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ORIGINAL ARTICLE

Acute neuromuscular and perceptual responses to blood flow restriction exercise in adults with severe haemophilia: A pilot study

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Abstract

Introduction: No previous studies have implemented a standard blood flow restriction (BFR) training session in people with severe haemophilia (PwH), where this type of training has been contraindicated.

Aims: The purpose of this study was to evaluate the tolerability, adverse events, and neuromuscular and perceptual responses to an acute session of low load (LL) knee extensions with BFR in PwH under prophylaxis.

Methods: Eight PwH performed one LL-BFR session with 40% arterial occlusion pressure (AOP). Perceptual responses and adverse effects were assessed, together with high-density surface electromyography of vastus medialis (VM) and lateralis (VL).

Results: Significant normalized root mean square differences were found within each set, but not between sets. Spatial distribution (centroid displacement ($p > .05$), modified entropy (VM, set two, cycles three and five, $p = .032$) and coefficient of variation (VM, set two, cycles four and five lower than cycle three ($p = .049$; $p = .036$)) showed changes within each set. Median frequency showed a slight increase during cycle four of set four ($p = .030$). Rate of perceived exertion slightly increased with each set while tolerability slightly decreased in the last set and fear of training with BFR generally decreased after the session.

Conclusions: In PwH, a LL-BFR session at 40% AOP is safe and feasible. Our results suggest that potential muscle impairments may blunt neuromuscular adaptations induced by BFR.

KEYWORDS
centroid, electromyography, entropy, muscle activation, strength training

1 | INTRODUCTION

Haemophilia is a congenital bleeding disorder due to an insufficiency or absence of coagulation factors VIII/IX (Haemophilia A/B), which can lead to spontaneous and/or trauma related bleedings.[1] About 70%–80% of bleedings occur in large synovial joints, like the knees, causing cartilage damage, synovitis and bone destruction,[2] leading to pain, progressive join destruction, altered joint mechanics, decreased muscle strength and altered muscle activity.[3] To handle these consequences, strengthening programs under prophylactic factor coverage are recommended.[4]

General recommendations for strength and hypertrophy involve moderate-heavy resistance training with loads approximating 60%–80% of the one-repetition maximum (1RM).[5] However, the high levels of mechanical stress imposed by such intensities might increase risk of bleeding, which remains a persistent challenge in people with haemophilia (PwH). Furthermore, high levels of exercise-induced pain are likely to be present when performing moderate-high intensity resistance training in some PwH, limiting tolerability, and impeding sufficient intensity to increase hypertrophy and strength adaptations or compromising adherence.[6] This may explain the scarcity of studies using high exercise intensities in this population, despite potential benefits. Thus, new paradigms that ensure sufficient stimulus to provide structural and neural adaptations while minimizing the risk of bleeding are needed among PwH. A novel method to tackle these issues is blood flow restriction (BFR) training (BFRT).[7] BFRT involves applying a pneumatic cuff proximally on the limb, with enough pressure to fully occlude venous outflow yet allow arterial inflow, while concurrently performing low-load (LL) resistance exercise at 20%–30% 1RM. Consequently, BFRT is increasingly being used in populations that have similarities with PwH with regard to knee arthropathy, like osteoarthritis and rheumatoid arthritis, seemingly allowing gains in muscle strength, muscle mass, and functional performance comparable to conventional high-load resistance training, although there is still uncertainty around that evidence.[8] The relationship between physical activity and bleeds is inconclusive, and sports participation was not found to be an important determinant of the bleeding hazard in PwH under adequate prophylaxis, as improvements in prophylaxis over recent decades have enabled PwH to become more physically active.[9,10] However, PwH who exercise strenuously show a higher proportion of bleeds due to traumatic reasons.[11] Even so, exercise is an effective way to treat haemophilia and has a low incidence of related adverse event,[12] so BFRT with its LL nature could prove useful among PwH, where training with moderate-high loads performed near task failure has usually been avoided. However, no previous studies have evaluated the neuromuscular responses to a standard BFRT session in PwH. Importantly, some potential safety concerns have been raised regarding the use of BFR among PwH, with a previous study classifying it as an absolute contraindication..[13] Nevertheless, that classification was not based on actual experimental data,[13] and BFRT performed using low levels of occlusion has demonstrated similar outcomes compared to high occlusion levels,[14] with low pressures potentially reducing risks. In this sense, preliminary data suggests a standard BFRT session would be safe in PwH.[15] Observational studies are needed as a first step to indicate whether BFRT can be performed safely in more long-term settings.

The purpose of this study was to evaluate the tolerability, adverse events, and the acute neuromuscular and perceptual responses to a single session of LL-BFR externally-resisted knee extensions among PwH.

2 | MATERIALS AND METHODS

2.1 | Participants

Participants 18 years and older, diagnosed with severe haemophilia and undergoing prophylactic treatment, were contacted by telephone by one of the authors and participated during April 2021. Candidates were excluded following these criteria: orthopaedic surgery during previous year, musculoskeletal bleeding during previous 3 months, or any medical condition contraindicating physical exercise. Participants gave written informed consent and participated voluntarily. The study conformed to the Declaration of Helsinki and was performed at the University of Valencia (Valencia, Spain). This article adheres to STROBE guidelines.

2.2 | Procedures

Haemophilia type, prophylaxis regimen, height and body mass were collected from participants' medical records. Participants performed a single experimental session, with several restrictions: no nourishment, high-calorie beverages or stimulants in the 2 h prior, and no physical activity more intense than basic activities 24 h before the session. They were also recommended to sleep a minimum of 7–8 h the night before. All measurements were performed by the same investigators and in the same facility.

Participants attended the session 2–4 h after receiving their routine coagulation factor prophylaxis treatment. Haemophilic arthropathy was evaluated using the Haemophilia Joint Health Score 2.1.[16] An ultrasound scan of the exercising leg (the dominant one) was performed by an expert examiner to assure that participants had no muscle bleeds before starting the experiment. Dominance was assessed with the following questions: "Which leg would you kick a ball with if you had to do it? Is it the same one that you would consider your dominant leg in the sense that it is the leg with which you feel most confident in the gestures of your daily life?" High-density surface electromyography (HDsEMG) was implemented as described elsewhere.[15] An amplifier (Sessantaquattro, 64-channel, 16-bit, OT Bioelettronica, Torino, Italy) recorded data from semi-disposable matrices of 32 (8 × 4) electrodes on the vastus medialis (VM) and vastus lateralis (VL) in monopolar derivation at 2000 Hz. Arterial occlusion pressure (AOP) of the exercising limb was measured, exactly as described elsewhere.[15]

Before exercising, as warmup and practice, participants practiced a submaximal isometric seated knee extension. Subsequently, they performed two maximum voluntary isometric contractions (MVIC) against fixed resistance to normalize HDsEMG (to whichever was higher, the highest MVIC, or the highest amplitude reached in session), standardized as described elsewhere.[15]

Training external resistance was identified using elastic bands (TheraBand CLX, Performance Health, Akron, USA) progressively from lowest to highest resistance (yellow colour to red, green, blue, black, silver or gold). Participants performed 2–3 sets of two reps with 60 s rests until they rated a two on Borg's CR10 Scale (corresponds to 30% 1RM).[17] Training included four seated knee extension sets (30, 15, 15, 15 reps; 60 s rests), with constant BFR (40% AOP).

Participants sat (knee at 90°; hip at 110°) during the exercise (performed at individual ROM) (Figure 1). For adequate intensity, the elastic bands were pre-stretched to add approximately 25% of the initial length (initial length, 1.5 m). A metronome ensured that they held a cadence of 1.5 s concentric/1.5 s eccentric during the exercise. Pulse oximetry (CMS50D+; Contec Medical Systems Ltd., Qinhuangdao, China) on the second toe was employed to ensure that blood flow was not completely halted by tissue oedema.

After the sets, participants rated their Rate of Perceived Exertion (RPE) on the Borg CR10 scale and their leg pain intensity with an 11-point numerical pain scale. Subsequently, participants rated the perceived tolerability using a Likert scale (very well tolerated, tolerated, neutral, not well tolerated, not tolerated). After the final set, participants completed a global change scale about the potential change in their fear of practicing BFRT (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse). After the session, and 72 h later, ultrasound scan was repeated to check for any muscle bleeds. Finally, 24, 48 and 72 h post session, participants were interviewed about any possible adverse effects, and instructed to report any they might feel during the week after.

FIGURE 1 Exercise setup.

2.3 | Data analysis

All raw HDsEMG signals from the exercises were processed using algorithms developed in MATLAB vR2018b (The MathWorks Inc., Natick, Massachusetts, USA) and preamplified to obtain EMG data in microvolts. A differentiation of the 32-monopolar channels was performed along the fibre directions (grid columns) to obtain arrays (7 columns × 4 rows) of bipolar signals. A Butterworth fourth-order zero-lag bandpass filter (10–350 Hz) was then applied to each signal to eliminate low and high frequency noise. Subsequently, a visual inspection was performed to discard excess noise signals. A moving root-mean-squared (RMS) smoothing filter was applied to the signals, with a 500 ms window (250 ms backward, 250 ms forward).

Once the EMG signals were filtered, automatic segmentation of the contractions was performed from the maximum and minimum peaks. For each contraction, the maximum RMS percentage (amplitude) and median frequency (MDF) were normalized relative to the highest RMS and MDF value reached during the session. After normalizing these variables in each signal of the map (7 × 4 matrix signals), the average normalized RMS (nRMS) and normalized MDF (nMDF) were obtained to evaluate muscle activation and neuromuscular fatigue respectively.

Spatial distribution of muscle activity was assessed through three HDsEMG nRMS parameters: (i) the map centroid displacement (x- and y-axis coordinates for the medial-lateral and cranial-caudal direction, respectively), (ii) the modified entropy, and (iii) the coefficient of variation (CoV). The nRMS spatial distribution measured by a migration of the HDsEMG map centroid has previously been used as an indicator of the ability to recruit motor units in different muscle regions, and also as an indicator of neuromuscular fatigue.[18] A higher modified entropy (from a maximum possible value of 4.81) represents less heterogeneity (i.e. higher homogeneity) in the spatial distribution of nRMS values within the electrode matrix, whilst a decrease in entropy indicates homogeneity to be reduced.[19] CoV was defined as the standard deviation (SD) of the 28 RMS values divided by the average of the 28 RMS values. When SD is small relative to the mean, this results in a smaller CoV. Therefore, when channel signals are more uniform, there will be a smaller CoV, to also indicate increased homogeneity (reduced heterogeneity). To allow statistical analysis, the repetitions of each set were averaged in successive cycles. In the case of set 1 (30 reps), each cycle consists of the average of 6 repetitions. In sets two to four (15 reps), each cycle is the result of averaging three reps. In all cases, five cycles were obtained.

2.4 | Statistical analysis

Results are expressed as means and standard deviation (SD), unless otherwise specified. Before comparisons, normality was tested using the Shapiro–Wilk test. Statistical significance was set at $p \leq .05$.

Differences in nRMS, nMDF, nRMS centroid, entropy and CoV were evaluated using 2-factor mixed analysis of variance (ANOVA) models [Set(4)*Cycles(5)] of repeated measures of the cycle factor for VM and VL muscles independently. If ANOVA reached statistical significance, pairwise comparisons were performed with Bonferroni adjustments. RPE, pain intensity and tolerability levels of the exercise sets are expressed as absolute values and percentages of participants. Statistical analyses were performed using SPSS v26.0 (IBM, Armonk, NY, USA).

3 | RESULTS

Eight participants with severe haemophilia A undergoing prophylaxis participated. Table 1 shows demographics and leisure-time physical activity. Most of the participants engaged in physical activity at least 2 days × week^{-1} in sessions lasting at least 30 min.

No adverse effects were reported during or after the experimental session, nor were any signs of complications encountered during the post-session ultrasound scans. Figure 2 shows mean nRMS for VM and VL during the exercise sets. nRMS showed significant increases within each set, but not between different sets.

Regarding HDsEMG nMDF, the only statistically significant difference occurred in VM, between sets one and four ($p = .030$), with nMDF increasing during cycle four of set four (Figure 3).

TABLE 1 Demographic and descriptive data.

(n = 8)	Mean (SD)
Age (years)	37.4 (9.7)
Height (cm)	174.1 (10.5)
Body mass (kg)	79.0 (11.1)
FVIII[a] dose (IU/kg)	27.6 (15.0)
FVIII[a] dose (IU/week)	5350.0 (2587.3)
HJHS[b] dominant knee	1.0 (2.1)
HJHS[b] nondominant knee	4.8 (6.9)
HJHS[b] total lower limbs	15.5 (9.7)
Leisure-time physical activity	
Frequency	***n* (%)**
Never	1 (12.5)
1 time/week	0 (0)
2–3 times/week	4 (50.0)
Almost daily	3 (37.5)
Intensity	
Take it easy	3 (37.5)
Push some	3 (37.5)
Near to exhaustion	1 (12.5)
Duration	
<15 min	0 (0)
16–30 min	0 (0)
30–60 min	3 (37.5)
>1 h	4 (50.0)
Resistance training experience	
Yes	5 (62.5)
No	3 (37.5)
Frequency	
1 time/week	0 (0)
2 times/week	3 (37.5)
3 times/week	2 (25.0)
4 times/week	0 (0)
Years of experience	
1 year	1 (12.5)
2 years	1 (12.5)
≥3 years	3 (37.5)
Intensity	
Moderate (60%–70% 1RM)	5 (62.5)
Heavy (>80% 1RM)	0 (0)

[a]Coagulation factor dose before the experimental session.
[b]HJHS: haemophilia joint health score.

Regarding the migration of the HDsEMG nRMS map centroid, there were no statistically significant differences between the sets or cycles in any of the muscles. Figure 4 depicts the mean locations for the HDsEMG nRMS map centroid values in the VM and VL muscles

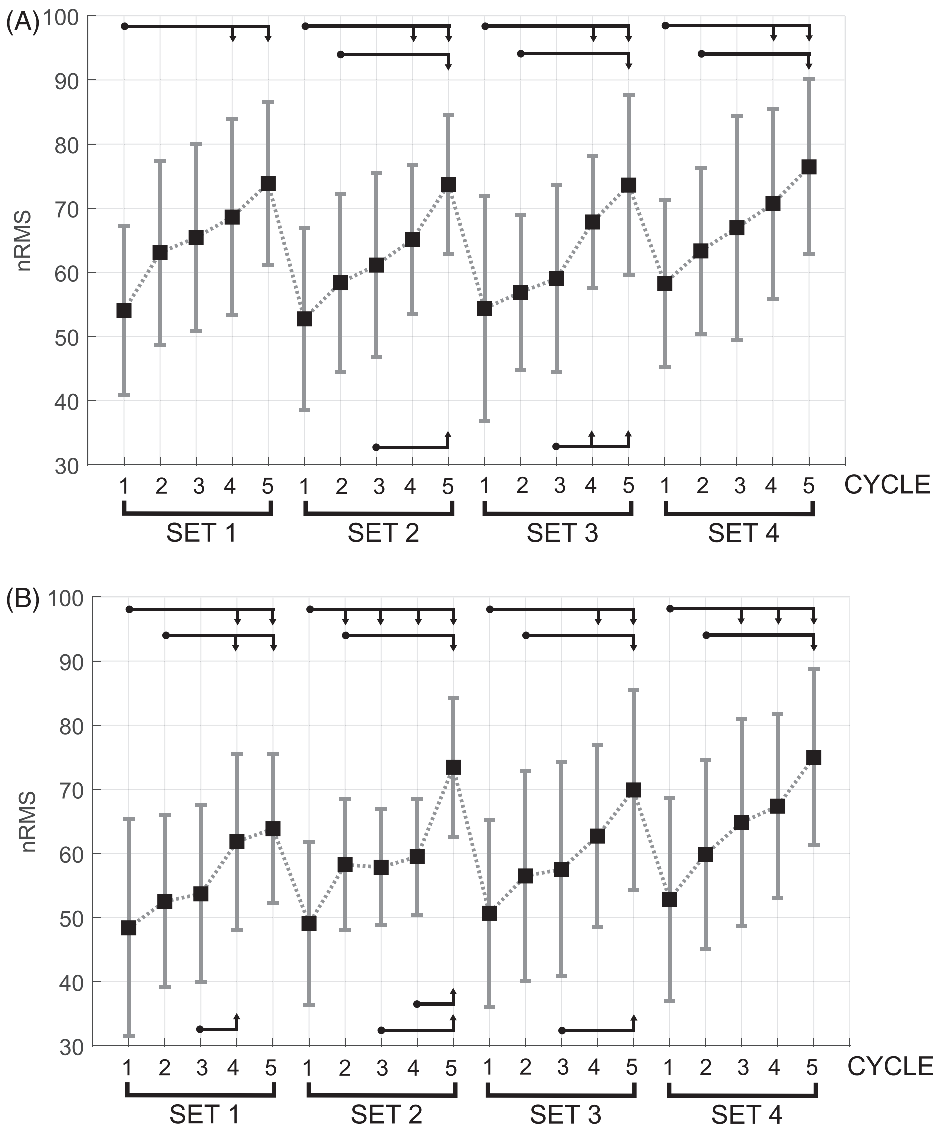

FIGURE 2 Normalised values (% of 100) of electromyographic amplitude (nRMS) for each cycle and set. (a) vastus medialis and (b) vastus lateralis. The squares indicate the mean value, while the bars express the 95% confidence interval of the mean. The point at the beginning of the black line marks the compared cycle and the vertical arrows indicate significant differences between cycles.

obtained in each set. Modified entropy only varied in the VM, during set two, between cycles three and five ($p = .032$) (Figure 5).

Regarding the CoV (Figure 5), the only statistically significant difference occurred in VM, during set two, with cycles four and five showing reduced CoV compared to cycle three ($p = .049$; $p = .036$, respectively).

Table 2 shows perceptual responses. RPE increased during sets three and four whereas no participant reported any pain, with generally high tolerability. Regarding the change in fear of practicing BFRT after the acute session, three participants reported that it had improved very much, two that it had improved much, a single participant reported that it had improved minimally, while two participants reported no change. Data on the arterial occlusion pressures used are shown in Supplementary material (Table S1).

4 | DISCUSSION

The main findings were that (1) an acute LL-BFR knee extensor exercise bout appeared safe and feasible in adults PwH, without causing acute or delayed musculoskeletal pain; (2) neuromuscular activity (nRMS) was modulated (progressively increased) within sets, but did not differ between sets; (3) nRMS spatial distribution as characterized by centroid displacement, modified entropy and CoV only varied during the second set; (4) nMDF showed a slight increase between sets one and four; (5) RPE slightly increased with each set while tolerability slightly decreased in the last set, whereas pain intensity did not change; (6) fear of training with BFR decreased after the session.

The present results indicate that BFR fails to augment the neuromuscular response of LL exercise across the different sets, which

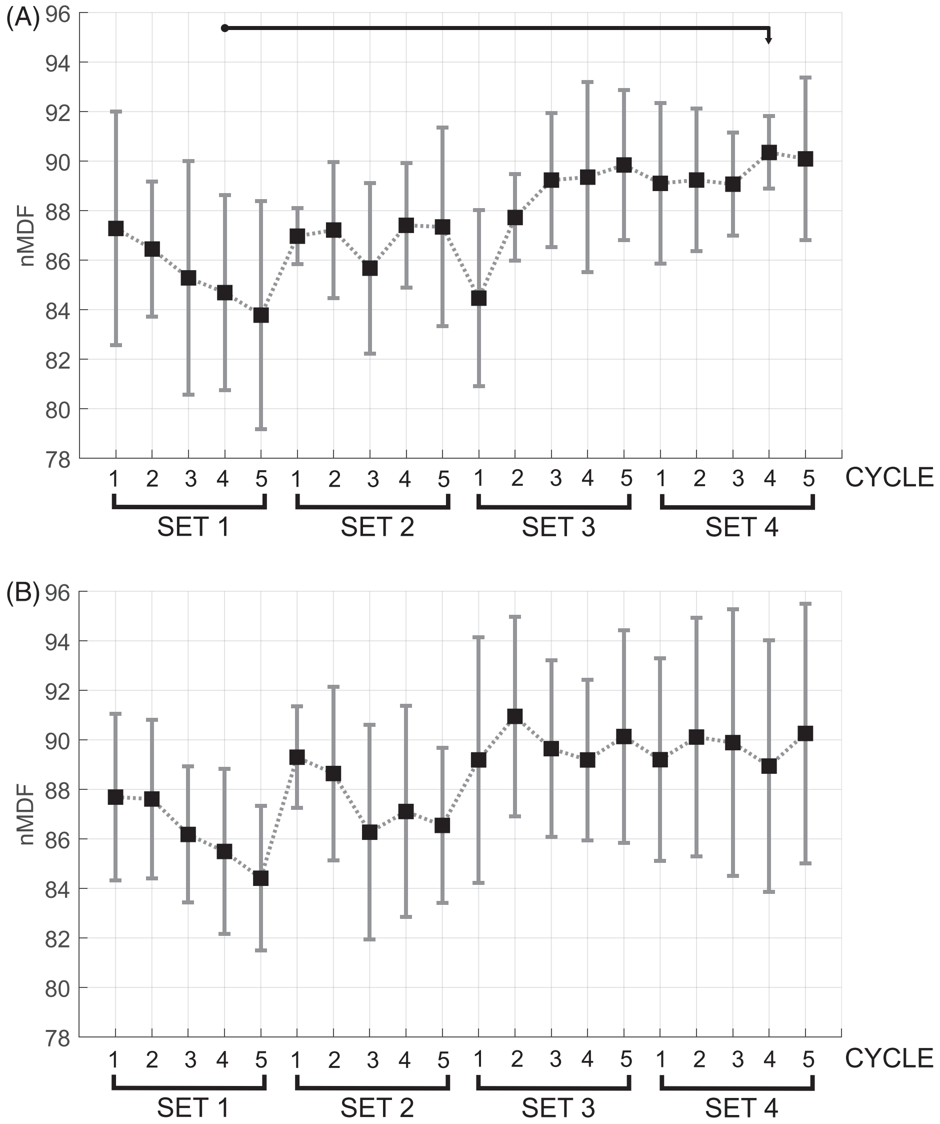

FIGURE 3 Normalised values (% of 100) of median frequency (nMDF) for each cycle and set. (a) vastus medialis and (b) vastus lateralis. The squares indicate the mean value, while the bars express the 95% confidence interval of the mean. The point at the beginning of the black line marks the compared cycle and the vertical arrows indicate significant differences between cycles.

contradicts our hypothesis and a previous study[14] conducted in healthy individuals that used 30% 1RM and 40% of AOP. Nevertheless, changes in central mechanisms (motor unit discharge rate and recruitment) reportedly compensate for a decline in contractile properties to maintain torque output in free-flow low intensity VM and VL isometric contractions to failure.[20] Although our participants did not exercise to failure, it is possible that the BFR-induced accumulation of metabolic by-products affected muscle fibre-contractile capacity, generating similar effects to low intensity exercise to failure. As such, the lack of neuromuscular activity changes between sets may be a unique feature of LL-BFR. Recent meta-analyses reported similar hypertrophy responses between LL-BFR and high-load (non-BFR) training but with different increases in strength.[21,22] Therefore, it might be speculated that differences in strength gains might be due to diverse neuromuscular responses between training regimes. It has been theorized that the traditional paradigm of early strength gains due to neural adaptations followed by muscular hypertrophy is potentially reversed with LL-BFR.[23] In addition, the 60 s rest periods could be excessive to evidence nRMS increases between sets. Perhaps, the fact that the first set had twice the repetitions than the others, generated a residual effect on the subsequent sets that allowed to achieve similar nRMS levels. In fact, in general, we only found nRMS increments between the first and the last cycles of each set, with a greater number of differences for the VL and lower nRMS values. This is in line with a previous study in PwH, reporting VL to have higher maximum nRMS threshold and earlier fatigue onset than VM during repeated submaximal knee extensions performed to task failure.[24] Further research seems warranted to investigate the effect of modulations in BFR cuff pressure in conjunction with different resistance exercise dosing.

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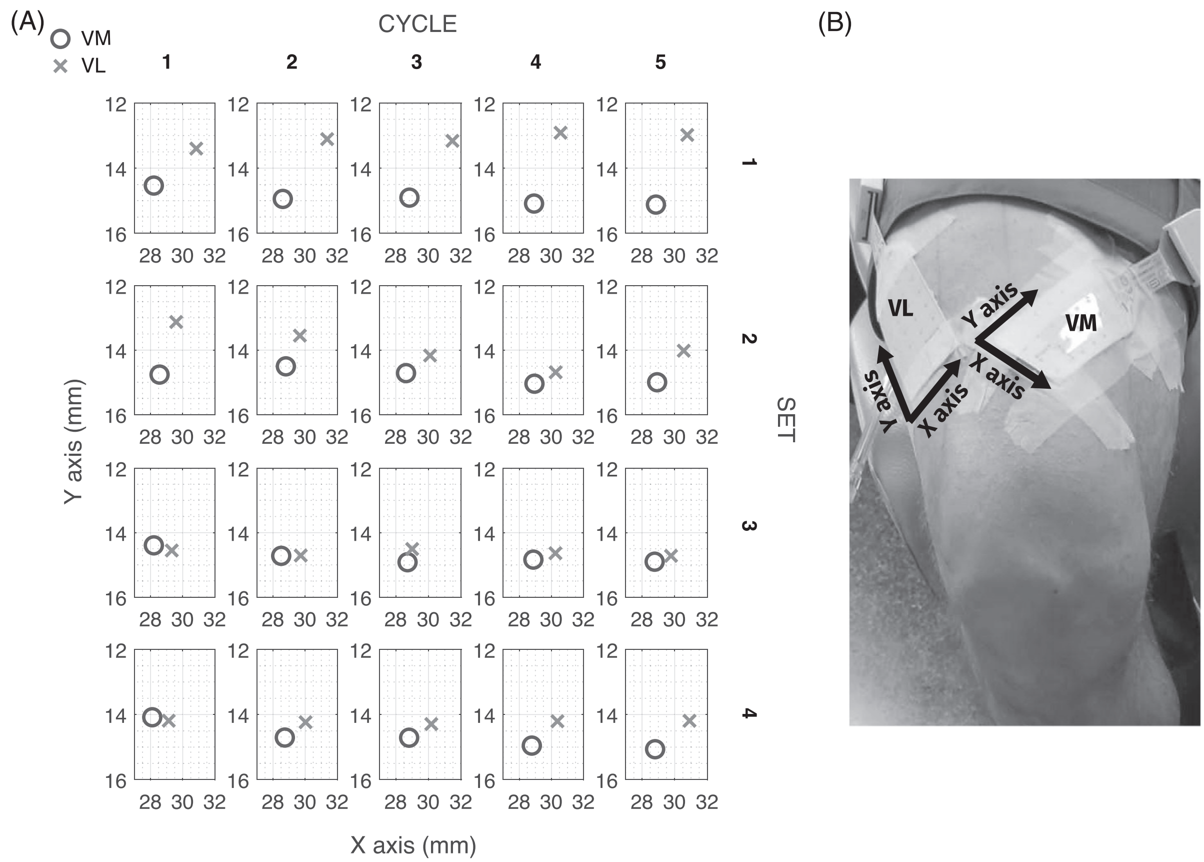

FIGURE 4 Mean values of nRMS maps centroid in each cycle (a) and placement of the high-density surface electromyography electrodes (b). VM, vastus medialis and VL, vastus lateralis.

During fatiguing exercise, changes in nRMS sptatial distribution measured by a migration of the HDsEMG map centroid may occur in the presence of muscle fatigue.[25,26] However, the recovery between sets and the low intensity of the exercise may have made our exercise protocol not excessively fatiguing, an observation that also seems supported by our nMDF data. In support of this notion, modified entropy, an entropy-based measure used to quantify the homogeneity in spatial distribution of HDsEMG activity, also failed to reveal changes, except for a slight increase observed in VM during set two that was accompanied by a slight decrease in CoV, both indicating an increase in homogeneity, possibly reflecting a residual effect of the first set that disappeared in sets three and four. Elderly.[27] and individuals with Parkinson's disease.[28] exhibit smaller EMG spatial distribution changes compared to young individuals, suggesting that the reduced musculoskeletal fitness and the disease status of our participants could reduce the ability to recruit motor units from different muscle regions. As our participants already presented high mean entropy levels, it may be speculated that the high spatial homogeneity, supported also by the present CoV data, could bear a relationship with the severity of their disease and reduced fitness, between other factors. Interestingly, Watanabe et al.[19] found that spatial distribution varied across different contraction levels but was not altered by training or detraining, suggesting that the spatial distribution of neuromuscular activity is not strongly influenced by resistance training or detraining, and that marked changes in inter-regional motor unit recruitment strategies are less likely to occur following resistance training. LL-BFR seems to improve strength and induce muscle hypertrophy without causing statistically significant changes in various measures of voluntary activation and neural drive.[29] It may be hypothesized that the low intensity or AOP%, slow contraction speeds, rest periods and most importantly, the intrinsic neuromuscular impairments potentially imposed by the disease, might have contributed to the absence of modulation in the HDEMG variables examined.

This is, to our knowledge, the first study to evaluate an acute bout of BFRT in PwH, and thus at every step we erred on the side of caution. Importantly, tolerability was high, pain did not emerge, and no adverse events were noted during the one-week post experiment follow-up. Moreover, fear of training with BFR was reduced after just one session in most of the participants, possibly reflecting their expectations and a previous high fear of engaging in resistance exercise. While the ongoing novelty of this approach precludes strong conclusions, this could imply that LL-BFR might have a high adherence and therefore be a therapeutic tool of clinical relevance in PwH. In this sense, a previous study that compared 12 weeks of LL-BFR lower-extremity training to traditional high-load training among individuals with rheumatoid arthritis found that pain scores improved only in the LL-BFR group, and also here in the absence of any adverse events.[30]

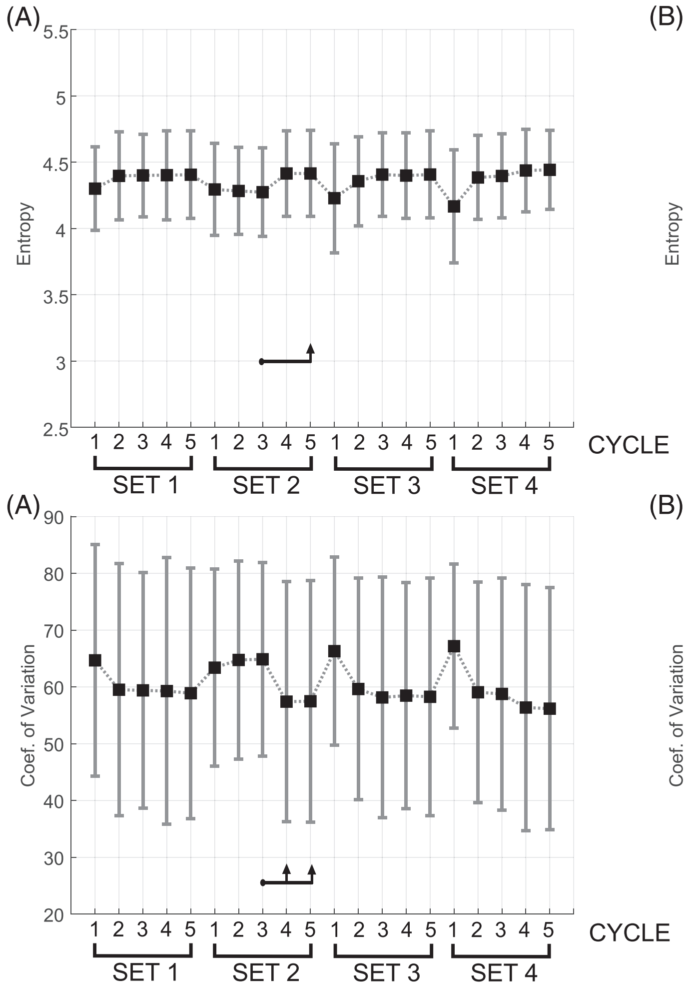

FIGURE 5 Modified entropy (maximum possible value of 4.81) and coefficient of variation in each cycle and set. (a) vastus medialis and (b) vastus lateralis. The squares indicate the mean value, while the bars express the 95% confidence interval of the mean. The point at the beginning of the black line marks the compared cycle and the vertical arrows indicate significant differences between cycles.

TABLE 2 Perceptual responses.

		SET 1	SET 2	SET 3	SET 4
RPE[a]	2	0 (0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)
	3	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)
	4	1 (12.5%)	2 (25.0%)	1 (12.5%)	1 (12.5%)
	5	3 (37.5%)	3 (37.5%)	2 (25.0%)	2 (25.0%)
	6	3 (37.5%)	1 (12.5%)	3 (37.5%)	2 (25.0%)
	7	0 (0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)
	8	0 (0%)	0 (0%)	0 (0%)	1 (12.5%)
Pain	Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tolerability	Very well tolerated	2 (25.0%)	2 (25.0%)	2 (25.0%)	2 (25.0%)
	Tolerated	5 (62.5%)	5 (62.5%)	5 (62.5%)	5 (62.5%)
	Neutral	1 (12.5%)	1 (12.5%)	1 (12.5%)	0 (0%)
	Little tolerated	0 (0%)	0 (0%)	0 (0%)	1 (12.5%)

[a]Rate of perceived exertion (0-10).

This study has limitations, allowing only inferences about possible long-term adaptations. Participant number was small, though these measurements were performed in a difficult-to-recruit population with a rare disease. Also, it should be noted that HDsEMG is highly reliable.[31,32] Furthermore, this study included relatively trained individuals (relative to their condition), which challenges generalization to other PwH with other arthropathy levels. Also, 6 of the 8 participants in this study participated in a previous study on acute responses to BFRT, so they had prior exposure to BFRT, although minimal (only three repetitions in each of 6 different conditions), possibly influencing tolerability and fear of practicing BFRT scores.[15] Consequently, specialists should carefully assess the individual acute response to LL-BFR as well as the individual pharmacological treatment. However, through direct AOP measurements, we ensured an individualized BFR. Importantly, this study could open new doors for exercise-based muskulosketal treatment paradigms in PwH and severe arthropathy. Future investigations should evaluate the long-term adaptations to BFR in PwH and assess whether acute changes to BFR exercise predict or correlate with chronic adaptations.

5 | CONCLUSIONS

In severe PwH undergoing prophylactic treatment, a single acute training session using LL knee extensions with BFR at 40% AOP appeared to be safe, feasible and did not increase perceived pain scores. Further, fear of training with BFR decreased after the session. However, acute BFRT did not increase neuromuscular activity and spatial distribution in the vasti muscles, suggesting that potential muscle impairments induced by the progression of the disease may blunt the range of neuromuscular adaptations with BFRT. Longitudinal intervention studies employing BFRT should be conducted to assess the long-term benefits of employing this modality in adults with severe haemophilia.

AUTHOR CONTRIBUTIONS

Joaquín Calatayud, Daniel C. Ogrezeanu, Sofía Pérez-Alenda and Carlos Cruz-Montecinos conceived and designed study; Joaquín Calatayud, Sergi Rodríguez, and Daniel C. Ogrezeanu collected raw data; Juan J. Carrasco, Lars L. Andersen and Eduardo Martinez-Valdes completed all data analyses; Joaquín Calatayud and Daniel C. Ogrezeanu wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, was approved by the local Ethics Committee (reference: 1579884) and was performed at the University of Valencia (Valencia, Spain). Study participants gave written informed consent prior to study procedures and participated voluntarily.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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