Received: 23 March 2023 | Revised: 8 September 2023 | Accepted: 2 October 2023

DOI: 10.1002/pmrj.13076

ORIGINAL ARTICLE

PM&R

Exercise-induced hypoalgesia with end-stage knee osteoarthritis during different blood flow restriction levels: Sham-controlled crossover study

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Abstract

Background: Blood flow restriction (BFR) training could be a valuable treatment to induce exercise-induced hypoalgesia (EIH) in patients with end-stage knee osteoarthritis. However, the use of BFR in these patients is poorly explored and there is no evidence about the training dosage needed.

Objective: To evaluate the effect of resistance training protocols with different occlusion levels of blood flow restriction (BFR) on EIH in patients with end-stage knee osteoarthritis.

Design: Crossover study.

Setting: University physical exercise laboratory.

Participants: 26 adults with end-stage knee osteoarthritis.

Interventions: Patients performed four sets (30, 15, 15, and 15 repetitions) separated by 1-minute rests of three protocols/sessions of low-load (30% one-repetition-maximum) seated knee extensions with elastic bands and BFR: placebo (sham BFR), BFR at 40% arterial occlusion pressure (AOP) and BFR at 80% AOP.

Main Outcome Measures: Pressure Pain Thresholds (PPT) and Visual Analog Scale (VAS) collected before, immediately after session, and after 10 minutes.

Results: No differences in EIH were found between the different levels of BFR. However, 80% AOP protocol worsened VAS scores immediately (mean difference [MD]: −21.2 (95% confidence interval [CI] −33.9 to −8.5) while improving PPT immediately (MD affected limb: −.6 [95% CI −1.1 to −.2]); contralateral: −.6 (95% CI −1.0 to −.2]) and at 10 minutes (MD affected limb: −.6 [95% CI) −1.2 to −.1]; contralateral: −.7 [95% CI −1.1 to −.2]; and forearm: −.5 [95% CI −.9 to −.05]) post-exercise compared to baseline.

Conclusions: There is no EIH difference after using different occlusion levels. EIH is modulated by pain-related psychological constructs and self-perceived health status.

INTRODUCTION

Knee osteoarthritis (OA) is a chronic multifactorial joint disease involving irreversible damage to cartilage, subchondral bone, ligaments and capsule, osteophyte formation, pain, and stiffness.[1] Knee OA is one of the leading causes of global functional disability health burden among adults[2–4] and a main contributor to loss of work.[2] Chronic knee pain is its dominant symptom, and knee characteristics (eg, worsening of radiographic OA,

higher knee pain at baseline, worsening of knee pain, lower knee extension muscle strength), clinical factors (eg, lower walking speed, higher comorbidity count), and psychosocial factors (eg, lower vitality, poor mental health, and depressive symptoms) have been shown to be predictors of deterioration in pain and physical functioning.[5] Moreover, this deterioration in physical functioning during walking appears to be closely associated with all-cause mortality in people with knee OA.[2] In addition, evidence suggests that pain sensitization, produced by alterations in nociceptive processing, is present in people with knee OA and may be associated with symptom severity.[6] With the combined effects of aging and increasing obesity and sedentary lifestyle in the world's population, global estimates suggest that its prevalence is expected to increase in the coming decades.[1,2] It is therefore important that health professions develop strategies to reduce the future knee OA burden on health services.

Consequently, therapies focused on pain reduction are paramount in knee OA treatment,[7] although knee replacement surgery is the usual choice at the end-stage of the disease.[8] However, resistance training is usually considered as part of a conservative management,[7] even more so in the early stages of the disease, due to its benefits before and after surgery.[9] One positive improvement of symptoms in patients with knee OA is the possibility of exercise-induced hypoalgesia (EIH),[6] which is an acute postexercise reduction in pain sensitivity that can affect both exercising and nonexercising areas of the body.[10] However, recommendations for resistance training to maximize EIH in patients with knee OA are scarce. Additionally, the presence of pain during exercise may limit force output and thus make the progression of exercise dose challenging.[11] Furthermore, traditional resistance training is usually performed with at least 60–70% of the one-repetition-maximum (1RM),[12] which can be especially stressful in patients with pain and low physical condition. In this context, blood flow restriction (BFR) training could be a valuable treatment alternative. This training for 6 weeks in women with knee OA demonstrated comparable improvements in pain, function, and quadriceps strength to a high-load traditional resistance training, but with less anterior knee pain during the sessions.[13] EIH has been studied during BFR application in healthy individuals and demonstrated a greater response with the use of high-pressure BFR in the exercising limb and to a lesser extent a systemic effect in comparison with other modalities of exercise.[10] Additionally, BFR enhanced EIH in active adults with anterior knee pain.[14] However, the use of BFR in patients with knee OA remains poorly explored. There is no evidence about the BFR training dosage needed to induce EIH.[15,16] This could provide promising practical applications since literature has reported that different levels of arterial occlusion pressure (AOP) during BFR training may provide dissimilar results.[10] The aim of the study was to evaluate the effects of different BFR protocols on EIH in patients with end-stage knee OA. The hypothesis was that the different protocols would induce EIH.

METHODS

Participants

Candidates for the present study were men and women at least 55 years old who had been diagnosed with severe knee OA (according to the clinical and radiographic criteria of the American College of Rheumatology Guidelines)[17] and scheduled for unilateral total knee arthroplasty (TKA) surgery in a local hospital during 2021–2022. Participants were excluded if there was pain in the contralateral (nonstudied) limb (maximum ≥80 of 100 mm on a visual analog scale (VAS) during daily activities), if they had undergone another hip or knee joint replacement in the previous year, if they had any medical condition in which exercise was contraindicated, or if they had participated in exercise programs (>2 days/week, training at intensities of 10–15RM) in the 6 months prior to the study. Participants were also excluded if they had history of stroke, brain surgery, major depression, or any self-perceived cognitive alterations that could affect the performance of study tasks. The study was performed at the University of Valencia (Valencia, Spain) during October 2021 to May 2022. All the participants were informed about the investigation, and written informed consent was obtained. The study conformed to the Declaration of Helsinki and was approved by the local ethics committee (reference number: 1895753). The study was registered at clinicaltrials.gov (NCT05274932). This article adheres to Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[18]

Procedures

Participant height, body mass, and body mass index were collected from medical records. Participants did not ingest food or sweetened beverages (eg, sodas or juices), alcohol, or stimulants (eg, caffeine) in the 2 hours prior to the session. They did not engage in any form of physical activity more intense than basic activities in the 24 hours before the sessions, and they were also recommended to sleep a minimum of 7–8 hours the night before data collection. All measurements were performed by the same four investigators and were conducted in the same facility.

Each participant performed three experimental sessions, separated by 3 days. In each of the sessions, patients were randomly assigned to an intervention (using a computer-based "random number generator"), all performing the same exercise, at the same speed,

and with the same external resistance, but with variations in the level of BFR: (1) placebo, which had a cuff in place, but no pressure; (2) occlusion at 40% of the AOP; and (3) occlusion at 80% of AOP.

During the experimental sessions, participants had their heart rate monitored with a wrist heart rate monitor (FT80, Polar Electro Oy, Kempele, Finland) wirelessly connected to a heart rate sensor (H1, Polar Electro Oy, Kempele, Finland).

On the first day, before the session, participants answered the following questionnaires: stiffness, pain, and physical function in the studied osteoarthritic knee (the first one to be replaced in bilateral cases) was clinically evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score;[19] kinesiophobia was assessed using the Tampa Scale for Kinesiophobia (TSK 11);[20] the level of tendency to catastrophism was evaluated through the Pain Catastrophizing Scale (PCS);[21] and, perceived self-efficacy and the ability to cope with the consequences of chronic pain were assessed using the Chronic Pain Self-Efficacy Scale (CPSS).[22]

Afterward, while the participants sat on the leg extension machine where they would perform the exercise, the AOP of the exercising lower limb was determined as detailed subsequently. Arterial blood flow was measured at rest for 30 seconds with a Doppler ultrasound scanner (U50, EdanUSA, San Diego, CA). Blood flow was determined by the presence of pulsed-wave Doppler mode velocity waveforms and B-mode color flow flashes and by the presence of a pulse using the pulsed-wave heart rate function, and occlusion was determined by their disappearance and absence. The AOP measurement position was chosen to coincide with the exercise position. Participants were seated while a 11-cm-wide, pneumatic cuff (SC10, Hokanson, Bellevue, WA) was placed most proximally on the thigh. The ultrasound probe was placed on the posterior tibial artery until presence of blood flow was established. The posterior tibial artery was chosen in favor of the femoral artery because of the difficulty to measure when cuffs are applied. The cuff was slowly inflated using a DS400 Aneroid Sphygmomanometer (Hokanson, Bellevue, WA) until there was no longer an indication of blood flow from the ultrasound scanner. Our inflation procedure was based on Crossley et al.[23] in which the cuff was inflated to 50 mmHg for 30 seconds and then deflated for 10 seconds. Each subsequent inflation was increased by 30 mmHg (30 seconds on, 10 seconds off) until full occlusion was reached. Once occluded, the pressure was decreased in 10 mmHg decrements until evidence of blood flow reappeared. Pressure was then increased in 1 mmHg increments until blood flow was no longer detected. The lowest cuff pressure at which arterial blood flow distal to the cuff was no longer detectable was defined as AOP. Once AOP was determined, the cuff was deflated, and the participants rested quietly for 5 minutes before training. For safety reasons, a pulse oximeter (FS20D, Hunan Accurate Bio-Medical Technology Co., Ltd., Changsha, China) was used on the second toe throughout the session to ensure that blood flow was not completely halted by tissue edema or vascular transduction failure.

To identify the low external load level of the exercise, yellow, red, green, blue, black, silver, and gold elastic band colors (TheraBand CLX, The Hygenic Corporation, Akron, OH) were used progressively from the lowest available resistance (ie, yellow band). Participants performed two to three sets of two reps of knee extension at a controlled speed of 1.5 sec/phase, with a 1-minute rest between sets until they rated a 2 on Borg's CR10 Scale.[24] This intensity was selected because it corresponds with the appropriate weight that is equivalent to 30% of 1RM[24] and is considered light loading.[25] A 5-minute rest was then taken before proceeding with BFR training.

In each experimental session, the corresponding randomized training session with BFR was carried out, using the previously determined intensity and AOP. Participants performed seated knee extensions with external low load combined with BFR. Before beginning the exercise, the participants performed a few repetitions of light intensity to warm up (non-BFR). The exercise protocol consisted of four sets of seated knee extensions (30, 15, 15, and 15 reps), separated by 1-minute periods, with constant BFR applied throughout the sets and rests. It was based on the recommendations of previous studies examining the implementation into clinical practice of resistance training with low loads and BFR, its considerations of methodology, safety, and physiological responses,[26–28] albeit we opted for 60-second rests instead of 30 seconds to minimize fatigue and discomfort and to avoid possible adverse effects, as concerns have been raised regarding the potential risk for muscle damage and rhabdomyolysis with very strenuous and unaccustomed BFR exercise under some circumstances.[28]

The participants were seated with a knee angle of 90° and a hip angle of 110° during the exercise. To achieve adequate exercise intensity, the elastic bands were prestretched to approximately 50% of the initial length (initial length, 1.5 m). The exercises were performed at each participant's maximal range of motion. Participants were asked to move their body and trunk as little as possible and to perform the exercise smoothly without stops or accelerations. A metronome was used to ensure that the participants held the cadence of 1.5 seconds for the concentric muscle action and 1.5 seconds for the eccentric muscle action during the exercise. If the participant could not maintain the cadence during a particular set, the set was stopped, and the participant rested for 60 seconds until the next set.

The pain outcomes studied were self-perceived knee pain intensity in the exercise leg on the VAS and pressure pain thresholds (PPT). A mechanical algometer (Wagner Instruments, Greenwich, CT) was used for PPT evaluations of three sites (vastus medialis of the affected limb, vastus medialis of the unaffected limb, and distal to the nondominant arm lateral epicondyle, in the common extensor muscle), according to a prior protocol.[29,30] VAS and PPT were assessed at three different time points: preexercise (pre), immediate postexercise (post), and 10 minutes after exercise (post 10 min).

Finally, 72 hours after each session, all participants were interviewed about any possible adverse effects (ie, pain or delayed onset muscle soreness) associated with the exercise bout. Furthermore, participants were instructed to report any adverse effect they might feel during the week after the sessions.

Statistical analysis

The statistical analysis was performed with SPSS software (version 22.0; IBM Corp, Armonk, NY). The normality of the variables was evaluated with the Shapiro–Wilk test. Descriptive statistics were used to summarize the data for continuous variables and are presented as mean ± SD, 95% confidence interval (CI). A two-way repeated measures analysis of variance (ANOVA) was conducted to study the effect of the between-participant "treatment group" factor in each of the three categories (40% AOP, 80% AOP, and placebo) and the within-participant "time" factor, also in each of the three categories (ie, pre-, post-1, and post-10 min). The inclusion of the scores of the TSK-11, PCSS, CPSS, and WOMAC questionnaires as covariates in the models was analyzed. The covariance structure used was autoregressive of order one. A post hoc analysis with Bonferroni correction was performed in the case of significant ANOVA findings for multiple comparisons between variables. The results of the variables VAS and PPT were interpreted using the change or increment (Δ) between measurements (post–pre). A correlation analysis (Spearman's rho) was performed between Δ VAS and Δ PPT variables and the results of the questionnaires (TSK-11, PCS, CPSS, WOMAC subscale for pain, and WOMAC global). Correlation coefficient values were considered as follows: close to 0 as no association, 0.1–0.3 as weak, 0.4–0.6 as moderate, 0.7–0.9 as strong, and 1 as perfect correlation.[31] The α level was set at .05 for all tests.

An a priori sample size calculation was performed using G*Power 3.1. Based on a previous study,[10] which identified significant differences with a moderate effect size ($d = 0.69$) in pain threshold to pressure in the dominant quadriceps after comparing different AOP levels of BFR, a total of 23 patients were estimated to be needed for each group ($f = 0.38$), with a power of 80% and a statistical significance of .05.

Role of the Funding Source

The funders played no role in the design, conduct, or reporting of this study.

RESULTS

A total of 26 adult patients (13 women), with a mean age of 67.1 years and end-stage knee OA participated in the study. Demographic and descriptive data are shown in Table 1. No adverse effects were reported during or after the experimental sessions. All the

TABLE 1 Demographic and baseline data($n = 26$).

	Minimum	Maximum	Mean	SD
Age (y)	55	83	67.1	8.3
Weight (kg)	55	120	76.6	13.9
Height (cm)	152	185	166.4	7.7
TSK11	18	44	32.3	8.3
PCS	2	51	17.7	12.3
CPSS self-efficacy subscale	0	80	60.0	20.1
CPSS performance subscale	0	60	50.2	14.7
CPSS management subscale	0	50	33.7	13.1
CPSS total score	0	190	143.9	45.5
WOMAC pain subscale	0	19	7.5	4.1
WOMAC stiffness subscale	0	7	2.8	2.1
WOMAC function subscale	1	65	21.9	15.8
WOMAC total score	3	91	32.3	20.8

Abbreviations: CPSS, Chronic Pain Self-Efficacy Scale; PCS, Pain Catastrophizing Scale; TSK-11, 11-item Tampa Scale for Kinesiophobia; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

participants in this study were programmed to receive TKA surgery in the studied knee in the weeks-to-months following this study.

BFR training with 80% AOP increased VAS scores immediately post-exercise (mean difference [MD]: −21.2 [95% CI −33.9 to −8.5]) although they were recovered after 10 minutes (MD: 16.6 [95% CI 8.3 to 24.9]). There were no differences in VAS scores between the placebo, 40% AOP, or 80% AOP conditions (Table 2). The effect of CPSS and WOMAC pain covariates were significant ($p < .05$).

Regarding PPT in the affected limb, 80% AOP increased PPT (ie, greater EIH) immediately after exercise (MD: −.6 [95% CI −1.1 to −0.2]) and 10 minutes after (MD: −0.6 [95% CI −1.2 to −0.1]). There were no differences between placebo, 40% AOP, or 80% AOP (Table 3).

In the contralateral limb, placebo increased PPT immediately after exercise (MD: −0.5 [95% CI −0.9 to −0.1]). BFR at 80% AOP increased PPT immediately after exercise (MD: −.6 [95% CI −1 to −0.2]) and up to 10 minutes (MD: −0.7 [95% CI −1.1 to −0.2]). There were no differences between placebo, 40% AOP, or

TABLE 2 VAS results.

Measure	Group	Mean ± SD			Mean difference (95% CI). (a) pre–post 1; (b) pre–post 10 min; (c) post 1–post 10 min
		Pre	Post	Post-10 min	
VAS	Placebo	12.8 ± 24.4	16.8 ± 25.1	10.5 ± 20.3	(a) -4 (−16.7 to 8.7)
					(b) 2.3 (−8.3 to 12.9)
					(c) 6.3 (−2 to 14.6)
	40%	8.5 ± 15.9	15.2 ± 20.1	8.2 ± 17.6	(a) -6.7 (−18.6 to 5.2)
					(b) 0.3 (−9.6 to 10.2)
					(c) 7 (−.7 to 14.7)
	80%	6.1 ± 13.6	27.3 ± 24.9	10.7 ± 18.1	(a) -21.2* (−33.9 to −8.5)
					(b) -4.6 (−15.2 to 6)
					(c) 16.6* (8.3 to 24.9)
Mean difference (95% CI)					
Placebo-40%		4.3 (−9.3 to 17.8)	1.6 (−15.8 to 18.9)	2.3 (−11.4 to 16)	
Placebo-80%		6.7 (−7.3 to 20.7)	−10.5 (−28.4 to 7.4)	−.2 (−14.4 to 13.9)	
40%–80%		2.4 (−11.2 to 16)	−12.1 (−29.4 to 5.3)	−2.5 (−16.2 to 11.2)	

Abbreviations: CI, confidence interval; VAS, visual analogue scale.
*Indicates $p < .05$.

TABLE 3 PPT results of the affected limb.

Measure	Group	Mean ± SD			Mean difference (95% CI). (a) pre–post 1; (b) pre–post 10 min; (c) post 1–post 10 min
		Pre	Post	Post-10 min	
PPT affected limb	Placebo	5.7 ± 3.2	6.0 ± 3.4	5.9 ± 3.3	(a) −.3 (−.8 to .1)
					(b) −.2 (−.7 to .3)
					(c) .1 (−.2 to .4)
	40%	5.0 ± 2.5	5.4 ± 2.9	5.4 ± 3.1	(a) −.3 (−.8 to .1)
					(b) −.4 (−.9 to .1)
					(c) −.1 (−.4 to .3)
	80%	5.3 ± 2.6	5.9 ± 3.0	5.9 ± 3.1	(a) −.6* (−1.1 to −.2)
					(b) −.6* (−1.2 to −.1)
					(c) −0.0 (−.3 to .3)
Mean difference (95% CI)					
Placebo-40%		.7 (−1.3 to 2.7)	.7 (−1.6 to 2.9)	.5 (−1.8 to 2.8)	
Placebo-80%		.4 (−1.7 to 2.5)	.1 (−2.2 to 2.5)	.0 (−2.4 to 2.4)	
40%–80%		-.3 (−2.3 to 1.8)	-.6 (−2.8 to 1.7)	−.5 (−2.8 to 1.8)	

Abbreviations: CI, confidence interval; PPT, pressure pain thresholds.
*Indicates $P < .05$.

TABLE 4 PPT results of the contralateral limb.

Measure	Group	Mean ± SD			Mean difference (95% CI). (a) pre–post 1; (b) pre–post 10 min; (c) post 1–post 10 min
		Pre	Post	Post-10 min	
PPT contralateral limb	Placebo	5.7 ± 3.5	6.2 ± 3.6	6.0 ± 3.4	(a) −.5* (−.9 to −.1)
					(b) −.3 (−.8 to .1)
					(c) .2 (−.2 to .5)
	40%	5.3 ± 2.9	5.4 ± 3.1	5.4 ± 3.3	(a) −.1 (−.5 to .2)
					(b) −.2 (−.6 to .3)
					(c) −0.0 (−.4 to .3)
	80%	5.2 ± 2.8	5.8 ± 3.3	5.9 ± 3.2	(a) −.6* (−1 to −.2)
					(b) −.7* (−1.1 to −.2)
					(c) −.1 (−.5 to .3)
Mean difference (95% CI)					
Placebo-40%		.4 (−1.8 to 2.7)	.8 (−1.7 to 3.2)	.6 (−1.8 to 3.0)	
Placebo-80%		.5 (−1.8 to 2.9)	.4 (−2.1 to 2.9)	.2 (−2.3 to 2.6)	
40%–80%		.1 (−2.2 to 2.3)	−.4 (−2.8 to 2.0)	−.4 (−2.9 to 2.0)	

Abbreviations: CI, confidence interval; PPT, pressure pain thresholds.
*Indicates $p < .05$.

TABLE 5 PPT results of the forearm.

Measure	Group	Mean ± SD			Mean difference (95% CI). (a) pre–post 1; (b) pre–post 10 min; (c) post 1–post 10 min
		Pre	Post	Post-10 min	
PPT forearm	Placebo	3.2 ± 1.6	3.5 ± 1.9	3.5 ± 1.9	(a) −.3 (−.7 to 0.0)
					(b) −.3 (−.7 to .1)
					(c) 0.0 (−.2 to .2)
	40%	3.3 ± 1.8	3.2 ± 1.6	3.3 ± 1.7	(a) 0.0 (−.3 to .4)
					(b) 0.0 (−.4 to .4)
					(c) −0.0 (−.2 to .2)
	80%	3.1 ± 1.6	3.4 ± 1.8	3.5 ± 1.9	(a) −.3 (−.7 to 0.0)
					(b) −.5* (−.9 to −.1)
					(c) −.2 (−.4 to .1)
Mean difference (95% CI)					
Placebo-40%		−.1 (−1.3 to 1.1)	.3 (−1.0 to 1.6)	.3 (−1.1 to 1.6)	
Placebo-80%		.2 (−1.1 to 1.4)	.2 (−1.2 to 1.5)	−0.1 (−1.4 to 1.4)	
40%–80%		.2 (−1 to 1.4)	−.1 (−1.4 to 1.2)	−.3 (−1.6 to 1.1)	

Abbreviations: CI, confidence interval; PPT, pressure pain thresholds.
*Indicates $p < .05$.

TABLE 6 Correlation analysisbetween covariates using Spearman's rho.

	CPSS	WOMAC pain	WOMAC total	TSK11	PCS
ΔVAS	−.078	.081	−.112	−.141	.147
ΔPPT affected	.153	−.255*	−.215*	−.183	−.237*
ΔPPT contralateral	.220	−.184	−.188	−.162	−.253*
ΔPPT forearm	.113	−.091	−.055	−.143	−.006

Abbreviations: Δ, Change between pre and post measurements; CPSS, Chronic Pain Self-Efficacy Scale; PCS, Pain Catastrophizing Scale; PPT, Pressure Pain Thresholds; TSK-11, 11-item Tampa Scale for Kinesiophobia; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
*Indicates $p < 05$.

80% AOP (Table 4). The effect of WOMAC total and WOMAC pain covariates were significant ($p < .05$).

PPT in the studied forearm increased with 80% AOP at 10 minutes post-exercise when compared with baseline (MD: −0.5 [95% CI −0.9 to −0.1]). There were no differences between placebo, 40% AOP, or 80% AOP (Table 5). The effect of TSK-11 covariate was significant ($p < .05$).

Significant weak correlations were found between PPT changes at the affected limb and baseline PCS and WOMAC measures, whereas PPT changes at the contralateral limb were significantly correlated with baseline PCS (Table 6).

DISCUSSION

The main finding of this study was the absence of EIH differences between BFR training with placebo (sham BFR), 40% or 80% AOP, despite a general immediate EIH after BFR training at 80% of AOP.

The present results indicate that there was an immediate postexercise increase in VAS scores with BFR training at 80% AOP, but there were no differences between conditions. However, in another study of patients with knee OA, the VAS showed a minimal clinically important difference of 2.25 cm,[32] which would suggest that the 2.12 cm increase seen here was not clinically relevant. A longitudinal study in women with rheumatoid arthritis that compared 12 weeks of leg press and knee extensions (30% 1RM) with BFR (70% AOP) to high-load resistance training (70% 1RM) found that VAS scores were slightly higher with BFR at baseline, and only BFR showed significant reduction in VAS after the intervention.[33] However, their study design did not specifically evaluate EIH.[33] Another study among elder women with knee OA showed similar pain reduction after 6 weeks of knee extensions with either low-load and BFR (30% 1RM, 200 mmHg) or high-load (70% 1RM).[13] Interestingly, the study found that the BFR group had lower levels of anterior knee discomfort during the training sessions than the high-load group.[13] Likewise, it was reported that among elder women with knee OA, 12 weeks of BFR training (30% 1RM, 70% AOP), but not high-load (80% 1RM), reduced WOMAC pain subscale score[34] and that 6 weeks of cycling-ergometer-based prehabilitation with BFR (40% AOP) reduced perceived pain measured with the Knee Injury and Osteoarthritis Outcome Score more than prehabilitation without BFR before TKA.[35] Despite these previous findings contrasting with our own, it seems that, generally, there is an improvement in pain intensity perception in patients when using BFR training, either acutely or chronically. Usually, BFR protocols are used with 40%–80% AOP in comparison with non BFR protocols,[10,26] so future studies should explore comparisons between low and high AOP, as well as using low or high AOP with other nonresistance training styles.

We found that PPT in the affected limb were augmented immediately and 10 minutes after BFR training at 80% AOP. The same occurred in the contralateral limb after BFR at 80% AOP. In addition, PPT in the contralateral limb also increased immediately after placebo. Surprisingly, we also found increased PPT 10 minutes after BFR at 80% AOP at the control forearm. However, there were no differences between conditions. A possible practical application would be using 40% AOP instead of 80% AOP because that presumably would result in less discomfort during rehabilitation while possibly ensuring positive adaptations. In contrast with our findings, a study in healthy individuals reported that all the BFR protocols augmented pain thresholds in the exercising quadriceps compared with low-load sans BFR, with 80% AOP inducing the greatest increase.[10] This difference with our findings could be explained due to some degree of pain sensitization and exacerbated levels of pain in our sample, in comparison with healthy individuals, which could also explain the effect at the control forearm after 80% AOP. In this vein, a study using PPTs in people with knee OA showed a dysfunctional EIH response to aerobic and isometric exercise in those with abnormal conditioned pain modulation and normal EIH in those with an efficient conditioned pain modulation response and controls.[36] Another study in healthy individuals[37] found that addition of BFR to low-intensity aerobic exercise can trigger both local and systemic EIH – measured with PPTs – not typically observed with this intensity of exercise. Moreover, BFR 80% AOP triggered greater and comparable EIH than high-intensity aerobic exercise, which is in accordance with another study[10] and with our own findings. Finally, no discernible distinctions in PPT outcomes were observed among healthy individuals after four sets of unilateral knee extensions to failure (30% 1RM) with and without BFR.[38] Research models have identified several possible mechanisms to explain EIH, like conditioned pain modulation, recruitment of high threshold motor units, a link between baroreceptors and pain pathways, and ischemic and metabolite-induced pain, which are thought to trigger descending inhibitory pathways.[10,16] Recently, first evidence for the underlying mechanisms of EIH with BFR resistance training hint at the endogenous opioid and endocannabinoid systems and conditioned pain modulation associated with the augmented physiological stress of BFR training.[10,37]

The discrepancy between findings, with a worsening of the self-reported perceived pain (VAS) and increased PPT could be explained by the different natures of the measures. The VAS gives a single-dimension estimation that does not differentiate between sensory and affective components of pain, nor other possible confounders (discomfort caused by cuff pressure and/or mechanical load, nocebo effect of psychological distress, etc.).[39] Meanwhile, PPTs, being a form of quantitative sensory testing, would purportedly

offer a clearer picture of somatosensory perception, evaluating the sensory-discriminative aspects of pain more specifically, thus evaluating treatment outcome more objectively.[40] Although cognitive factors are believed to influence EIH, their impact on EIH remains poorly understood, especially in chronic pain.[41,42] Interestingly, our results suggest that both VAS and PPT changes are modulated by pain-related psychological constructs (PCS, CPSS, TSK-11) and self-perceived health status (WOMAC total and WOMAC pain). In fact, we found significant weak correlations between PPT changes at the affected limb with baseline PCS and WOMAC measures, whereas PPT changes at the contralateral limb were only significantly correlated with baseline PCS.

The present study has limitations. First, PPTs were not blindly assessed. Second, long-term inferences or extrapolation to OA patients with other stages cannot be made. Although this was not the aim of our study, future studies should explore the chronic pain effects of using BFR training in knee OA. Also, it should be considered that our patients could have overestimated the exercise intensity due to their pain levels.

CONCLUSIONS

There is a similar EIH among patients with end-stage knee OA after performing knee extensions with sham BFR, BFR at 40% or at 80% AOP. 80% AOP protocol worsened VAS scores immediately while improving PPT immediately post-exercise compared to baseline. Both VAS and PPT changes are modulated by pain-related psychological constructs (PCS, CPSS, TSK-11) and self-perceived health status (WOMAC total and WOMAC pain).

ACKNOWLEDGMENTS

We would like to thank all the patients who participated in this research for their contribution. Author D.C.O. received the predoctoral research grant "Becas de Colaboración en Departamentos universitarios para el curso académico 2021/2022" awarded by the Spanish "Ministerio de Educación y Formación Profesional." For the remaining authors none were declared.

DISCLOSURES

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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How to cite this article: Ogrezeanu DC, López-Bueno L, Sanchís-Sánchez E, et al. Exercise-induced hypoalgesia with end-stage knee osteoarthritis during different blood flow restriction levels: Sham-controlled crossover study. *PM&R*. 2023;15(12):1565-1573. doi:10.1002/pmrj.13076