takarada et al	2000	Non-randomized controlled trial	1st day post-op to 14th day post-op	Sham BFR, cuff not inflated	No	16 (8/8)
Iverson et al	2016	Randomized controlled trial	2nd day post-op to 16 days post-op	Same post-operative rehabilitation without BFR	No	24 (12/12)
Curran et al	2019 (presented)	Randomized controlled trial	8 weeks post-op to 16 weeks post-op	Same post-operative rehabilitation without BFR	No	36 (18/18)
Lambert et al	2019 (presented)	Randomized	10 days post-op, for 12 weeks, to approx 13.5 weeks post-op	Same post-operative rehabilitation without BFR	No	14 (7/7)

		controlled trial				
BFR Intervention after post-ACLR rehabilitation						
Kilgas et al	2019	Controlled before-and-after study	5+/-2 years after ACL reconstruction for 4 weeks	Uninjured group performing same exercises without BFR	Yes	18 (9/9)

Risk of Bias Analyses

Curran et al[30] and Lambert et al[29] could not be assessed for risk of bias. Both were abstracts presented in conferences and do not have full text available at the time of this review. There is concern for both to have a high risk of bias without the ability to fully appraise.

Randomized Controlled Trials

Average PEDro score was 5/10 for the six included RCTs (Table 2). Scores ranged from 4/10 to 6/10. A PEDro score of greater than or equal to 6/10 is considered moderate to low risk of bias. The higher a PEDro score is, the lower the risk of bias.[34] Four studies specified inclusion and exclusion criteria. No studies randomized participants per PEDro standards, which recognizes methods such as coin-tossing or dice-rolling as randomization. PEDro does not consider quasi-randomization, such as record number allocation or alternation, as true randomization. Group allocation was concealed in two studies. Five studies specified that groups were similar at baseline regarding important prognostic criteria. Subjects were blinded to group allocation in two studies. No studies blinded therapists administering the BFR intervention. Two studies blinded all assessors of at least one outcome. Four studies obtained outcome measures from at least 85% of participants initially allocated into groups. The outcome measures of all studies were from participants who received the treatment or control conditions; this means that no subjects were included that did not receive the intervention or control condition. All studies reported between-groups statistical analyses for at least one outcome. Five studies provided both point estimates as well as measures of variability for at least one outcome.

Table 2. PEDro Scores

PEDro criteria	**Zargi et al 2018**	**Zargi et al 2016**	**Hughes et al 2018**	**Hughes et al 2019**	**Iverson et al**	**Ohta et al**
1. eligibility criteria were specified.	✗	✓	✓	✓	✓	✗
2. subjects were randomly allocated to groups (in crossover study, subjects were randomly allocated an order in which treatments were received)	✗	✗	✗	✗	✗	✗

3. allocation was concealed	✗	✗	✓	✓	✗	✗
4. the groups were similar at baseline regarding the most important prognostic indicators	✓	✓	✗	✓	✓	✓
5. there was blinding of all subjects	✓	✓	✗	✗	✗	✗
6. there was blinding of all therapists who administered the therapy.	✗	✗	✗	✗	✗	✗
7. there was blinding of all assessors who measured at least one key outcome.	✗	✓	✗	✗	✓	✗
8. measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.	✗	✗	✓	✓	✓	✓
9. all subjects for whom outcome measures were available received the treatment or control condition allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat."	✓	✓	✓	✓	✓	✓
10. the results of between-group statistical comparisons are reported for at least one key outcome.	✓	✓	✓	✓	✓	✓
11. the study provides both point measures and measures of variability for at least one key outcome.	✓	✓	✓	✓	✓	✗
Total PEDro score	**5/10**	**6/10**	**5/10**	**6/10**	**6/10**	**4/10**

Non-randomized Studies

Two studies were non-randomized studies. Both had high risk of selection bias and detection bias. Both had low risk of performance bias and reporting bias.[22,24] Kilgas et al had a high risk of selection bias due to inadequate consideration of confounding variables.[24] Takarada et al had a low risk of selection bias due to inadequate consideration of confounding variables.[22] Kilgas et al had a low risk of attrition bias while Takarada et al had an unclear risk of attrition bias.[22,24]

Table 3. RoBANS Criteria

Domain	**Description**	**Kilgas et al**	**Takarada et al**
		Domain Risk of Bias	
Selection of Participants	Selection bias caused by inadequate selection of participants.	High	High
Confounding variables	Selection bias caused by inadequate confirmation and consideration of confounding variable.	High	Low
Intervention (exposure) measurement	Performance bias caused by inadequate measurement of intervention (exposure)	Low	Low
Blinding of outcome assessment	Detection bias caused by inadequate blinding of outcome assessment.	High	High
Incomplete outcome data	Attrition bias caused by inadequate handling of incomplete outcome data.	Low	Unclear
Selective outcome reporting	Reporting bias caused by selective outcome reporting.	Low	Low

Blood Flow Restriction Parameters

The parameters for application of BFR varied greatly between each study (Table 4). Ohta et al, Curran et al, and Lambert et al did not specify cuff dimensions nor brand.[23] All other included studies specified cuff dimensions and/or a brand for the cuff, seen in Table 2. Six studies specifically named the thigh or proximal thigh as the location for the cuff application. Five studies used limb occlusion pressure (LOP) for cuff pressure. Three studies used specifically prescribed mmHg standard for all participants. Three studies adjusted cuff pressure either self-selected by the participant, manually adjusted to match a prescribed LOP, or adjusted based on the intervention protocol. Six studies used an electronic or automated tourniquet system, most frequently manufactured by Delfi Medical Innovations in Canada. Two studies used a hand pump tourniquet. Two studies did not specify the utilized tourniquet system.

Table 4. Blood Flow Restriction Parameters

	Cuff	**Location**	**Tourniquet System**	**Cuff pressure**
Zargi et al (2018)	14 cm wide contoured pneumatic tourniquet cuff (VariFit Conture Thigh Cuff, Delfi Medical Innovations, Canada)	Proximal thigh	Pressure regulating system: Portable Tourniquet System, Delfi Medical Innovations, Canada)	150 mmHg (intervention); 20 mmHg (control)
Zargi et al (2016)	14 cm wide contoured pneumatic tourniquet cuff (VariFit Conture Thigh Cuff, Delfi Medical Innovations, Canada)	Proximal thigh	Pressure regulating system: Portable Tourniquet System, Delfi Medical Innovations, Canada)	150 mmHg (intervention); 20 mmHg (control)
Hughes et al (2018)	Dual-purpose easy-fit variable contour nylon cuff (11.5 cm x 86 cm, 5 mm thick)	Not specified	Automatic personalized tourniquet system for BFR (Delfi Medical, Vancouver, BC, Canada)	80% LOP
Hughes et al (2019)	dual-purpose easy-fit variable contour nylon cuff (11.5 cm x 86 cm, 5 mm thick)	Not specified	Automatic Personalised Tourniquet System (Delfi Medical, Vancouver, BC, Canada)	80% LOP
Kilgas et al	18-cm wide aneroid sphygmomanometer (Briggs Healthcare, Waukegan, IL, USA)	Not specified	none	50% LOP; exact LOP determined with Doppler Ultrasound; mean LOP 182±28 mmHg; mean BFR training pressure 91±14 mmHg

Ohta et al	Air tourniquet	Proximal thigh	Hand-pumped tourniquet	180 mmHg
Takarada et al	pneumatic occlusion cuff (width: 90 mm; length: 700 mm)	Proximal thigh 100 mm below the hip joint	Not specified	initially 180 mmHg; gradually elevated 10 mmHg steps at a time; max pressure 238±8 mmHg; range 200-260 mmHg
Iverson et al	14-cm wide contoured pneumatic occlusion cuff (Delphi low pressure cuff 9-7450-003)	Proximal thigh	Portable blood pressure hand pump (Trigger Anaeroid DS66;; Welch Allyn, Skaneateles Falls, NY, USA)	start 130 mmHg, increase in 10 mmHg every 2nd day, to max of 180 mmHg. Participants self-selected highest tolerable pressure.
Curran et al	Unspecified cuff	Thigh	Not specified	80% LOP
Lambert et al	Automated tourniquet	Proximal thigh	Doppler system (Delfi Medical Innovations, Canada)	80% arterial occlusion pressure (AOP)

Strength

Eight studies included strength measures. BFR intervention before surgery, and during early, middle, and late recovery after ACL reconstruction surgery did not yield consistent results for strength measures across the included studies. BFR intervention before ACL reconstruction did not yield significant effects on strength versus the sham BFR, as demonstrated in Zargi et al 2016[21] and Zargi et al 2018.[20] BFR intervention during early recovery after ACL reconstruction results in conservation of knee extensor cross-sectional area, but not knee flexor cross-sectional area, compared to sham BFR.[22] There were no significant differences between control and BFR intervention group for Iverson et al.[25]

BFR intervention during middle recovery additionally showed mixed results. Ohta et al[23] and Hughes et al 2019[27] demonstrated a greater preservation of strength from pre-operative to 12-16 weeks post-operative by the BFR intervention group versus the usual care for their respective strength measures. Conversely, Curran et al showed no significant differences between the BFR intervention group and usual care during middle recovery.[30] Kilgas et al showed significant improvement in strength and quadriceps thickness symmetry in the BFR intervention group 5±2 years after ACL reconstruction surgery.[24]

Table 5. Strength Measures

Study / Comparators	Outcome Measure	Time points	Analysis	Results
BFR intervention before ACL reconstruction surgery				
Zargi et al 2018 (BFR vs sham BFR)	Maximal voluntary isometric contraction (MVIC)	Pre-operative & 12 weeks post-operative	2-way (Group×Time) ANOVA with repeated measures for time factor. Significant main effect analyzed via Tukey's post-hoc test. Significance set at $\alpha<0.05$.	No significant differences between groups nor over time ($p>0.001$)
	Sustained contraction time at 30% pre-operative MVIC	Pre-operative, 4 weeks & 12 weeks post-operative	2-way (Group×Time) ANOVA with repeated measures for time factor. Significant main effect analyzed via Tukey's post-hoc test. Multivariable linear regression analysis of changes, with time as the dependent variable, for pooled data and separately for each group. Significance set at $\alpha<0.05$.	No significant decrease in BFR intervention group from baseline to 4-week post-op ($p>0.001$). Significant decrease in control group from baseline to 4-weeks post-op ($p<0.001$). At 12 weeks post-op, BFR intervention group still had no significant change, control group returned to pre-operative levels.
Zargi et al 2016 (BFR vs sham BFR)	Maximal voluntary isometric contraction	Pre-operative, 12 weeks post-operative	2×2×3 (Leg×Group×Time) ANOVA with repeated measures on time factor. Significant main effect underwent Tukey's post-hoc test. Deficits in MVIC and muscle volume of operative leg leg calculated as: [(Operative leg value – Contralateral leg value)/Contralateral leg value] x 100 Significance 0.80 power, $p<0.05$.	Significant decrease for operative leg for BFR intervention ($p<0.05$) and control ($p<0.01$). No significant difference between groups.
	Vastii muscle volume	Pre-operative, 4 weeks & 12 weeks post-operative		Significant overall decrease in both groups' operative leg ($p<0.001$) from pre-operative to 4 weeks post-op. This deficit lessened, but was still significant, at 12 weeks post-operative ($p<0.001$) for both groups. No significant differences between groups' operative legs at any time point ($p>0.001$).
	Rectus femoris muscle volume			No significant change over time for both groups. No significant difference between groups at any time point.
BFR intervention during early recovery				
Takarada et al (BFR vs sham BFR)	Knee extensors cross-sectional area	3 days & 2 weeks post-operative	Non-parametric, Mann-Whitney U-test. Changes in variables for individuals examined	Significant decrease from 3 days to 2 weeks post-op for both groups ($p<0.05$) CSA of knee extensors of BFR intervention group decreased to

			with Wilcoxon signed-ranks test. Significance set at p<0.05. Data reported as means (SD).	a significantly smaller extent versus the control (p=0.046)
	Knee flexors cross-sectional area			Significant decrease from 3 days to 2 weeks post-op (p<0.05). No significant difference between groups (p=0.69).
Iverson et al (BFR vs usual care)	Quadriceps anatomical cross-sectional area	2 days & 2 weeks post-operative	Parametric unpaired *t*-test. Data reported as means (SD) and mean change between time points.	Significant decrease over time for both groups (p<0.0001). No significant difference in loss between groups (p=0.6265).
BFR intervention during middle recovery				
Ohta et al (BFR vs usual care)	Maximum voluntary isometric contraction at 60 degrees of knee flexion	Pre-operative, 16 weeks post-operative	Mann-Whitney U-test. Significance set at p<0.05. Reported at both time points as a ratio of operative leg: non-operative leg mean percentages and their respective standard deviations.	Pre-operatively, all ratios were "about the same" or "similar" between groups.[23] BFR group had a significantly greater ratio preservation at 16 weeks versus the control group (p<0.05).
	Isokinetic strength – knee flexion & extension, 60 degrees per second & 180 degrees per second			Pre-operatively, all ratios were "about the same" or "similar" between groups.[23] BFR had a significantly greater ratio preservation at 16 weeks versus the control group (p<0.05) except for knee flexion at 60 degrees per second (p=0.05).
	Cross-sectional area, knee extensor muscle groups & knee flexor and adductor muscle groups		Mann-Whitney U-test. Significance set at p<0.05. Reported pre-operatively as ratio of operative leg: non-operative leg mean percentages and their standard deviations. Reported post-operatively as pre-operative value:16 weeks post-operative value mean percentages and their standard deviations.	Pre-operatively there was no significant different in CSA ratios between groups. The post-operative ratio of CSA of the knee extensor muscle group on the operative leg was significantly greater than the control group (p=0.04).
Hughes et al 2019 (BFR vs heavy load resistance training without BFR)	Isokinetic strength peak torque – knee extension at 60, 150, and 300 ˚/s	8 days pre-operative, 12 weeks post-operative	Mean difference between time points, 2x2 (Group×Time) repeated-measures ANOVA (group allocation as between-subject independent factor, time as within-subject dependent factor). Alpha	From pre-operative to 12 weeks post-operative, the injured limb at 60˚/s had a significant decrease in both groups (p<0.01) with no difference between groups (p=0.20,d=0.50); at 150 and 300 ˚/s, the injured limb had a significantly greater decrease for the control group versus the BFR intervention group(p<0.01),

			significance p<0.05. Effect size (Cohen's d).	which had no significant change. The uninjured limb had a significant increase in both groups (p<0.01) with no significant difference between groups (p>0.01) for all speeds.
	Isokinetic strength peak torque – knee flexion at 60, 150, and 300 ˚/s			From pre-operative to 12 weeks post-operative, the injured limb at all speeds had a significant decrease in peak torque for both groups (p<0.01); the control group had a significantly greater decrease versus BFR group for all speeds(p<0.01). The uninjured limb had a significant increase for both groups at all speeds (p<0.01) with no significant difference between groups (p>0.01).
	10 repetition maximum (unilateral, leg press)	Pre-operative, and approx 3.5 weeks, 6 weeks, and 12 weeks post-operative,	Percent change between time points, 2x4 repeated-measures ANOVA (group allocation as between-subject independent factor, time as within-subject dependent factor). Alpha significance p<0.05. Effect size (Cohen's d).	No statistically significant interaction for either limb. Significant main effect of time for operative limb and non-operative limb (p<0.01, d=1.0; p<0.01, d=1.0, respectively). Pre- to post-operative, decreased significantly in operative limb and did not significantly change in non-operative limb, with no differences between groups. Both groups and both limbs had significant increase in percent change from 3.5 weeks post-operative to 12 weeks post-operative with no differences between groups (p=0.22, d=0.3 for operative limbs, 0.39, d=0.3 for non-operative limbs).
Curran et al (BFR vs usual care)	Isometric strength of quadriceps at 90˚ degrees of knee flexion	Pre-operative, 16 weeks post-operative	Peak strengths used to calculate symmetry indices: ((operative limb value/non-operative limb value) × 100). Then change from baseline was calculated: ((16-week index – pre-operative index)/pre-operative index). One-way analysis of variance tests to analyze between-groups differences. Effect sizes (Cohen's	No significant change over time for either isometric strength nor isokinetic strength symmetry indices (p>0.05). Effect sizes for both isometric strength and isokinetic strength symmetry indices were small (d=0.16; d=0.28, respectively), and confidence intervals crossed zero (CI=0.-49, 0.80; CI=-0.37,0.93, respectively).
	Isokinetic strength of quadriceps at 60˚/s			

			d) and 95% confidence intervals. Significance set a priori p<0.05.	
BFR intervention during late recovery				
Kilgas et al (BFR vs same exercise program without BFR)	10 repetition maximum	5±2 years, then after 4 week-long intervention	Brzycki's equation for 1 repetition maximum then reported as percent change. Also used to calculate symmetry indices. 2 (operative/non-operative) x 2 (baseline/post-training) repeated measurers ANOVA. Paired t-test for difference in baseline vs post-training symmetry indices for ACL reconstruction group only. Independent t-tests for difference in symmetry indices ACL reconstruction group and control. Significance p<0.05.	At baseline, operative leg for ACL reconstruction group was significantly less than non-operative leg (p<0.01). ACL reconstruction group symmetry index was significantly less than the control (p<0.01). Significant leg×time interaction. Knee extensor strength significantly increased over time in the operative leg (p<0.01) while the non-operative leg did not significantly change over time (p=0.09). ACLR group symmetry index increased over time (p<0.01) and was not different from the uninjured control group after training (p=0.95).
	Rectus femoris thickness		Reported as symmetry indices. Independent t-test for baseline differences between symmetry indices. 2 (operative/non-operative) x 2 (baseline/post-training) repeated measurers ANOVA. Paired t-test for difference in baseline vs post-training symmetry indices for ACL reconstruction group only. Independent t-tests for difference in symmetry indices ACL reconstruction group and control. Significance p<0.05.	At baseline, operative leg for ACL reconstruction group was significantly less than non-operative leg(p<0.01). ACL reconstruction group symmetry index was significantly less than the control (p<0.01). Significant leg×time interactions (p<0.01). After training, involved leg significantly increased (p<0.01) while uninvolved leg did not (p=0.76). Significant difference between involved and uninvolved legs after training (p=0.03). Significant difference between involved and uninvolved legs after training (p=0.02). After training, ACLR group had significant change over time (p<0.01) without difference from the control (p=0.28).
	Vastus lateralis thickness			At baseline, operative leg for ACL reconstruction group was significantly less than non-operative leg(p<0.01). ACL reconstruction group symmetry

				index was significantly less than the control (p<0.01). Significant leg×time interactions(p<0.01). After training, involved leg significantly increased (p<0.01) while uninvolved leg did not (p=0.47). After training, there still existed a significant difference between legs after training. Significant difference between involved and uninvolved legs after training (p=0.03). After training, ACLR group had significant change over time (p<0.01) but remained significantly less than the control (p=0.03).

Pain

Two studies included measures for pain. Overall, BFR intervention groups demonstrated greater levels of muscle pain and knee pain, but with a generally quicker relief of pain across intervention sessions.[26-28] Hughes et al 2019 specifically showed greater average muscle pain for BFR intervention, but lower knee joint pain for BFR intervention, versus the control.[26]

Study	Measure	Timepoints	Statistics	Results
Hughes et al 2018 (non-injured light-loading BFR, vs ACL reconstruction with light loading and BFR, vs ACL reconstruction with heavy loading and no BFR)	Muscle pain	Before and after single intervention session, approximately 3-4 weeks post-operative	Mean, standard deviations, 95% Cis. One-way subjects' ANOVA. Statistically significant interactions underwent Bonferroni post-hoc analysis.	Statistically significant difference between groups (p<0.01). Significantly greater in ACL reconstruction with BFR intervention group versus no operation with BFR intervention group (p<0.05, 95% CI:0.292-5.058). Significantly greater in ACL construction with BFR intervention group versus ACL reconstruction with heavy loading and no BFR intervention group (p<0.01, 95% CI: 2.942-7.758). Significantly greater in no operation with BFR intervention group versus ACL reconstruction with heavy loading group (p<0.05, 95% CI: 0.242-5.058).
	Knee joint pain (ACLR group only)	During and 24 hours after single intervention session,	Logarithmic transformation applied (data non-normally distributed).	No statistically significant interaction between groups and timepoints ($F_{(1,36)} = 0.123$, p>0.05). Significant main effect of treatment ($F_{(1,38)} = 21.992$,

		approximately 3-4 weeks post-operative	Normally distributed (p>0.05) data analyzed with two-way between subjects' ANOVA. Statistically significant interactions underwent Bonferroni post-hoc analysis.	p<0.001). Significantly lower mean difference in ACL reconstruction with BFR intervention group versus the ACL reconstruction group with heavy loading (p<0.01, 95% CI: -1.890, -0.750).
Hughes et al 2019 (BFR vs heavy load resistance training without BFR)	KOOS pain subscale	Pre-operative, and approx 3.5 weeks, 6 weeks, and 12 weeks post-operative	Mean difference between time points, 2x4 repeated-measures ANOVA (group allocation as between-subject independent factor, time as within-subject dependent factor). Alpha significance p<0.05. Effect size (Cohen's d).	Statistically significant group×time interaction. Significant decrease pre- to post-operative with no significant difference between groups (p>0.05). Significantly greater mean difference in BFR group versus control group for 3.5-6 weeks and 3.5-12 weeks post-operative (p<0.01 for all). Significant group × time interaction effect.
	Muscle pain during intervention session	Each session during an 8-week long intervention (starting at 3-4 weeks post-operative) for 16 session	2×16 (Group×Session) repeated measures ANOVA; group allocation for between-subjects factor, session as within-subjects dependent factor. Statistically significant results further processed with Bonferroni post-hoc analysis. Significance set a priori p<0.05. Effect size (Cohen's d).	Operative leg: mean muscle pain was significantly higher in BFR group versus control during all sessions (all p<0.05). Average muscle pain was significantly greater in the BFR group versus the control (p<0.05). The BFR group peaked at session 1 and significantly decreased by sessions 15 and 16 (p<0.05, d=0.5, 95% CI: 0.3-0.7; p<0.05, d=0.8, 95% CI: 0.7-0.9, respectively). The control group peaked at session 1 and significantly decreased by sessions 15 and 16 (p<0.05, d=0.7, 95% CI: 0.6-0.8; p<0.05, d=0.8, 95% CI: 0.7-0.9). Non-operative leg: average muscle pain was significantly greater in the BFR group (p<0.05). The BFR peaked at session 1 and significantly decreased by sessions 14, 15, and 16 (p<0.01, d=0.8, 95% CI:

				0.6-2.0; p<0.01, d=0.9, 95% CI: 0.8-1.0; p<0.01, d=1.0, 95% CI: 0.8-1.2, respectively). The control group peaked at session 1 and significantly decreased by session 15 and 16 (p<0.05, d=0.7, 95% CI: 0.6-0.8; p<0.05, d=0.7, 95% CI: 0.6-0.8, respectively).
	Knee joint pain during intervention session (operative leg only)			Mean session knee pain for BFR group significantly less than control for every session (p<0.05, mean d=2.5, 95% CI: 2.2-2.8). For the BFR group, mean session knee pain peaked in the first session and significantly decreased by session 4 (p<0.01, d=0.5, 95% CI: 0.4-0.7) and remained significantly lower throughout the rest of the intervention sessions (all p<0.05, mean d=1.2, 95% CI: 0.7-1.4). The control group session knee joint pain peaked in the first session and significantly decreased by session 6 (p<0.05, d=0.2, 95% CI: 0.1-0.3) and remained significantly lower throughout the rest of the intervention sessions (all p<0.05, mean d=0.5, 95% CI: 0.4-0.7).
	Knee joint pain 24-hours after intervention session (operative leg only)			Mean post-training knee pain for BFR group was significantly less than the control group for all timepoints (p<0.01, mean d=3.1, 95% CI: 2.9-3.3). The BFR group peaked after session 1 and significantly decreased after session 3 (p<0.05, mean d=0.7, 95% CI: 0.6-0.8) and remained significantly lower for all remaining sessions (all p<0.01, mean d=2.9, 95% CI: 2.7-3.2). The control group also peaked after session 1 and significantly decreased after session 3 (p<0.05, mean d=0.3, 95% CI: 0.2-0.4) and remained significantly lower for all remaining sessions (all p<0.01, mean d=1.7, 95% CI: 1.3-2.0). After sessions 4-10 there was a greater decrease in BFR group compared to peak mean versus

				control (all p<0.01, mean d=1.9, 95% CI: 1.7-2.2).

Range of Motion (ROM)

Two studies addressed ROM. There were no significant effects of BFR intervention on knee extension ROM.[23,27] Hughes et al 2019 showed a significant improvement in flexion ROM and total ROM differences between groups.[27]

Study	Outcome Measure	Time points	Statistics	Results
Ohta et al (BFR vs usual care)	Knee extension limit and flexion range of motion for operative leg only	Pre-operative, 16 weeks post-operative	Mann-Whitney U-test. Significance set at p<0.05.	No significant differences between groups pre- or 16 weeks post-operative (p>0.05)
Hughes et al 2019 (BFR vs heavy load resistance training without BFR)	Range of motion differences between affected and unaffected legs	Pre-operative, and approx 3.5 weeks, 6 weeks, 12 weeks post-operative	Mean difference between time points. Effect size (Cohen's d). Unspecified ANOVA. Alpha significance p<0.05.	Significant group×time interaction for flexion difference and overall range of motion difference from pre- to 6 weeks post-operative with no differences between groups (p=0.22/d=0.5, p=0.17/d=0.5 respectively). Significantly greater decreases in flexion differences and overall range of motion difference with BFR group vs control (p<0.01). No significant changes over time or differences between groups for extension range of motion (p>0.05).

Function

One study included self-reported measures of function and 3 studies included performance measures of function. BFR intervention demonstrated significantly greater effects on self-reported functional outcome measures versus control.[27] Hughes et al 2019 showed a greater improvement in the modified Star Excursion Balance Test (SEBT) for the BFR intervention group versus the control,[27] but, conversely, Zargi et al 2016 showed no significant differences between groups for the anterior reach component of the SEBT at similar time points.[21] Lambert et al did not find any significant differences between groups for any of their respective performance functional measures.[29]

Self-reported

Study	Outcome Measure	Time points	Statistics	Results

Hughes et al 2019 (BFR vs heavy load resistance training without BFR)	International Knee Documentation Committee score	Pre-operative, and approx 3.5 weeks, 6 weeks, and 12 weeks post-operative	Mean difference between time points, 2x4 repeated-measures ANOVA (group allocation as between-subject independent factor, time as within-subject dependent factor). Alpha significance p<0.05. Effect size (Cohen's d).	Significant decrease pre- to 3.5 weeks post-operative, no significant difference between groups (p>0.05). Significantly greater mean difference in scores at all time points for BFR group versus the control (p<0.05). Significant group × time interaction effects.
	Knee Injury and Osteoarthritis Outcome Score			Significant decrease pre- to post-operative with no significant difference between groups (p>0.05). Significantly greater mean difference in BFR group versus control group for pain, symptoms, and ADL subscales for 3.5-6 weeks and 3.5-12 weeks post-operative (p<0.01 for all). The BFR intervention group had a significantly greater mean difference for the quality of life subscale for weeks 6-12 weeks and 3.5-12 weeks (p<0.05,p<0.01, respectively). Significant group × time interaction effects for all subscales.
	Lower Extremity Functional Scale score			Significant decrease pre- to post-operative. Significantly greater mean difference in BFR group versus control group at 3.5-6 weeks post-op and 3.5-12 weeks post-op (p<0.05, p<0.01, respectively). Significant group × time interaction effects.
	Lysholm Knee Scoring Scale			Significant decrease pre- to post-operative. Significantly greater mean difference in BFR group versus control at 3.5-6 weeks and 3.5-12 weeks post-op(p<0.01). Significant group × time interaction effects.

Performance

Study	**Outcome Measure**	**Time points**	**Statistics**	**Results**
Hughes et al 2019 (BFR vs heavy load resistance training without BFR)	Modified Star Excursion Balance Test	Pre-operative, and approx 3.5 weeks, 6 weeks, and 12 weeks post-operative	Mean difference between time points, 2x4 repeated-measures ANOVA (group allocation as between-subject independent factor, time as within-subject dependent factor). Alpha significance p<0.05. Effect size (Cohen's d).	All 3 components (anterior direction, posteromedial direction, & posterolateral direction) decreased significantly from pre- to post-operative for both groups (p<0.01). Significant improvement all 3 components at 12 weeks post-operative (p<0.01). Operative leg of BFR group demonstrated significantly greater increases in all 3 components at 12 weeks post-operative versus control group (p<0.01).

Zargi et al 2016 (BFR vs sham BFR)	Anterior reach component of the Star Excursion Balance, operative leg only	2 weeks pre-operative and 12 weeks post-operative	Factorial 2×2×3 (Leg×Group×Time) ANOVA with repeated measures on time factor. Alpha significance $p<0.05$ for mean comparison, 0.80 for power.	No significant differences at any time points nor between groups. No significant time-group interaction.
Lambert et al (BFR vs usual care)	Single leg squat distance Y-balance test Leg curl Leg press	Approx 9.5 weeks and approx 13.5 weeks post-operative	2×2 (Group×Time) ANOVA. Significant interactions underwent Tukey's post hoc test. Alpha significance $\alpha=0.05$.	No significant differences between groups for all performance measures from approx 9.5 weeks to approx 13.5 weeks post-operative

Discussion

After ACL reconstruction, persistent impairments and functional limitations can last for several years after the initial surgery. This study sought to review what effect, if any, of BFR intervention on patients' strength, ROM, pain, and function before or after ACL reconstruction surgery.

Strength

Strength measures for BFR intervention before ACL reconstruction surgery, and during early and middle recovery, and many years after ACL reconstruction surgery did not yield consistently significant results for strength measures across the included studies. BFR intervention before surgery and during early recovery after surgery showed insignificant differences between the experimental groups and their respective controls.[22,25] During middle recovery, BFR intervention showed some potential for greater preservation of strength versus studies' respective controls.[23,27] However, the heterogeneity in control, parameters of BFR intervention, and adjuvant post-operative rehabilitation protocols make it difficult to draw certain conclusions between studies. Far after ACL reconstruction surgery, Kilgas et al demonstrated a potential for BFR in alleviation of long-lasting limb strength asymmetries. However, the inclusion of an uninjured control group without ACL reconstruction surgery does not offer insight as to whether BFR was superior to usual care.[24] Additionally, Kilgas et al was a non-randomized study with a high risk of selection and detection biases, and thus at a higher risk of bias.[24] Ultimately, there are insufficient results to definitively dictate that BFR intervention is effective for improving strength measures around ACL reconstruction surgery or to declare its superiority over typical rehabilitation.

Pain

BFR intervention may result in greater levels of muscular pain. Hughes et al 2019 and Hughes et al 2018 both demonstrated BFR intervention groups with higher levels of muscular pain during and after intervention sessions compared to their respective control groups.[26,28] Opposed to this is the KOOS pain subscale also included in Hughes et al 2019, which showed a significantly greater mean difference in BFR intervention group versus the control group; however, the lack of reporting of raw data makes it unclear whether this is due to a significantly lower pain score, or because the BFR intervention group had a higher baseline pain score compared to the control.[27]

Range of motion

Range of motion was addressed in two studies, Ohta et al and Hughes et al 2019. Ohta et al[23] found no significant differences over time nor between groups, while Hughes et al 2019[27] did find a significantly greater improvement in flexion difference and total ROM difference in operative versus non-operative legs. Similar to strength measures, there were no consistently significant results to draw definitive conclusions.[23,27]

Function

Hughes et al 2019 was the only study to include self-report functional outcome measures, and showed significantly greater mean differences in the respective incorporated measures for the BFR intervention group versus the control.[27] In contrast, the performance measures by Hughes et al 2019,[27] Zargi et al,[21] and Lambert et al[29] did not demonstrate consistently significant results. This indicates BFR intervention affect the patient's perceptions of function more than objective outcomes.

BFR Parameters

BFR parameters varied significantly between the studies. Some used a set pressure, specified in mmHg, across all patients. Secondary to differences in body composition, this does not ensure that the actual arterial occlusion was the same for all patients. Actual occlusion may vary based on an individual's subcutaneous fat, muscularity, etc. Different magnitudes of compression have been shown to produce different physiological responses.[1,2] Some studies used a percentage limb occlusive pressure, which creates a more uniform occlusion between patients.[31] Some studies used devices particularly tailored to BFR intervention in the rehabilitation setting, while others used traditional blood pressure cuffs, or sphygmomanometers. Equipment variations may also affect physiological response to BFR.[15] This significant variation in BFR parameters between studies also calls into question the extent to which measures can be compared between them, as the BFR intervention itself is not equivalent amongst the studies.[1,2,16,31]

Risk of bias

The included studies themselves, on average, had a moderate risk of bias. Risk of bias could be lower with a greater dedication to truly random randomization processes. Also, while blinding of therapists and patients is notoriously difficult in therapeutic intervention studies, it is a reasonable expectation to blind outcome assessors. Increased efforts to decrease risk of bias in the included studies would have provided greater confidence in the conclusions drawn from them.

Limitations

There were several limitations for this systematic review. There was, on average, a moderate risk of bias amongst the studies. The included studies demonstrated high variability of multiple important factors, making comparison between them difficult. For example, the inconsistency of the comparison group amongst studies makes it challenging to synthesize results. Studies' comparison groups ranged from uninjured controls, heavy loading, low loading, or usual care. BFR is thought to mimic the physiological processes of heavy loading; thus, it can be seen that it should inherently lead to different results versus a low loading comparison group.[1,2,7,14-17] Amongst usual care, post-operative rehabilitation protocols varied considerably which is consistent with how rehabilitation often occurs in the clinical setting.[9,19] However, a standardized post-operative protocol should be considered for the purposes of research in order to increase efficacy of comparisons between studies. These variations between key components of the included studies limit the extent to which results can be confidently compared and contrasted.

Future Directions

BFR intervention is currently a popular topic in musculoskeletal rehabilitation. Shortly after the search for this review was conducted, a randomized controlled trial by Curran et al 2020 involving BFR intervention after ACL reconstruction surgery was published in the *American Journal of Sports Medicine.* Similar to the findings of this review, Curran et al 2020 also found no significant effects of BFR intervention versus usual care.[32] Additionally, a randomized controlled trial protocol has been published by Erickson et al in *Physical Therapy*, which will look at the effects of BFR intervention both before and after ACL reconstruction surgery.[33] Greater numbers of high quality RCTs are needed. Future studies in this focus should be vigilant to include appropriate comparison groups, optimize BFR intervention parameters, include blinded outcomes assessors, and standardize post-operative rehabilitation.

Conclusions

At this time, it cannot be said that BFR intervention yields superior results to usual care on strength, pain, ROM, and functional outcomes following ACL

reconstruction. This finding is consistent for BFR intervention before surgery, and during early, middle, and late recovery after ACL reconstruction surgery. A greater number of higher-quality studies is needed to draw definitive conclusions on the application of BFR intervention before or after ACL reconstruction.

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APPENDIXES

Appendix A. Search Terms

CINAHL search

Search	Terms	Results
S12	S10 AND S11	18
S11	S4 OR S5 OR S6 OR S7 OR S8 OR S9	2154
S10	S1 OR S2 OR S3	12620
S9	occlusive training	3
S8	ischemic training	44
S7	occlusion training	47
S6	kaatsu	12
S5	vascular occlusion	1773
S4	blood flow restriction	316
S3	“anterior cruciate ligament”	11420
S2	(anterior cruciate ligament)	11478
S1	ACL	7324

Embase

Search	Terms	Results
#12	#10 AND #11	28
#11	#4 OR #5 OR #6 OR #7 OR #8 OR #9	6087
#10	#1 OR #2 OR #3	33967
#9	occlusive training	1
#8	ischemic training	29
#7	occlusion training	62
#6	kaatsu	145
#5	vascular occlusion	5484
#4	blood flow restriction	608
#4	“anterior cruciate ligament”	26922
#2	(anterior cruciate ligament)	27802
#1	ACL	21484

PEDro

Search	Terms	Results
12	anterior cruciate ligament blood flow	5
11	anterior cruciate ligament vascular occlusion	0
10	anterior cruciate ligament kaatsu	0
9	anterior cruciate ligament occlusion training	1
8	anterior cruciate ligament ischemic training	1
7	anterior cruciate ligament occlusive training	1
6	acl blood flow	2
5	acl vascular occlusion	0
4	acl kaatsu	0

3	acl occlusion training	1
2	acl ischemic training	1
1	acl occlusive training	1

ProQuest Health Administration

Search	Terms	Results
S12	(acl OR (anterior cruciate ligament) OR “anterior cruciate ligament”) AND ((blood flow restriction) OR (vascular occlusion) OR kaatsu OR (occlusion training) OR (ischemic training) OR (occlusive training))	195
S11	(blood flow restriction) OR (vascular occlusion) OR kaatsu OR (occlusion training) OR (ischemic training) OR (occlusive training)	29497
S10	acl OR (anterior cruciate ligament) OR “anterior cruciate ligament”	10436
S9	occlusive training	725
S8	ischemic training	7010
S7	occlusion training	2358
S6	kaatsu	26
S5	vascular occlusion	14143
S4	blood flow restriction	8806
S3	“anterior cruciate ligament”	6774
S2	(anterior cruciate ligament)	7247
S1	ACL	8158

PubMed

Search	Terms	Results
#17	(((((ACL) OR (anterior cruciate ligament)) OR “anterior cruciate ligament”)) AND ((((((((((blood flow restriction) OR vascular occlusion)) OR kaatsu)) OR occlusion training)) OR ischemic training)) OR occlusive training)	44
#16	(((((((((blood flow restriction) OR vascular occlusion)) OR kaatsu)) OR occlusion training)) OR ischemic training)) OR occlusive training	92321
#15	(((((((blood flow restriction) OR vascular occlusion)) OR kaatsu)) OR occlusion training)) OR ischemic training	91706
#14	(((((blood flow restriction) OR vascular occlusion)) OR kaatsu)) OR occlusion training	76705
#13	(((blood flow restriction) OR vascular occlusion)) OR kaatsu	73899
#12	(blood blow restriction) OR vascular occlusion	73878
#11	(((ACL) OR (anterior cruciate ligament))) OR “anterior cruciate ligament”	26042
#10	(ACL) OR (anterior cruciate ligament)	26042
#9	occlusive training	918
#8	ischemic training	16135

#7	occlusion training	4138
#6	kaatsu	112
#5	vascular occlusion	70569
#4	blood flow restriction	3457
#3	“anterior cruciate ligament”	20976
#2	(anterior cruciate ligament)	21607
#1	ACL	26042

Scopus

Search	Terms	Results
12	((TITLE-ABS-KEY (acl)) OR (TITLE-ABS-KEY ((anterior AND cruciate AND ligament))) OR (TITLE-ABS-KEY (“anterior cruciate ligament”))) AND ((TITLE-ABS-KEY (blood AND flow AND restriction)) OR (TITLE-ABS-KEY (vascular AND occlusion)) OR (TITLE-ABS-KEY (kaatsu)) OR (TITLE-ABS-KEY (occlusion AND training)) OR (TITLE-ABS-KEY (ischemic AND training)) OR (TITLE-ABS-KEY (occlusive AND training)))	59
11	(TITLE-ABS-KEY (blood AND flow AND restriction)) OR (TITLE-ABS-KEY (vascular AND occlusion)) OR (TITLE-ABS-KEY (kaatsu)) OR (TITLE-ABS-KEY (occlusion AND training)) OR (TITLE-ABS-KEY (ischemic AND training)) OR (TITLE-ABS-KEY (occlusive AND training))	83108
10	(TITLE-ABS-KEY (acl)) OR (TITLE-ABS-KEY ((anterior AND cruciate AND ligament))) OR (TITLE-ABS-KEY (“anterior cruciate ligament”))	36409
9	TITLE-ABS-KEY (occlusive AND training)	859
8	TITLE-ABS-KEY (ischemic AND training)	3897
7	TITLE-ABS-KEY (occlusion AND training)	4091
6	TITLE-ABS-KEY (kaatsu)	167
5	TITLE-ABS-KEY (vascular AND occlusion)	69665
4	TITLE-ABS-KEY (blood AND flow AND restriction)	6151
3	TITLE-ABS-KEY (“anterior cruciate ligament”)	27668
2	TITLE-ABS-KEY ((anterior AND cruciate AND ligament))	28523
1	TITLE-ABS-KEY (acl)	23142

SportDiscus

Search	Terms	Results
S12	S10 AND S11	15
S11	S4 OR S5 OR S6 OR S7 OR S8 OR S9	580
S10	S1 OR S2 OR S3	10935
S9	occlusive training	3
S8	ischemic training	11
S7	occlusion training	59
S6	kaatsu	147
S5	vascular occlusion	173

S4	blood flow restriction	430
S3	“anterior cruciate ligament”	10135
S2	(anterior cruciate ligament)	10157
S1	ACL	7021

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Search	Terms	Results
#12	#11 AND #10	56
#11	#9 OR #8 OR #7 OR #6 OR #5 OR #4	45369
#10	#3 OR #2 OR #1	35980
#9	ALL FIELDS: (occlusive training)	455
#8	ALL FIELDS: (ischemic training)	5131
#7	ALL FIELDS: (occlusion training)	5199
#6	ALL FIELDS: (kaatsu)	204
#5	ALL FIELDS: (vascular occlusion)	32643
#4	ALL FIELDS: (blood flow restriction)	4014
#3	ALL FIELDS: (“anterior cruciate ligament”)	20741
#2	ALL FIELDS: ((anterior cruciate ligament))	22258
#1	ALL FIELDS: (ACL)	25526