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Safety, feasibility, and neuromuscular activity of acute low-load resistance exercise with or without blood flow restriction in patients with severe hemophilia

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Abstract

Objective: To compare the safety, feasibility, and neuromuscular activity of acute low-load resistance exercise with/without blood flow restriction (BFR) in people with severe hemophilia (PwH).

Methods: Eight PwH under prophylaxis (5 with resistance training experience) performed 6 randomly ordered conditions of 3 intensity-matched knee extensions: no external load and no BFR, no external load and light BFR (20% of arterial occlusion pressure [AOP]), no external load and moderate BFR (40% AOP), external low load and no BFR, external low load with light BFR, and external low load with moderate BFR. Rated perceived exertion, pain, exercise tolerability, and adverse effects were assessed. Normalized root-mean-square (nRMS), nRMS spatial distribution, and muscle fiber-conduction velocity (MFCV) were determined using high-density surface electromyography for the vastus medialis and lateralis.

Results: Exercises were tolerated, without pain increases or adverse events. Externally resisted conditions with/without BFR provided greater nRMS than nonexternally resisted conditions ($p < 0.05$). Spatial distribution and MFCV did not vary between conditions.

Conclusions: In these patients, knee extensions with low external resistance and BFR at 20% or 40% AOP appear safe, feasible and do not cause acute/delayed pain. However, BFR during three consecutive repetitions does not increase nRMS nor changes nRMS spatial distribution or MFCV.

KEYWORDS
electromyography, entropy, muscle activity, strength training

Joaquín Calatayud and Daniel C. Ogrezeanu contributed equally to the study.

Novelty statement

What is the new aspect of your work? To date, whether people with hemophilia can perform blood flow resistance (BFR) training remains unknown. What is the central finding of your work? In people with severe hemophilia under prophylaxis, BFR training appears safe, feasible, and without causing acute or delayed increases in muscle pain. However, BFR during non-fatiguing exercise consisting of three consecutive repetitions by itself does not increase electromyographic amplitude nor changes electromyographic amplitude spatial distribution or muscle fiber-conduction velocity. What is the specific clinical relevance of your work? Physical therapists could safely use BFR training at 20% or 40% of arterial occlusion pressure when people with severe hemophilia are not able to use high loads or to introduce training variations in rehabilitation.

1 | INTRODUCTION

Hemophilia is a coagulation disorder present in males, determined by the expression of a recessive gene on chromosome X, and is caused by deficiencies in factors VIII/IX (hemophilia A/B).[1] Spontaneous and/or trauma-related bleedings produced by this disease, especially hemarthroses among large synovial joints,[2] lead to proliferative synovitis and irreversible damage to joint cartilage and bone.[3] The interaction between these processes induces a vicious circle of pain,[4] local joint disuse and decreased physical activity, which finally alters joint mechanics and mobility, muscle strength, and activation patterns,[5] while reducing quality of life.[2]

Mitigation strategies to counteract the above observations should ideally also include strengthening programs with sufficiently high intensity to stimulate skeletal muscle anabolism and limit muscle loss for people with severe hemophilia (PwH) under prophylactic factor coverage.[6] Nonetheless, no clear recommendations about strength exercise intensity, tolerability, and adverse effects currently exist for PwH. More so, although strength training reduces and prevents bleedings and associated pain,[7] with a low incidence of adverse events,[8] avoidance of physical exercise is still prevalent in PwH.[9] Most importantly, if physically active, this population typically performs conventional nonresisted exercises with low intensity, which are likely not effective of facilitating significant muscle strength gains or morphological adaptations.[9]

The general recommendation for increasing muscular strength and neural adaptations in healthy individuals is to engage in moderate- or heavy-load resistance training with loads approximating 60%–80% of the one-repetition maximum (1RM).[10] However, the high joint stress derived from such intensities is often challenging for PwH and might increase the risk of adverse consequences, so strategies that would safely allow improvement while minimizing joint stress may be warranted. Low-load (LL) resistance training performed concurrently with partial blood flow restriction (BFR) is a novel approach that uses loads as low as 20%–30% 1RM. BFR training involves decreasing muscle blood flow by applying a pressurized cuff on the proximal aspect of a limb to mechanically compress the underlying vasculature, fully occluding venous outflow yet allowing arterial inflow. BFR can have a positive impact on numerous physiological adaptations, enhancing the exercise stimulus of LL exercise.[11,12] For instance, a study reported that electromyographic (EMG) activity during BFR among healthy adults can be increased depending on the occlusion level,[13] albeit new investigations are needed to determine whether this response can be extrapolated to other conditions (i.e., BFR vs. free-flow) or in PwH. Importantly, LL BFR training has been shown in recent years to induce significant adaptations in muscle hypertrophy and strength in healthy people[11,14] as well as in different clinical populations (e.g., osteoarthritis, rheumatoid arthritis).[11,15,16] However, no previous studies have used BFR in PwH.

The main objective of the present study was to compare the safety, feasibility, and neuromuscular response to acute lower-body LL exercises performed with and without BFR. We hypothesized that the addition of BFR would not increase the neuromuscular response of LL exercise and that this type of training would be safe and tolerable in PwH.

2 | MATERIALS AND METHODS

2.1 | Participants

Persons who were at least 18 years old, diagnosed with severe hemophilia (A or B), and undergoing prophylactic treatment were considered candidates for the present study. Candidates were excluded based on the following criteria: orthopedic surgery during the previous 12 months, musculoskeletal bleeding during the previous 3 months, or any medical condition that would contraindicate an exercise intervention. The study was performed at the University of Valencia (Valencia, Spain). All the participants were informed about the objectives and content of the investigation, and written informed consent was obtained. The study conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the University of Valencia (reference number: 1579884). This article adheres to STROBE guidelines.[17]

2.2 | Procedures

The type of hemophilia, severity, and prophylaxis regimen were collected from medical record. Each participant carried out a single

experimental session. Participants adhered to several restrictions: no nourishment, high-calorie or alcoholic beverages or stimulants (e.g., caffeine) were consumed 2 h prior to the session, and they did not engage in any physical activity more intense than basic activities 24 h before the training bout. They were also recommended to sleep a minimum of 7–8 h the night before data collection. All measurements were made by the same two investigators and were conducted in the same facility.

The participants attended the experimental session 2–4 h after receiving their routine coagulation factor prophylaxis treatment. In the experimental session, height (determined with a stadiometer; model IP0955 [Invicta Plastics Ltd., Leicester, UK]) and body mass (determined with a body composition analyzer; model BF-350 [Tanita, Tokyo, Japan]) were obtained. Participants also had their blood pressure assessed with and automatic blood pressure monitor (M2 HEM-7121-E, OMRON Healthcare, Kyoto, Japan) before and immediately after the training bout. The degree of hemophilic arthropathy was clinically evaluated using the Hemophilia Joint Health Score 2.1. This instrument scores each joint (knees, ankles and elbows) from 0 to 20 points, with higher scores reflecting worse conditions (having a maximum score of 120 points).[18] Subsequently, participants answered a short questionnaire about leisure-time physical activity and their resistance training experience.[19]

As a safety precaution measure prior to the initiation of the experimental protocol, an ultrasound scan of the exercising leg (the dominant one) was performed by an expert examiner to assure that participants had no active muscle bleeding before the experiment. Afterwards, the high-density electromyographic (HDsEMG) protocol started with the marking of the skin according to the *Atlas of muscle innervation zones* guidelines for the vastus medialis (VM) and vastus lateralis (VL).[20] Then, guided by the described markings, HDsEMG signals were initially recorded during a brief voluntary contraction during which a linear nonadhesive electrode array (16 electrodes, with an inter-electrode distance [i.e.d.] of 5 mm) was moved over the skin to detect the location of the innervation zone to ensure optimal electrode placement.[21] After the skin was shaved and abraded to remove dead skin and cleaned with cotton wool dipped in alcohol, the electrode grids were positioned on the previously determined optimal zones, with the electrode columns oriented along the muscle fibers. The reference electrodes were placed just over the ankle. Specifically, HDsEMG was recorded in monopolar derivation with semi-disposable adhesive matrices (GR10MM0804, OT Bioelettronica, Torino, Italy) of 32 (8 × 4) equally spaced electrodes (10 mm i.e.d.). HDsEMG signals were sampled at 2000 Hz and digitally converted using a 16-bit analog to digital converter (Sessantaquattro, 64-channel HDsEMG amplifier, OT Bioelettronica, Torino, Italy). All data were stored on a computer hard disk for later analysis.

At the beginning of the experimental session, as a warmup and as a practice trial, all participants performed a submaximal isometric seated knee extension against a fixed resistance, in a standardized muscle testing position for the VM and VL muscles (with a knee angle of 70° and a hip angle of 110°). In this position, with a 2-min rest interval, they were subsequently asked to complete two maximum voluntary isometric contractions (MVIC) that would be used to normalize EMG data (to whichever was higher, the highest MVIC result, or the highest amplitude value reached by the participant during the session). The patients performed a 2 s progressive ramp contraction and then maintained a maximum contraction effort for the next 3 s. Strong verbal encouragement was provided to motivate participants to reach their maximal effort.

After the MVICs, the arterial occlusion pressure (AOP) was determined. Resting arterial blood flow was measured for 30 s with a Doppler ultrasound scanner (U50, EdanUSA, San Diego, CA) on the exercising leg. 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, while occlusion was determined by their disappearance and absence. AOP measurement position was chosen to coincide with the exercise position. As such, participants were seated while an 11 cm wide, pneumatic cuff (SC10, Hokanson, Bellevue, WA) was placed on the most proximal portion of their thigh. The ultrasound probe was placed on the posterior tibial artery until the 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. Inflation procedure was based on that described by Crossley et al.[22] and was performed as follows. The cuff was inflated to 50 mmHg for 30 s and then deflated for 10 s. Each subsequent inflation was increased by 30 mmHg (30 s on, 10 s off) until occlusion was reached. Once occluded, the pressure was decreased by 10 mmHg-steps until evidence of blood flow reappeared. Occlusion pressure was then increased in 1 mmHg increments until blood flow was no longer detected. AOP was defined as the lowest cuff pressure at which arterial blood flow distally to the cuff was no longer detectable. Once AOP was determined, the cuff was deflated and participants rested quietly for 5 min, seated in the same machine used for the exercise.

Participants performed 3 repetitions of a seated knee extension exercise with external LL provided by elastic bands or without external load and with or without BFR. All 6 conditions were randomly (using a computer-based random number generator) performed. To assess the external LL, participants performed 2–3 sets of 2 reps and 60 s rest between sets were allowed until they rated a 2 on Borg's CR10 Scale.[23] For this purpose, yellow, red, green, blue, black, silver, and gold elastic band colors were available (TheraBand CLX, The Hygenic Corporation, Akron, OH, USA) and used in a progressive manner from the lowest elastic resistance available (i.e., yellow elastic band). This intensity was selected because it seems to correspond with the appropriate weight that is equivalent to 30% of 1RM[23] and is considered a light intensity.[24] Conditions consisted of 3 repetitions of seated knee extension using no external load and no BFR (NL00), no external load and light BFR [20% AOP (NL20)], no external load and moderate BFR [40% AOP (NL40)], external low load and no BFR [2 on Borg's CR10 Scale (LL00)], external low load with light BFR [2 on

Borg's CR10 Scale 20% AOP (LL20)], or external low load with moderate BFR [2 on Borg's CR10 Scale 40% AOP (LL40)]. Participants rested for 2 min between conditions, with the pneumatic cuff deflated.

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 pre-stretched to add approx. 25% of the initial length (initial length, 1.5 m). The exercises had to be performed within each participant's available knee joint ROM. 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 s for the concentric muscle action and 1.5 s for the eccentric muscle action during the exercise. The HDsEMG signal was recorded during exercise, with or without external LL and/or BFR, according to condition. For safety reasons, a pulse oximeter (CMS50D+, Contec Medical Systems Co., Ltd., Qinhuangdao, China) on the second toe was used during the entire session to ensure that blood flow was not completely halted by tissue edema.

After performing each condition, a researcher showed the Borg CR10 scale to the patients on which they were asked to score their Rate of Perceived Exertion (RPE). Then, they were asked about their pain intensity in the leg used to perform the exercise with an 11-point numerical pain scale. Subsequently, patients were asked about the degree of perceived tolerability using a five-point scale (i.e., very well tolerated = 5, tolerated = 4, neutral = 3, not well tolerated = 2 and not tolerated = 1). Having completed the experimental session, the ultrasound scan of the exercising leg was repeated to check for any possible muscle bleeds that might have developed during the session and the participants were asked to come in 72 h later to repeat the scan. Finally, 24, 48, 72 h and 1 week after the session, the participants were asked about any possible adverse effects (i.e., bleeding or pain intensity with the above-mentioned scale). Furthermore, participants were instructed to report any adverse effects arising during the week after the session.

2.3 | Data analyses

The HDsEMG signals acquired during the exercises were processed off-line using algorithms developed in MATLAB (The MathWorks Inc., Natick, Massachusetts, USA, version R2018b). The raw HDsEMG signals were amplified to obtain the EMG data in micro-Volts. Subsequently, differentiation of the 32-monopolar HDsEMG channels was carried out along the orientation of the fibers (columns of the grid) to obtain arrays of 7 columns x 4 rows of bipolar signals. A band pass filter (10–350 Hz) was then applied to each signal to eliminate low- and high-frequency noise. Subsequently, a visual inspection was carried out to discard signals with excess noise. A moving root-mean-squared (RMS) smoothing filter was applied to the bipolar HDsEMG signals, implemented with a 500 ms window width (250 ms backward and 250 ms forward) for each signal sample.

Once the signals were filtered, an automatic segmentation of the contractions was carried out from the maximum and minimum peaks of each signal. In each of the contractions, the maximum RMS activation percentage (amplitude) was obtained by normalizing the result to the highest RMS activation value reached by the participant during the session. After obtaining these normalized variables in each signal of the map (7 × 4 matrix signals), the average nRMS values were

TABLE 1 Demographic and descriptive data.

(*n* = 8)	Mean (SD)
Age (years)	44.5 (7.8)
Height (cm)	175.9 (8.2)
Body mass (kg)	80.4 (10.3)
FVIII[a] dose (IU/Kg)	20.1 (5.7)
FVIII dose (IU/week)	3850.0 (1476.5)
HJHS dominant knee	1.5 (2.1)
HJHS non-dominant knee	6.4 (6.9)
HJHS total lower limbs	20.0 (9.1)
Leisure-time physical activity n (%)	
Frequency	
Never	1 (12.5)
1 time/week	0 (0)
2–3 times/week	5 (62.5)
Almost daily	2 (25.0)
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 n (%)	
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)

Abbreviations: FVIII, coagulation factor VIII; HJHS, hemophilia Joint health score; 1RM, one repetition maximum.
[a]Coagulation factor dose before the experimental session.

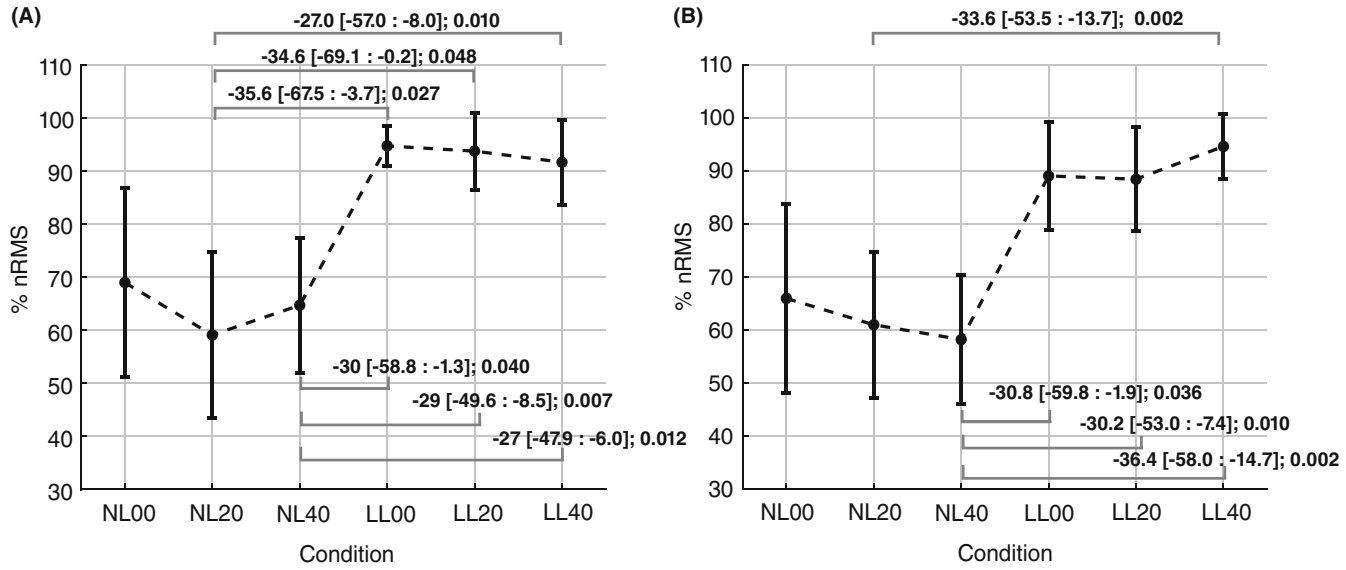

FIGURE 1 Normalized values of electromyographic amplitude (nRMS) for each condition. (A) VM, vastus medialis and (B) VL, vastus lateralis. Square brackets indicate conditions with significant differences (mean differences [95% confidence intervals]; *p* value). The points indicate the mean value, while the bars express the 95% confidence interval of the mean. LL00, external low load and no BFR; LL20, external low load with 20% AOP; LL40, external low load with 40% AOP; NL00, no external load and no blood flow restriction (BFR); NL20, no external load and 20% of arterial occlusion pressure (AOP); NL40, no external load and 40% AOP.

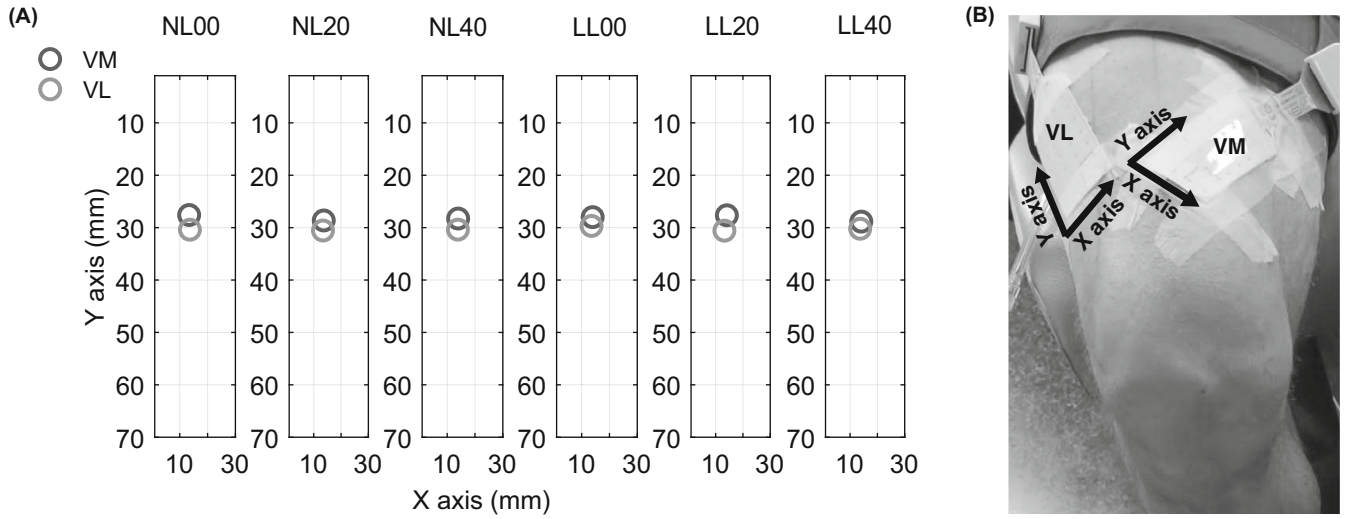

FIGURE 2 Mean values of normalized values of electromyographic amplitude (nRMS) maps centroid in each condition (A) and placement of the high-density surface electromyography electrodes (B). LL00, external low load and no BFR; LL20, external low load with 20% AOP; LL40: external low load with 40% AOP; NL00, no external load and no blood flow restriction (BFR); NL20, no external load and 20% of arterial occlusion pressure (AOP); NL40, no external load and 40% AOP; VM, vastus medialis; VL, vastus lateralis.

obtained, as well as the coordinates of the HDsEMG nRMS map centroid (x- and y-axis coordinates for the medial-lateral and cranial-caudal direction, respectively) and the modified entropy. The average nRMS HDsEMG from all channels on the matrix was used as a parameter of muscle activation, while the displacement of the centroid and variations in the modified entropy was used to assess HDsEMG activity spatial distribution. A higher modified entropy (from a maximum possible value of 4.81) represents less heterogeneity in the spatial distribution of nRMS values within the electrode matrix, ergo higher homogeneity, whilst a decrease in entropy indicates a decrease of homogeneity.[25]

In addition, muscle-fiber action potential conduction velocity (MFCV) was obtained using OT BioLab+ software (OT Bioelettronica, Torino, Italy, version 1.5.5.0). After the differentiation of the signals, three contiguous columns channels with high propagation were selected in each row. Subsequently, MFCV and cross-correlation

propagation was calculated using the Conduction Velocity Phase Delay algorithm. This algorithm estimates the delay between the signals through least squares in the frequency domain.[26] Finally, MFCV values with the highest cross-correlation propagation in each repetition were selected and averaged.

2.4 | Statistical analyses

All the results are expressed as mean and standard deviation (SD), unless otherwise specified. Before comparisons, all variables were tested for normality using the Shapiro–Wilk test. Statistical significance was set at $p < 0.05$.

Differences in nRMS, nRMS centroid, entropy, and MFCV between the 6 conditions (NL00, NL20, NL40, LL00, LL20, and LL40) were assessed with a one-way repeated-measures analysis of variance (ANOVA) for VM and VL muscles independently. If the repeated-measures ANOVA was significant, pairwise comparisons were performed with Bonferroni adjustments. RPE, pain intensity, and tolerability levels of all the experimental conditions are expressed as absolute values and percentages of patients. All statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA).

3 | RESULTS

A total of 8 PwH participated in the study. Demographic and leisure-time physical activity data are shown in Table 1. Most of the participants in this study had a history of resistance training and were

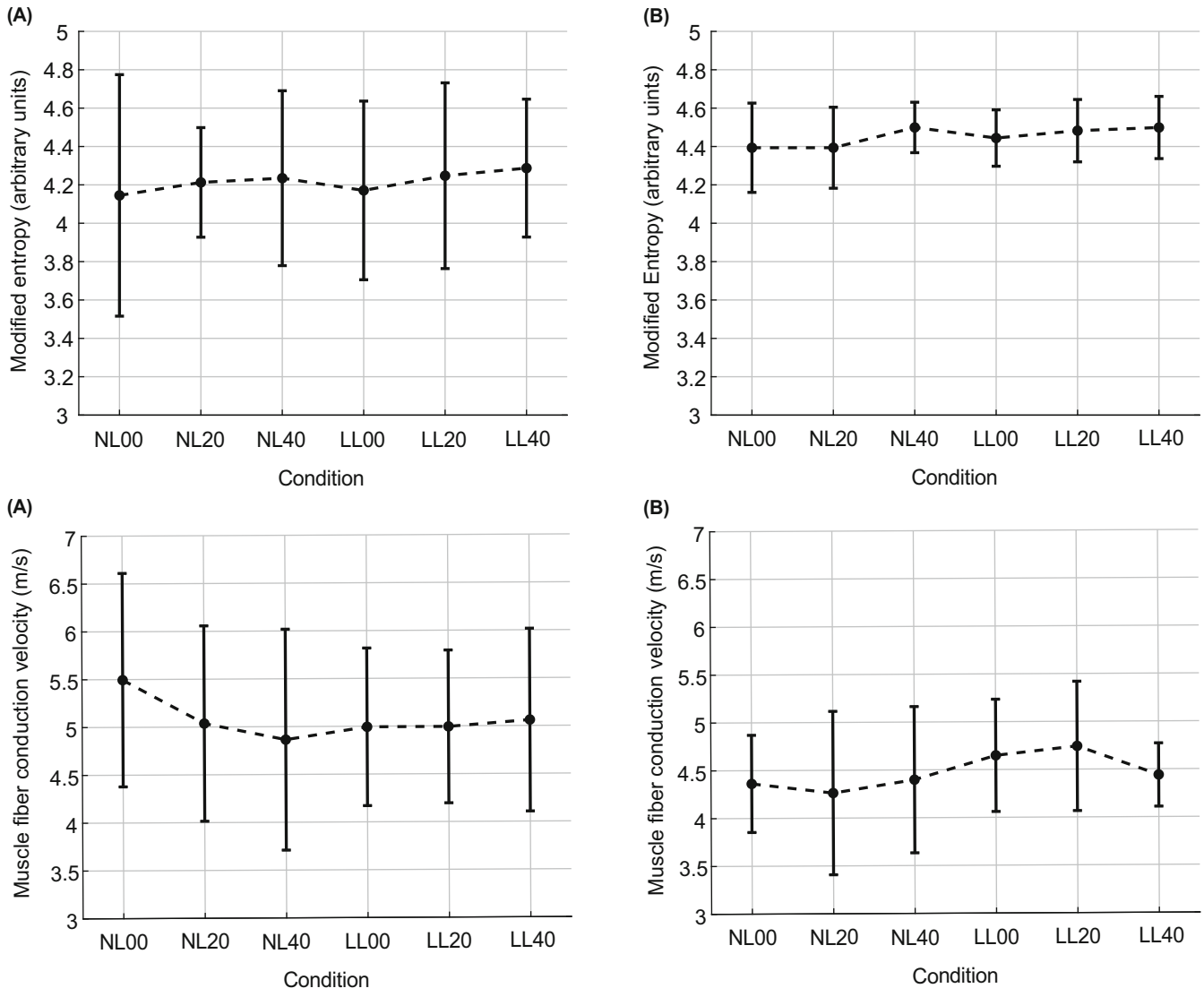

FIGURE 3 Modified entropy and muscle fiber-conduction velocity in each condition. (A) VM, vastus medialis and (B) VL, vastus lateralis. The points indicate the mean value, while the bars express the 95% confidence interval of the mean. LL00, external low load and no BFR; LL20, external low load with 20% AOP; LL40, external low load with 40% AOP; NL00, no external load and no blood flow restriction (BFR); NL20, no external load and 20% of arterial occlusion pressure (AOP); NL40, no external load and 40% AOP.

TABLE 2 Perceptual responses. Results expressed as absolute values and percentage of patients.

		NL00	NL20	NL40	LL00	LL20	LL40
RPE	0	6 (75%)	5 (62.5%)	3 (37.5%)	0 (0%)	0 (0%)	0 (0%)
	1	2 (25%)	2 (25%)	3 (37.5%)	2 (25%)	0 (0%)	0 (0%)
	2	0 (0%)	1 (12.5%)	1 (12.5%)	5 (62.5%)	2 (25%)	2 (25%)
	3	0 (0%)	0 (0%)	0 (0%)	1 (12.5%)	5 (62.5%)	3 (37.5%)
	4	0 (0%)	0 (0%)	1 (12.5%)	0 (0%)	0 (0%)	2 (25%)
	5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (12.5%)	1 (12.5%)
Pain	0	7 (87.5%)	8 (100%)	8 (100%)	7 (87.5%)	7 (87.5%)	7 (87.5%)
	1	1 (12.5%)	0 (0%)	0 (0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)
Tolerability	Very well tolerated	8 (100%)	7 (87.5%)	6 (75%)	7 (87.5%)	7 (87.5%)	6 (75%)
	Tolerated	0 (0%)	1 (12.5%)	2 (25%)	1 (12.5%)	1 (12.5%)	2 (25%)

Note: LL00, external low load and no BRF; LL20, external low load with 20% AOP; LL40, external low load with 40% AOP; NL00, no external load and no blood flow restriction (BFR); NL20, no external load and 20% of arterial occlusion pressure (AOP); NL40, no external load and 40% AOP; RPE, rate of perceived exertion (0–10).

engaged in physical activity for at least 2 days a week and lasting for more than 30 min.

No adverse effects were reported after the experimental session, nor were any signs of complications encountered during the post-session ultrasound scans. Figure 1 shows neuromuscular activation (mean %nRMS for VM and VL) during the six experimental conditions.

Regarding the displacement of the HDsEMG nRMS map centroid, ANOVA models showed no statistically significant differences ($p > 0.05$) between different experimental conditions in any of the muscles. Figure 2 depicts the mean locations for the HDsEMG nRMS map centroid values in the VM and VL muscles obtained in each experimental condition.

There were no statistically significant differences in modified entropy, nor in MFCV between the different experimental conditions for any of the muscles examined (Figure 3).

Table 2 shows perceptual responses to the acute exercise bouts performed. RPE increased with increasing occlusion pressure and load, respectively. However, pain intensity scorings remained low, and all patients showed high tolerability levels.

4 | DISCUSSION

The main findings of the present study were that[1] BFR at 20% or 40% AOP during knee extensions with low external resistance appeared to be safe, feasible, and without causing acute or delayed pain,[2] nRMS did not increase when adding BFR to a given loading condition,[3] there were no changes in MFCV and nRMS spatial distribution,[4] RPE increased with load and pressure while tolerability slightly decreased, and pain intensity did not change.

Our results support the notion that the difference in external loading of the knee extensors was most likely the cause for the observed differences in neuromuscular activation (nRMS EMG amplitudes). Accordingly, RPE increased with both load and cuff pressure. These findings do not align with the results reported by other studies in healthy individuals.[12,13] Nevertheless, greater activation of fibers without necessarily increasing the neural drive (number of motor neuron action potentials) has been reported in unrestricted (i.e., free-flow) low-intensity exercise to failure. Martinez-Valdes et al., observed that although participants reached maximal effort during a sustained isometric contraction at 30% of the maximum torque until failure, the discharge rate and muscle activation did not reach the level of a nonfatiguing contraction at 50% of the maximum torque.[27] Although none of our test conditions were fatiguing, it is possible that due to greater accumulation of metabolic by-products affecting muscle fiber-contractile capacity, BFR generates similar effects to low-intensity exercise to failure. Consequently, changes in central mechanisms (motor unit (MU) discharge rate and recruitment) should compensate for a decline in contractile properties in order to maintain torque output.[27] In addition, the lack of changes in nRMS values when adding BFR could arise from the fact that only 3 repetitions were performed in each condition to avoid fatigue. However, nRMS increases were evident when adding external load, so in this case, it could be plausible that BFR needs additional repetitions to increase nRMS. Furthermore, the lack of significant neural changes when adding BFR to the LL conditions may be due to a unique characteristic of LL-BFR. Since hypertrophy seems comparable between low-load BFR (LL-BFR) and high-load (HL) training,[28,29] it might be speculated that their neuromuscular responses differ. In this regard, Loenneke et al. proposed that the traditional paradigm of early strength gains due to neural adaptations followed by muscular hypertrophy is potentially reversed with LL-BFR training.[30] Further research seems warranted to investigate the manipulation of BFR cuff pressure in conjunction with different structures of resistance exercise, as higher volumes with possibly shorter rest periods could create a more potent acute neuromuscular response. Finally, differences in the level of arthropathy among patients, musculoskeletal fitness and training experience among other factors may also have contributed to the high variability reported in the current study.

In the presence of muscle fatigue, changes in regional MU recruitment patterns may occur, as characterized by a migration of the nRMS

HDsEMG map centroid during a fatiguing task.[31] As none of our test conditions were fatiguing in nature, this could explain the absence of a shift of the centroid. In the same vein, we did not observe changes through modified entropy, which is an entropy-based measure used to quantify HDsEMG activity spatial distribution. Elderly people[32] and individuals with Parkinson's disease[33] exhibit smaller changes in HDsEMG nRMS spatial distribution compared to young and healthy populations, respectively. Therefore, it would stand to reason that the spatial distribution of HDsEMG activity could possibly reflect a reduced ability to recruit MUs from different muscle regions, which has been associated with aging and disease status. As our findings cannot reflect a change in modified entropy, attention is drawn to the fact that our sample already presented a high mean entropy value. It can only be speculated that the increased homogeneity present among our participants could bear a relationship with the severity of their disease and reduced musculoskeletal fitness and resistance training, between other factors. Studies in various human skeletal muscles show that increases in the contraction level and contraction time may induce alterations in HDsEMG spatial distribution.[32,34] The fact that no spatial changes at different levels of effort and loads were observed in the present study may be related at least in part to a potential inability to recruit additional groups of MUs in our patients. MFCV results provide support to this observation. MFCV is a size-principle parameter that has been associated with MU recruitment.[35] A previous study reported similar MFCV values during dynamic contractions (cycle ergometer), with greater values for VM than VL, as presented herein.[36] However, contrary to our study, MFCV increased with exercise load. Altogether the lack of differences in spatial distribution and in MFCV suggest that our patients cannot activate different muscle regions or recruit additional MUs at different exercise intensities, signaling the possibility that the differences observed between NL and LL nRMS depended more on MU discharge rate than on additional MU recruitment. Finally, the low intensity of the exercise performed and the slow contraction speeds could also have a role in the absence of differences in the spatial distribution and/or MFCV.

Importantly, this is the first study to explore the use of BFR in PwH, and thus we evaluated not only the acute neuromuscular response, but also perceptual responses and adverse events since BFR training has been reported as an absolute contraindication in hemophilia.[37] Importantly, there were no adverse events up to the 1-week post experiment follow-up, according to our hypothesis, and we found that all conditions were well tolerated by this group of PwH patients, even if tolerability slightly decreased with increasing load and pressure, confirming our expectations. Moreover, perceived pain did not change, allowing to infer that LL-BFR may increase adherence to long-term exercise and make its therapeutic application of strong clinical relevance in PwH. This agrees with previous data from a study involving individuals with rheumatoid arthritis, which compared 12 weeks of LL-BFR lower-extremity training to traditional high-load training and found that pain scores improved only in the LL-BFR group, in the absence of any adverse events.[16] However, one of our participants reported very low pain (scoring 1) following the low-load exercise, although not a clinically relevant change.[38] This could be due to his state of arthropathy, lack of experience in strength training, or other psychological manifestations among other factors that might also have contributed.

This study has limitations. The number of participants was small, although HDsEMG has high reliability,[39] and measurements were conducted among patients with a rare disease. As we are only assessing some of the acute muscular responses to these exercise conditions performed with a low number of loaded repetitions (relative to a resistance training session), studies comparing a higher number of repetitions are necessary. However, the present approach has been widely used to test EMG differences across conditions, while avoiding the confounding effects of fatigue.[40,41] In addition, the low number of repetitions was considered optimal as a first step to introduce BFR training in PwH. Although we estimated exercise intensity by using a subjective method, previous studies have used this approach in PwH and found comparable EMG when RPE was matched during different exercise variations.[40,41] Moreover, a moderate to very strong association has been reported between RPE, actual loading, and normalized EMG amplitude.[42,43] In addition, most participants had a history of resistance training, so caution should be taken when generalizing regarding safety and feasibility to other PwH outside such a population. Specialists should, therefore, carefully assess the individual acute objective and subjective response as well as individual prophylactic coverage.

5 | CONCLUSIONS

In people with severe hemophilia undergoing prophylactic treatment, 3 consecutive repetitions of knee extension exercise performed with LL resistance and concurrent BFR at 20% or 40% AOP appear safe, feasible, and without causing acute or delayed increases in muscle pain. However, BFR by itself increased neither HDsEMG activity (nRMS or nRMS spatial distribution) nor fatigue (MFCV).

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. Each of the authors has read and concurs with the content in the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict interest.

DATA AVAILABILITY STATEMENT

The data are available writing to the corresponding author.

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