Blood Flow–Restricted Training for Lower Extremity Muscle Weakness due to Knee Pathology: A Systematic Review

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Context: Blood flow–restricted training (BFRT) has been suggested to treat lower extremity muscle weakness. The efficacy of BFRT for muscle problems related to knee pathology is unclear.

Objective: To determine whether BFRT (1) improves muscle strength and cross-sectional area (CSA) for chronic knee-related lower extremity atrophy and (2) prevents muscle atrophy after knee surgery.

Data Sources: A systematic review of the literature from 1974 to 2017 was conducted using the PubMed and Cochrane databases.

Study Selection: Controlled trials that used BFRT to treat chronic knee-related lower extremity muscle atrophy or to prevent muscle atrophy after knee surgery that measured the effects on quadriceps or hamstrings muscle strength or CSA were included.

Study Design: Systematic review.

Level of Evidence: Level 2.

Data Extraction: Data were extracted as available from 9 studies (8 level 1, 1 level 2). Assessment of study quality was rated using the Physiotherapy Evidence Database or Methodological Index for Non-Randomized Studies instruments.

Results: BFRT was used after anterior cruciate ligament reconstruction and routine knee arthroscopy and in patients with knee osteoarthritis or patellofemoral pain. There were a total of 165 patients and 170 controls. Vascular occlusion and exercise protocols varied; all studies except 1 incorporated exercises during occlusion, most of which focused on the quadriceps. Six of 7 studies that measured quadriceps strength reported statistically significant improvements after training. Few benefits in quadriceps CSA were reported. Hamstrings strength was only measured in 2 studies. There were no complications related to training.

Conclusion: Published limited data show BFRT to be safe and potentially effective in improving quadriceps muscle strength in patients with weakness and atrophy related to knee pathology. The use of short-duration vascular occlusion and light-load resistance exercises appears safe after knee surgery or in arthritic knees. This treatment option requires further investigation to refine protocols related to cuff pressure and exercise dosage and duration.

Keywords: blood flow resistance training; quadriceps strengthening; resistance training

Weakness and atrophy of the quadriceps and hamstrings is a common problem in patients who have noteworthy chronic osteoarthritis and after major operations such as anterior cruciate ligament (ACL) reconstruction.[6,19,44] Patients with patellofemoral or tibiofemoral arthritis may have difficulty achieving strength gains even with formal rehabilitation due to pain incurred with heavy-load resistance exercises.[8,32,45] The American College of Sports Medicine recommends a minimum resistance training load of 60% to 70% of 1 repetition maximum (1 RM) to gain strength

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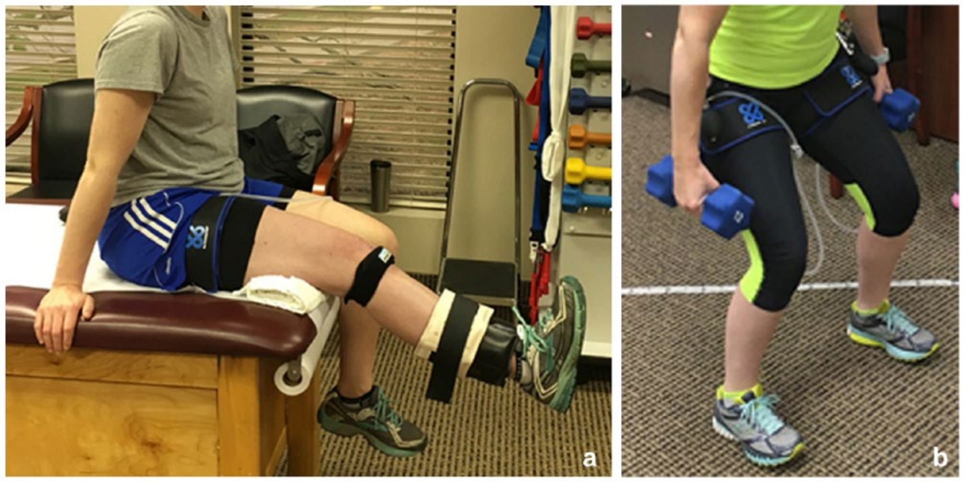

Figure 1. Examples of blood flow restriction exercise training that may be done nonweightbearing, such as (a) during knee extension, or weightbearing, such as (b) during partial squatting.

and 70% to 85% of 1 RM to achieve muscle hypertrophy.[1] Training with these high loads may not be possible or may even be deleterious in painful arthritic knees. Many studies have reported lingering quadriceps weakness many months or even years after ACL reconstruction that impairs return to normal function.[16,30] This occurs despite the immediate implementation of physical therapy and preventative measures such as electrical muscle stimulation, early weightbearing, and use of both closed and open kinetic chain exercises. With the focus of surgery and rehabilitation targeting return to preinjury sports activity levels in many investigations, the prevention of muscle atrophy and early recovery of muscle strength and neuromuscular function are considered paramount for athletic patients.[2,3,28]

Recently, studies have begun to explore the use of blood flow–restricted training (BFRT) with low-resistance loads (such as 30% of 1 RM) in individuals who cannot tolerate high-load resistance training (Figure 1). Many investigations have shown a positive benefit of BFRT in healthy participants and athletes[21,23,36,41] and in elderly individuals.[7,31,33,39,46,48] Various hypotheses for the potential effectiveness of BFRT in increasing muscle strength and hypertrophy have been proposed. Hughes et al[13] hypothesized that an ischemic and hypoxic muscular environment is generated during BFRT that causes high levels of metabolic stress and mechanical tension when exercise is combined with training. Metabolic stress and mechanical tension have been theorized to activate various mechanisms that induce muscle growth, such as elevated systematic hormone production, cell swelling, production of reactive oxygen species, intramuscular anabolic/anticatabolic signaling, and increased fast-twitch fiber recruitment.

Hughes et al[13] systematically reviewed 20 studies in which BFRT was used for clinical musculoskeletal rehabilitation. These authors concluded that low-load BFRT had a moderate effect on increasing strength but was less effective than heavy-load training. This review contained a wide variety of studies involving ACL reconstruction, knee osteoarthritis, older adults at risk for sarcopenia, and patients with sporadic inclusion body myositis. All types of upper and lower body BFRT were included, such as elastic band resistance training, low- to moderate-intensity walk training, body weight exercises, and low-load resistance training. Because of the heterogenic nature of this review, the effect of low-load resistance BFRT on muscle weakness and atrophy specifically related to knee pathology remains uncertain.

The purposes of this systematic review were to determine whether BFRT is effective in (1) improving quadriceps and hamstrings strength and cross-sectional area (CSA) for chronic knee-related lower extremity muscle atrophy and (2) preventing muscle atrophy after knee surgery.

METHODS

Literature Search Strategy

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed in conducting this study.[20] An online search was performed using PubMed for all years through 2017 and the key phrases and words *blood flow restriction training, blood flow restricted exercise, occlusion resistance training, KAATSU training*, and *low load resistance training*. The full text was accessed if the abstract suggested that this might be a clinical study in the topic of interest. In addition, reference lists from general review articles, systematic reviews, and meta-analyses obtained from the search were examined to find any other original research investigations not otherwise obtained.

Study Selection and Quality Assessment

To be included in the review, studies were required to be a controlled trial (randomized or nonrandomized), be published in English, use BFRT either to treat chronic lower extremity muscle atrophy or to prevent muscle atrophy after a knee operation, and report a measured effect of BFRT on quadriceps and/or hamstrings muscle strength or CSA.

Exclusion criteria included studies that (1) were off-topic; (2) investigated the acute effects of BFRT (ie, after 1 training session); (3) included trained healthy participants; (4) concerned trained patients with cardiovascular disease, obesity, or polymyositis; (5) included trained elderly patients; (6) included trained patients after voluntary immobilization; (7) included trained upper body muscles; and (8) did not provide measurement of quadriceps or hamstrings strength or CSA. General or systematic reviews, meta-analyses, editorials, case series, case reports, and laboratory animal studies were also excluded.

Study quality was evaluated using the Physiotherapy Evidence Database (PEDro) scale[27] for randomized investigations or the Methological Index for Non-Randomized Studies (MINORS) criteria for nonrandomized controlled trials.[40] The MINORS score is reported as a percentage of the total available points, as recommended by Wylie et al.[47]

Data Extraction

The following data were extracted from each article when available: study design, sex, age, diagnosis, number of training sessions, cuff pressure, occlusion protocol, exercise protocol, quadriceps and hamstrings strength measurements (isokinetic, isometric, or maximum leg press), CSA measurements for quadriceps and hamstrings using magnetic resonance imaging (MRI) or ultrasound, results of muscle biopsy, data from clinical outcome instruments, and information related to pain or discomfort during training. Effect sizes (ESs) were calculated when the data were available according to Cohen[5] and were interpreted as small effects (≤0.2), moderate effects (0.5), and large effects (≥0.8).

RESULTS

The search identified 534 articles, of which 525 were excluded (Table 1), leaving 9 studies for our review. The average PEDro score in the 8 level 1 randomized studies[4,8,11,17,29,37,38,42,43] was 8 (range, 6-10), and the MINORS score in the 1 nonrandomized level 2 study[42] was 79%.

The effect of BFRT in preventing muscle atrophy after knee operations was assessed in 3 studies after ACL reconstruction[17,29,42] and in 1 study after routine knee arthroscopy[43] (Table 2). BFRT was used to treat chronic muscle weakness due to knee osteoarthritis in 4 studies[4,8,37,38] and patellofemoral pain in 1 study.[11] BFRT was used in 165 patients (93 women, 72 men) whose mean age was 42.2 years. There were 170 control participants (100 women, 70 men) whose mean age was 40.6 years.

Four studies[4,8,37,38] used power analyses to determine sample sizes, and 2 investigations[8,11] calculated ESs in addition to *P* values. Data provided in the investigations allowed the calculation of ES in 2 additional studies.[4,29]

Table 1. Reasons for 525 articles excluded

Exclusion Criteria	Articles, n
Off-topic	205
Acute effects training	92
Training in healthy participants or athletes	55
Physiology-based study	38
General review	28
Upper body training	22
Training in elderly patients	22
Case report or series	12
Study effect of cuff pressure	11
Editorial	11
Systematic review/meta-analysis	8
Laboratory (animal) study	7
Effects training after immobilization	5
Study protocol only (no results)	4
Study diseases (cardiovascular, obesity, polymyositis)	4
Survey	1

Occlusion Protocols

The vascular occlusion protocols varied in all studies except 2 from the same investigators in which the cuff pressure was gradually increased (from 160-200 mm Hg) during individual training sessions.[37,38] Three studies[8,11,43] set cuff pressures to a percentage of the total arterial occlusion pressure (60%-70%), 2 studies[4,29] set the pressure to 1 value for all patients throughout the duration of the investigation (180-200 mm Hg), and 2 studies[17,42] gradually increased the pressure throughout the duration of the investigation. Typically, occlusion was maintained during exercise sets and deflated during rest between sets. Placebo cuffs were used in the control group in 2 studies.[11,42]

Exercise Protocols

All studies except 1[42] incorporated exercises that were done with vascular occlusion. In 6 investigations,[4,8,11,37,38,43] a percentage of 1 RM was selected for lower extremity exercises, and in 2 studies,[17,29] low-load training was done, but not

Table 2. Study protocols

	Study Group			Protocol		
Study (Level of Evidence), Diagnosis	BFRT	Control	Treatment Sessions (Total Possible)	Cuff Material, Size, Pressure	Occlusion	Exercise During Occlusion
Ohta et al[29] (1), ACL reconstruction	19 males 9 females Mean age, 30.0 ± 9.7 y	12 males 10 females Mean age, 28.0 ± 9.7 y	2×/day weeks 2-16 p.o. (210), at home	Air tourniquet, 180 mm Hg	Inflate duration of training, maximum 15 min. Remove 15-20 min, resume if required	Straight-leg raises, hip abduction and adduction isometrics, quadriceps isometrics, half-squats, step-ups, walk in deep flexion, elastic tube squat resistance. 20 reps 2×/day
Takarada et al[42] (2), ACL reconstruction	4 males 4 females Mean age, 22 ± 0.9 y	4 males 4 females Mean age, 23 ± 1.0 y	2×/day days 1-15 p.o. (30), in hospital	Pneumatic cuff width 9 cm, length 70 cm. 180 mm Hg, gradually elevated 10 mm Hg depending on patient tolerance (range, 200-260 mm Hg). Placebo cuff control group	Inflate 5 min, deflate 3 min, repeat 5×	None
Iversen et al[17] (1), ACL reconstruction	7 males 5 females Mean age, 24.9 ± 7.4 y	7 males 5 females Mean age, 29.8 ± 9.3 y	2×/day days 2-16 p.o. (30), at home	Delphi low-pressure cuff, 14-cm wide. 130 mm Hg, increased 10 mm Hg, maximum 180 mm Hg	Inflate 5 min during exercise, deflate 3 min, repeat 5×	Quadriceps isometrics, leg extensions over knee roll, straight-leg raises. 20 reps each × 5 per session
Tennent et al[43] (1), routine knee arthroscopy	7 males 3 females Mean age, 37.0 y	5 males 2 females Mean age, 27.0 y	12 sessions weeks 3-9 p.o. (12), in clinic	Easy-Fit Tourniquet cuff, size varied based on thigh size. Set to 70% of total arterial occlusal pressure	Inflate during exercise, maximum 5 min	30% 1 RM BFRT: leg press, knee extension, reverse press, 1 set 30 reps, 3 sets 15 reps Exercises for controls not detailed
Segal et al[37] (1), knee osteoarthritis	19 males Mean age, 58.4 ± 8.7 y	22 males Mean age, 56.1 ± 7.7 y	3×/wk × 4 wk (12), in clinic	Kaatsu Master BFR device, width 6.5 cm, length 65 cm. 160-200 mm Hg, gradually increased during training sessions	Inflate 5 min during exercise, deflate 1.5 min rest between sets	30% 1 RM both groups: leg press, 1 set 30 reps, 3 sets 15 reps

(continued)

Table 2. (continued)

	Study Group			Protocol		
Study (Level of Evidence), Diagnosis	BFRT	Control	Treatment Sessions (Total Possible)	Cuff Material, Size, Pressure	Occlusion	Exercise During Occlusion
Segal et al[38] (1), knee osteoarthritis	19 females Mean age, 56.1 ± 5.9 y	21 females Mean age, 54.6 ± 6.9 y	3×/wk × 4 wk (12), in clinic	Kaatsu Master BFR device, width 6.5 cm, length 65 cm. 160-200 mm Hg, gradually increased during training sessions	Inflate 5 min during exercise, deflate 1.5 min, rest between sets	30% 1 RM both groups: leg press, knee extension, reverse press, 1 set 30 reps, 3 sets 15 reps
Bryk et al[4] (1), knee osteoarthritis	17 females Mean age, 62.3 ± 7.0 y	17 females Mean age, 60.4 ± 6.7 y	3×/wk × 6 wk (18), in clinic	Cuff details NA. 200 mm Hg	Inflate during quadriceps exercises (time NA)	30% 1 RM BFRT, 70% 1 RM controls: knee extension machine. BFRT 3 sets 30 reps, controls 3 sets 10 reps
Ferraz et al[8] (1), knee osteoarthritis	12 females Mean age, 60.3 ± 3.0 y	HR group: 10 females Mean age, 59.9 ± 4.0 y LR group: 12 females Mean age, 60.7 ± 4.0 y	2×/wk × 12 wk (24), in clinic	Cuff details NA. Set to 70% of total arterial occlusion pressure. Mean, 97.4 mm Hg	Inflate during exercises and rest periods	30% 1 RM BFRT and LR controls, 80% 1 RM HR controls. 4-5 sets × 10 reps
Giles et al[11] (1), patellofemoral pain	16 males 24 females Mean age, 28.5 ± 5.2 y	20 males 19 females Mean age, 26.7 ± 5.5 y	3×/wk × 8 wk (24), in clinic	Cuff details NA. Set to 60% of total arterial occlusion pressure. Placebo cuff control group	Inflate during exercise (time NA), deflate 30 s, rest between sets	30% 1 RM BFRT, 70% 1 RM controls: leg press, knee extension. BFRT 1 set 30 reps, 3 sets 15 reps. Controls 3 sets 7-10 reps

ACL, anterior cruciate ligament; BFRT, blood flow–restricted training; HR, high resistance; LR, low resistance; NA, not available; p.o., postoperative; reps, repetitions; RM, repetition maximum.

according to a percentage of 1 RM (Table 2). While some investigations focused solely on quadriceps strengthening, others included hamstrings exercises. Although not evaluated as part of the BFRT protocol, hip (abduction-adduction side-lying leg raises and Theraband resistance) and gastrocnemius-soleus exercises were also included in 2 studies.[4,29]

Muscle Strength

Quadriceps muscle strength was measured isokinetically in 4 studies (Table 3).[29,37,38,43] The BFRT group had significantly greater improvements (measured at 60 deg/s) compared with controls in 3 investigations, with the largest magnitude of improvement noted in the study by Tennent et al.[43] Two other studies[4,11] measured quadriceps strength isometrically, and although neither of these studies reported a significant between-group difference, both the BFRT and control group had significant within-group improvements.

Segal et al[37,38] determined changes in 1 RM by comparing the pretraining leg press value with that obtained on completion of the investigation. While there was no between-group difference in this value in men with knee osteoarthritis, women with osteoarthritis in the BFRT group had a greater increase compared with controls (mean improvement, 28.3 kg and 15.6 kg, respectively; $P < 0.05$). Ferraz et al[8] determined changes in 1 RM in leg press and knee extension values between the BFRT group and 2 control groups. Patients in the high-resistance control group had similar significant improvements in these values to those in the BRFT group. However, patients in the low-resistance control group failed to significantly improve these strength indices.

Hamstrings strength was measured in only 2 studies.[29,43] Ohta et al[29] reported that ratios of the involved limb/uninvolved limb showed significant differences between the BFRT and control groups 16 weeks after ACL reconstruction at 60 deg/s (81% ± 14% and 72% ± 15%, respectively; $P = 0.05$; ES, 0.62) and at 180 deg/s (84% ± 18% and 74% ± 12%, respectively; $P = 0.04$; ES, 0.65). Tennent et al[43] reported significant improvements in isokinetic hamstrings strength in both the BFRT (99.83-141.68 N·m/kg; $P = 0.002$) and control groups (105.51-132.71 N·m/kg; $P < 0.05$); however, there was no between-group significant difference. Of note, the BFRT group had a larger deficit in hamstring strength at the onset of the study (approximately 3 weeks postoperatively) compared with the control group (31.09 and 7.77 N·m/kg, respectively).

Muscle CSA

The 3 studies on ACL reconstruction all measured CSA using MRI on completion of BFRT, which varied from 16 days to 16 weeks postoperatively.[17,29,42] Ohta et al[29] reported a significant between-group effect for the quadriceps involved/uninvolved ratio but not for the hamstrings ratio. The BFRT group in the study by Takarada et al[42] had a significantly smaller percentage decrease in quadriceps CSA compared with the control group (9.4% and 20.7%, respectively; $P < 0.05$; ES, –5.87) 15 days postoperatively; however, there was no between-group difference in the percentage decrease in hamstrings CSA. Iversen et al[17] reported no between-group difference in the percentage decrease in quadriceps CSA measured 16 days postoperatively.

Segal et al[38] detected negligible increases of quadriceps volume after 4 weeks of training women with knee osteoarthritis in both the BFRT and the control groups (1.3% and 0.01%, respectively). Giles et al[11] used ultrasound to measure quadriceps muscle thickness in patients with patellofemoral pain and reported minimal change in size in either group after 8 weeks of training. Ferraz et al[8] reported significant increases in CSA measured with computed tomography in both the BRFT group (7% increase; $P < 0.0001$; ES, 0.39) and the high-resistance control group (8% increase; $P < 0.0001$; ES, 0.54), but no change in the low-resistance control group.

Outcome Scales

Outcome instruments were used in 6 studies (Table 4).[4,8,11,37,38,43] Overall, significant improvements were reported in symptoms and function in both the BFRT and the control groups at the conclusion of these investigations, but few between-group differences were found. For instance, Bryk et al[4] reported significant improvements in the Lequesne scale after 6 weeks of training in both BFRT and control groups; however, the BFRT group had less anterior knee pain during training sessions. Giles et al[11] reported no differences between BFRT and control patients in the Kujala patellofemoral score after training, but the BFRT group reported a greater reduction in pain with daily activities (ES, 0.53).

Recommendations for BFRT

Overall, 6 of the 8 studies concluded BFRT was effective and should be considered after ACL reconstruction,[29,42] after routine knee arthroscopy,[43] in arthritic knees,[4,38] and in cases of patellofemoral pain (Table 5).[11] Segal et al[37] found no benefit in 19 men with knee arthritis, and Iversen et al[17] reported unsatisfactory results in 12 patients after ACL reconstruction.

Adverse Events

Adverse events related to BFRT were rarely encountered. Dropouts occurred due to discomfort with training in the series of Ohta et al[29] (2 of 24 [8%] enrolled) and Segal et al[37] (1 of 20 [5%] enrolled). No other adverse events were reported.

DISCUSSION

The limited published data show BFRT to be safe and potentially effective in improving quadriceps strength in patients with knee-related weakness and atrophy. There were no complications related to BFRT. Improvements in study design and refinements in protocols related to cuff pressure and exercise dosage and duration are required to further advance our knowledge of this treatment option.

The low-resistance load of 30% 1 RM used in 6 studies was effective in improving quadriceps strength without eliciting a pain response that may be incurred with high-load resistance levels.

Table 3. Changes in quadriceps strength and muscle cross-sectional area after training[a]

	Quadriceps Strength			Muscle CSA, Biopsy		
Study	**Data**	**Within-Group**	**Between-Groups**	**Data**	**Within-Group**	**Between-Groups**
Ohta et al[29] ACL reconstruction 16 wk postop	Involved-uninvolved ratios			MRI CSA I/N ratios (preop: 16 wk postop)		
	60 deg/s: BFRT, 76% ± 16%; control, 55% ± 17%	NA	$P < 0.001$, ES = 1.4	Quadriceps: BFRT, 101% ± 11%; control, 92% ± 12%	NA	$P = 0.04$, ES = 0.78
	180 deg/s: BFRT, 77% ± 13%; control, 65% ± 13%	NA	$P = 0.004$, ES = 0.92	Hamstrings: BFRT, 105% ± 19%; control, 102% ± 23%	NA	$P =$ NS
	Isometric: BFRT, 84% ± 19%; control, 63% ± 19%	NA	$P < 0.001$, ES = 1.10	Diameters type 1, 2 fibers medial vastus lateralis	NA	$P =$ NS
Takarada et al[42] ACL reconstruction	Not measured			MRI CSA % decrease from 3rd to 14th postop day		
				Quadriceps: BFRT, 9.4% ± 1.6%; control, 20.7% ± 2.2%	$P < 0.05$	$P < 0.05$, ES = −5.87
				Hamstrings: BFRT, 9.2% ± 2.6%; control, 11.3% ± 2.6%	$P < 0.05$	$P =$ NS
Iversen et al[17] ACL reconstruction	Not measured			MRI CSA % decrease from 2nd to 16th postop day		
				Quadriceps: BFRT, 13.8% ± 1.1%; control, 13.1% ± 1.0%	NA	$P =$ NS
Tennent et al[43] Knee arthroscopy 9 wk postop	60 deg/s N·m/kg (% improvement[b])		$P = 0.03$	Not done		
	BFRT pre: 99.83; post: 211.92 (75%)	$P = 0.002$				
	Control pre: 126.7; post: 171.5 (33.5%)	$P = 0.2$				

(continued)

Table 3. (continued)

	Quadriceps Strength			Muscle CSA, Biopsy		
Study	**Data**	**Within-Group**	**Between-Groups**	**Data**	**Within-Group**	**Between-Groups**
Segal et al[37] Knee osteoarthritis males 4 wk posttraining	60 deg/s N·m mean increase (% improvement)		$P = \text{NS}$	Not done		
	BFRT: –0.1 ± 3.3 N·m (0.4%)	$P = \text{NS}$				
	Control: 7.0 ± 3.0 N·m (6.7%)	$P < 0.05$				
	Leg press 1 RM kg mean increase (% improvement)		$P = \text{NS}$			
	BFRT: 11.3 ± 14.0 (3.1%)	$P = 0.003$				
	Control: 13.5 ± 16.8 (4.7%)	$P < 0.002$				
Segal et al[38] Knee osteoarthritis females 4 wk posttraining	60 deg/s N·m/kg mean increase		$P < 0.01$	MRI volume % increase		$P = \text{NS}$
	BFRT: 0.07 ± 0.03	$P = 0.02$		Quadriceps: BFRT, 1.3% ± 0.80%; control, 0.01% ± 0.73%		
	Control: –0.05 ± 0.03	$P = 0.05$				
	Leg press 1 RM kg mean increase		$P < 0.05$			
	BFRT: 28.3 ± 4.8	$P < 0.001$				
	Control: 15.6 ± 4.5	$P = 0.005$				
Bryk et al[4] Knee osteoarthritis 6 wk posttraining	Isometric kg force/kg body weight (% improvement)		$P = \text{NS}$	Not done		
	BFRT pre: 23.2 ± 8.4; post: 40.0 ± 0.2 (17%)	$P = 0.001$, ES = 2.83				
	Control pre: 24.1 ± 10.1; post: 33.5 ± 12.9 (9%)	$P = 0.001$, ES = 0.81				

(continued)

Table 3. (continued)

	Quadriceps Strength			Muscle CSA, Biopsy		
Study	**Data**	**Within-Group**	**Between-Groups**	**Data**	**Within-Group**	**Between-Groups**
Ferraz et al[8] Knee osteoarthritis 12 wk posttraining	Leg press 1 RM % improvement			CT CSA % increase quadriceps		
	BFRT: 26%	$P < 0.0001$ ES = 1.01	$P = 0.0004$ vs LR $P =$ NS vs. HR			
	High-resistance group: 33%	$P < 0.0001$ ES = 0.82	$P < 0.0001$ vs LR	BFRT: 7%	$P < 0.0001$ ES = 0.39	$P = 0.02$ vs LR $P =$ NS vs HR
	Low-resistance group: 8%	$P =$ NS ES = 0.23				
	Knee extension 1 RM % improvement			High-resistance group: 8%	$P < 0.0001$ ES = 0.54	$P = 0.007$ vs LR
	BFRT: 23%	$P < 0.0001$ ES = 0.86	$P = 0.0005$ vs LR $P =$ NS vs HR			
	High-resistance group: 22%	$P < 0.0001$ ES = 0.83	$P = 0.0004$ vs LR	Low-resistance group: 2%	$P =$ NS ES = 0.12	
	LR control: 7%	$P =$ NS ES = 0.21				
Giles et al[11] Patellofemoral pain 8 wk posttraining	Isometric N·m (% improvement)		$P =$ NS	Ultrasound quadriceps size (cm)		$P =$ NS
	BFRT pre: 131.2 ± 61.9; post: 166.4 ± 59.4 (27%)	$P < 0.001$, ES = 0.58		BFTR pre: 7.9 ± 1.3; post: 8.0 ± 1.1	NS	
	Control pre: 135.1 ± 55; post: 158.7 ± 57.4 (17%)	$P < 0.001$, ES = 0.42		Control pre: 7.7 ± 1.4; post: 7.9 ± 1.2	NS	

ACL, anterior cruciate ligament; BFRT, blood flow–restricted training; CSA, cross-sectional area; CT, computed tomography; ES, effect size; HR, high resistance; I/N, involved/noninvolved; LR, low resistance; MRI, magnetic resonance imaging; NA, not available; NS, not significant; RM, repetition maximum.

[a] Data are shown as means ± SDs (when available). Percentage improvement data provided when available. ESs calculated according to Cohen when possible.

[b] When outliers (1 from each group) removed.

Table 4. Effect of training on outcome scales

		BFRT Group			Control Group			
Study	**Outcome Scale**	**Pre-training**	**Post-training**	***P***	**Pre-training**	**Post-training**	***P***	**Between-Group Comparison, *P***
Tennent et al[43] Knee arthroscopy	KOOS							
	Pain	52.8	75.0	0.0001	69.4	77.8	0.04	NS
	Symptoms	47.1	76.8	0.003	67.9	71.4	NS	NS
	ADL	58.1	88.2	0.0009	73.5	75.0	NS	NS
	QOL	31.3	59.3	0.003	43.8	62.5	NS	NS
	Sport	10.0	47.5	0.0009	35.0	70.0	0.04	NS
	VR-12							
	PCS	0.86	46.3	0.001	36.5	47.7	0.04	NS
	MCS	51.20	60.2	0.04	57.6	56.2	NS	0.01
Segal et al[37] Knee osteoarthritis, males	KOOS							
	Pain	~83	~86	NS	~76	~81	NS	NS
Segal et al[38] Knee osteoarthritis, females	KOOS							
	Pain	~80	~82	NS	~76	~78	NS	NS
Bryk et al[4] Knee osteoarthritis	Lequesne scale	11.5	6.5	0.001	13.0	7.0	0.001	NS
	VAS knee pain	6.5	3.2	0.001	6.0	3.5	0.001	NS
	VAS knee pain with training	—	2.5	—	—	6.2	—	0.01

(continued)

Table 4. (continued)

		BFRT Group			Control Group			
Study	**Outcome Scale**	**Pre-training**	**Post-training**	***P***	**Pre-training**	**Post-training**	***P***	**Between-Group Comparison, *P***
Ferraz et al[8] Knee osteoarthritis	WOMAC				HR	HR		
	Pain	6.9	4.0	0.02	7.2	4.0	NS	NP
	Stiffness	3.6	2.1	0.01	3.5	2.0	NS	NP
	Physical function	21.0	10.3	0.02	25.9	14.6	0.02	NP
	Total score	31.5	17.1	0.008	36.6	21.2	0.02	NP
	WOMAC				LR	LR		
	Pain				7.9	4.0	0.001	NP
	Stiffness				2.8	1.8	NS	NP
	Physical function				24.4	12.7	NS	NP
	Total score				35.1	18.4	0.005	NP
Giles et al[11] Patellofemoral pain	Kujala patellofemoral score	73.6	86.5	<0.001	72.6	83.2	<0.001	NS, ES = 0.23
	VAS worst pain	55.7	27.4	<0.001	51.4	25.6	<0.001	NS, ES = 0.27
	VAS ADL	58.2	21.6	<0.001	42.5	24.1	< 0.001	0.02, ES = 0.53

ADL, activities of daily living; BFRT, blood flow–restricted training; ES, effect size; HR, high resistance; KOOS, Knee injury and Osteoarthritis Outcome Scores; LR, low resistance; MCS, mental component score; NP, not provided; NS, not significant; PCS, physical component score; QOL, quality of life; VAS, visual analog scale; VR-12, Veterans RAND 12-Item Health Survey; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 5. Overall results[a]

			Quadriceps Strength		Quadriceps CSA		Outcome Scales: Pain		
Study	Total No. Training Sessions Possible	Major Muscle Groups Exercised	Improved in BFRT Group?	BFRT Significantly Greater Than Control?	Improved in BFRT Group?	BFRT Significantly Greater Than Control?	Improved in BFRT Group?	BFRT significantly Greater Than Control?	BFRT Recommended?
Ohta et al[29] ACL reconstruction	210	Quadriceps, hamstrings, hip	—	Yes	—	Yes	—	—	Yes
Takarada et al[42] ACL reconstruction	30	None	—	—	Yes	Yes	—	—	Yes
Iversen et al[17] ACL reconstruction	30	Quadriceps	—	—	—	No	—	—	No
Tennent et al[43] Knee arthroscopy	12	Quadriceps, hamstrings	Yes	Yes	—	—	Yes	No	Yes
Segal et al[37] Knee osteoarthritis males	12	Quadriceps	No	No	—	—	No	No	No
Segal et al[38] Knee osteoarthritis females	12	Quadriceps, hamstrings	Yes	Yes	No	No	No	No	Yes
Bryk et al[4] Knee osteoarthritis	18	Quadriceps, hamstrings, hip, gastrocnemius	Yes	No	—	—	Yes	Yes	Yes
Ferraz et al[8] Knee osteoarthritis	24	Quadriceps	Yes	Yes vs LR No vs HR	Yes	Yes vs LR No vs HR	Yes	No	Yes
Giles et al[11] Patellofemoral pain	24	Quadriceps	Yes	No	No	No	Yes	No	Yes

ACL, anterior cruciate ligament; BFRT, blood flow–restricted training; CSA, cross-sectional area; HR, high resistance; LR, low resistance.

[a] — = factor not analyzed in study.

Ferraz et al[8] reported a dropout rate of 25% in patients in the high-resistance training control group due to exercise-induced knee pain. Few effects of training were noted in quadriceps CSA, and future data are required to determine whether changes in training dose or duration may improve this finding. Hamstrings strength was measured after training in only 2 studies,[29,43] and conclusions could not be reached regarding the efficacy of BFRT on this factor. One study that included isolated hamstrings exercises (reverse press) at 30% 1 RM reported an approximate 40% increase in hamstrings strength in the treatment group and a 17% increase in the control group.[43]

The study protocols varied in cuff pressures selected for training, with pressures ranging from a mean of 97.4 mm Hg[8] to as high as 260 mm Hg (depending on patient tolerance[42]). Only 4 studies provided information regarding cuff type and size.[17,37,38,42] Three studies set the pressure to a percentage of total arterial occlusal pressure. Patterson et al[32] recommended this type of approach to determine the appropriate blood flow–restricted pressure to minimize any cardiovascular risk and underlying tissue compression damage. These authors recommended using a handheld Doppler to make individual patient measurements and selected a range of 40% to 80% of limb occlusion for training. Four studies in our review gradually increased cuff pressure during training sessions or over the course of the study as tolerated. Systematic reviews of healthy participants have noted large variations in cuff pressure, as well as exercise doses and durations.[21,25,36,41] Slysz et al[41] included 47 studies of healthy participants in their review; muscular strength changes were available for 400 participants, and muscular hypertrophy data were available for 377 participants. The authors noted that no single cuff pressure produced equal blood flow restriction between participants and noted the need for the development of a model that would produce equal occlusion for all patients. With the data available, these authors recommended a cuff pressure of >150 mm Hg, a resistance load of 30% 1 RM, and a training duration of at least 8 weeks to produce noteworthy increases in muscle strength and size. Others have recommended cuff pressures be individually adjusted based on cuff width, limb circumference, and composition of muscle and fat in the limb to produce equivalent blood flow restriction.[22,35] A recent study by Hughes et al[14] compared interface pressure, perceived exertion, and pain among 3 different blood flow restriction systems in 18 healthy male participants. The study concluded that a system that automatically adjusts pressure during exercise is most likely the most beneficial tool to use for patient tolerance and adherence to a BFRT program.

In our review, it appeared that a minimum of 12 sessions is required to achieve measurable strength gains. The time of cuff inflation in the other studies was typically 5 minutes, although 3 studies noted inflation of the cuff during exercise periods that were not timed. Further work is necessary to determine the appropriate cuff pressure and training dose and duration for rehabilitation of knee-related muscle atrophy and to determine whether a protocol similar to that used for healthy participants should be followed.

In healthy participants and athletes, BFRT has been shown to produce significant gains in muscle strength and hypertrophy[21,25,36,41]; however, the underlying mechanisms responsible for these findings remain unclear.[13,34] The reduced blood flow is hypothesized to bring about an ischemic/hypoxic environment that increases levels of metabolic stress, increases recruitment of fast-twitch muscle fibers, elevates systematic hormones, induces cell swelling, and increases production of reactive oxygen species.[13,34] In addition, authors[34] have theorized that mechanical tension acts in a synergistic manner with metabolic stress to produce muscle hypertrophy. BFRT does not appear to induce acute skeletal muscle damage, as Loenneke et al[24] noted in a review of studies that reported no prolonged decrements in muscle function or swelling and no elevation in blood biomarkers of muscle damage. Mechanisms for potential improvements in quadriceps and hamstrings strength in patients with knee-related muscle atrophy after BFRT are unknown at present.

A few small case series were found in this systematic review that assessed the effects of BFRT after total knee arthroplasty (3 patients)[10] and in patients with chronic atrophy after lower extremity trauma (7 patients).[15] The results were encouraging, with all patients demonstrating improvements in isokinetic strength and no complications reported. Although these series were not included in our formal review, the positive results provide further evidence of the safety and efficacy of this training to augment traditional rehabilitation protocols.

One problem highlighted in this review is that only 2 studies provided ES calculations in addition to *P* values. ES measures the magnitude of the effects of treatment and is especially relevant in studies with small sample sizes.[9] It is probable that some statistically significant findings ($P < 0.05$) may have limited clinical relevance. The question of what percentage of muscle strength gain from BFRT represents a minimal clinically important difference (MCID)[18] remains questionable. In musculoskeletal disorders, this may be influenced by the diagnosis and magnitude of muscle weakness and atrophy. For instance, one may arbitrarily set a value of strength gain of 10% as the MCID; however, if a deficit of quadriceps peak torque between limbs at baseline is 50%, a 10% gain in strength may not be clinically meaningful to the patient. An additional problem detected in this review was the sample size selected in many studies. Only 4 studies[4,8,37,38] conducted a prospective power calculation of the size required to discern a detectable difference (95% CI) between BFRT and control groups. Future studies should calculate both ESs and sample sizes to minimize the occurrence of a type II statistical error.[12] Another problem noted in our review was the lack of consistency in reporting muscle strength data. One study[29] provided only limb ratios (involved/uninvolved limb), and another study[37] reported only the percentage change from baseline values of knee extensor strength. Future studies should report the peak torque values at baseline and follow-up and normalize all data by body weight.

A history of deep venous thrombosis was considered a contraindication for training in the investigations of Segal et al.[37,38] Giles et al[11] excluded patients at elevated risk of deep vein thrombosis (lower limb surgery within the previous 6 months, cardiovascular conditions, or high blood pressure). Tennent et al[43] performed bilateral lower extremity duplex ultrasounds before and on completion of their investigation, to rule out vascular problems. All studies were negative, and no adverse events were reported. In the study by Bryk et al,[4] a vascular surgeon assessed femoral and tibial pulses to exclude potential vascular risks before patients were entered in the trial. Hughes et al[13] reviewed 20 studies of BFRT used for musculoskeletal rehabilitation and reported few to no adverse events reported. The conclusion was made that correct implementation of this training option presents no greater risk than traditional training modes.[26]

CONCLUSION

Published data show BFRT to be potentially effective in improving quadriceps strength in patients with knee-related weakness and atrophy. The use of short-duration vascular occlusion and low-load resistance exercises appears safe and not deleterious after knee surgery or in arthritic knees. This treatment option requires further investigation to refine protocols related to cuff pressure and exercise dosage and duration.

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