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Title:

Upper-Body Exercises With External Resistance Are Well Tolerated and Enhance Muscle Activity in People With Hemophilia

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Background. Conventional nonresisted therapeutic exercises for people with hemophilia involve a careful, low-intensity approach to avoid injuries. Externally resisted exercise is known to be highly efficient for increasing muscle strength in healthy adults, but its feasibility for people with hemophilia remains unknown.

Objective. The purpose of this study was to evaluate muscle activity during upper-body rehabilitation exercises with 2 types of external resistance and without external resistance (conventional) and to examine tolerability, kinesiophobia, and possible adverse effects derived from the session.

Design. This was a cross-sectional study.

Methods. Twelve people with hemophilia A/B (11 with severe hemophilia undergoing prophylactic treatment, 1 with mild hemophilia) participated. During the experimental session, participants completed the Tampa Scale of Kinesiophobia and performed 2 exercises—elbow flexion and shoulder abduction—with 3 conditions for each exercise: elastic resistance (externally resisted), free weights (externally resisted), and conventional nonresisted. Surface electromyography (sEMG) signals were recorded for the biceps brachii, triceps brachii, upper trapezius, and middle deltoid muscles. After the session, exercise tolerability and kinesiophobia were assessed. Adverse effects were evaluated 24 hours and 48 hours after the session.

Results. Externally resisted exercises provided greater muscle activity than conventional nonresisted therapeutic exercises. The exercises were generally well tolerated and there was no change in kinesiophobia following the session. No adverse effects were observed in the following days.

Limitations. Small sample size is the main limitation.

Conclusions. In people with severe hemophilia undergoing prophylactic treatment, elbow flexion and shoulder abduction exercises with external resistance at moderate intensities are feasible and provide greater muscle activity than nonresisted conventional exercises.

Hemophilia is an inherited bleeding disorder caused by an x-linked deficiency of coagulation factors VIII (hemophilia A) and IX (hemophilia B).¹ Hemophilia leads to spontaneous bleeding episodes, especially in the joints,² which cause synovitis and cartilage and bone destruction.³ To prevent this, prophylactic replacement of the deficient clotting factor is usually used.¹ However, joint disease affects 90% of people

with severe hemophilia.⁴ Elbows and shoulders are the most affected upper-body joints,¹ limiting the performance of basic daily living activities such as get dressed, driving or working. To avoid this, strengthening exercise is usually advised to people with hemophilia (PWH) with the aim of improving function in those with chronic arthropathy, during recovery after hemarthrosis or muscle bleed episodes, or to be protected from new bleeding episodes.⁵

As in pharmacologic treatments, the dosage of exercise is a key factor to generate desirable therapeutic results. The magnitude of the effort - i.e., exercise intensity - is one of the most important factors when designing training programs.⁶ Recently, Lobet and coworkers suggested that an ideal training session for PWH needs to include strengthening exercises with sufficient resistance to stimulate muscle anabolism and limit the muscle mass loss.⁷ However, there are still no clear recommendations about intensity, patient tolerance, and adverse effects. Thus, conventional non-resisted therapeutic exercises with low intensity still prevail.⁸ Prescribing exercise with intensities that are less stressful than daily life activities seems insufficient, as it will not make PWH capable of safely pulling, pushing, catching or carrying external loads, something that usually occurs during shopping, working or even playing with kids, therefore predisposing PWH to injuries and bleeding.

Surface electromyography has been widely used for years in the selection of proper exercises for prevention and rehabilitation.^{9,10} This method provides a non-invasive way of evaluating the neuromuscular system and the intensity of muscle contraction.⁹ For instance, previous EMG studies found that externally resisted exercises generally resulted in greater leg muscle activity than exercises performed without external

resistance other than the load of the body segment (conventional), either in healthy patients⁹ or in patients with chronic stroke.¹¹ However, to our knowledge, there are no studies comparing muscle activity during conventional prescribed exercises with/without external resistance in PWH. As a consequence, exercise selection for PWH has been routinely based on data from healthy subjects. Hence, evidence-based patient-specific advice is necessary for physical therapists to deliver a safe and effective treatment for PWH.

Two ways of providing external resistance for therapeutic strengthening programs is by using free weights or elastic bands. These types of resistance have demonstrated effectivity in providing high muscle activity during shoulder¹⁰ and elbow¹² exercises, with comparable levels when the exercises were intensity-matched. Nevertheless, such comparison between different types of resistance in PWH remains unknown. Evaluating different types of equipment and their tolerability during the same exercise can provide valuable information regarding which exercises should be prescribed in a therapeutic training program. Elastic band-based exercises are especially interesting in this population, since they can minimize or avoid sudden impacts or accidents occurring with traditional free weights, likely helping in preventing bleedings, self-injuries or possible fear of training. Not in vain, the most common mechanisms of injury during strength training are weights being dropped on the person (65.5%), a body part being smashed/crushed between weights (10.4%) and hitting one self (9.8%).¹³

The aim of the present study was to evaluate muscle activity with 2 types of external resistance (elastic and free-weight) and without external resistance (conventional),

during 2 common upper-body rehabilitation exercises (elbow flexion and shoulder abduction), as well as to test tolerability of these conditions in PWH. A secondary aim was to assess possible changes in kinesiophobia and possible adverse effect derived from the experimental session. We hypothesized that externally resisted exercises would provide greater muscle activity than conventional counterparts, without EMG differences between free-weight and elastic-resisted exercises.

[H1] Methods

[H2] Participants

Patients above 18 years old, diagnosed with hemophilia and visiting a local hospital during 2017 were considered candidates for the present study and were asked to participate. Participants were excluded if they had undergone a joint replacement in the previous year, if they had joint or muscle bleeding in the last 3 months or if they had any medical condition in which exercise was contraindicated. A total of 12 patients (10 patients with severe hemophilia A and 1 patient with severe hemophilia B; 1 patient with mild hemophilia A) voluntarily participated in the study, which was performed during June 2017. Most of the patients were performing exercise at least once a week when they participated in the study. All participants were informed in advance about the purpose and content of the investigation. Written informed consent was obtained from all individual participants included in the study. The study conformed to the Declaration of Helsinki and was approved by the University of Valencia Ethical Committee (H1461147538087).

[H2] Procedures

Each participant took part in one experimental session. Several restrictions were imposed on the volunteers: no food, drinks or stimulants (e.g. caffeine) to be consumed 2 hours before the sessions and no physical activity more intense than daily activities 24 hours before the exercises. They were instructed to sleep at least 7-8 hours the night before data collection. All measurements were made by the same 3 investigators and were conducted in the same facility at the University. The 3 investigators had previous experience with EMG measurements and were: an exercise physiologist (PhD) and Strength & Conditioning Specialist (CSCS), an exercise physiologist and physical therapist (PhD) and a doctoral student (MsC physical therapist).

Two days before the experimental session, the participants received a video with the exercises that had to be performed in order to visualize the proper exercise technique. The participants with severe hemophilia had the experimental session 1-2 hours after receiving the prophylactic treatment. During the experimental session, height (IP0955, Invicta Plastics Limited, Leicester, England) and body mass (Tanita model BF- 350, Tokyo, Japan) were obtained. Secondly, the Haemophilia Joint Health Score 2.1 (HJHS 2.1) was used to evaluate joint health in the domain of body structure and function. The HJHS provides joint specific scores ranging from 0 to 20 (higher scores reflect worse condition).¹⁴ Afterwards, the Tampa Scale for kinesiophobia (TSK-11)¹⁵ was used to assess fear of movement beliefs and analyze their possible changes through the experimental session. This questionnaire was chosen since people with hemophilia may have increased fear of movement due to repeated bleeding episodes or injuries,

especially considering the general absence of strength training experience at moderate intensities. Subsequently, subjects answered a short questionnaire about leisure-time physical activity¹⁶ and their resistance training experience. Later, the EMG protocol started with the preparation of subjects' skin, followed by electrode placement, maximum voluntary isometric contraction (MVIC) collection and exercise performance. Hair was shaved from the skin overlying the muscles of interest and the skin was then cleaned by rubbing with cotton wool dipped in alcohol for the subsequent electrode placement. Electrodes were placed according to SENIAM recommendations¹⁷ on the biceps brachii, triceps brachii, upper trapezius and middle deltoid on the dominant side of the body. Pre-gelled bipolar silver/silver chloride surface electrodes (Blue Sensor M-00-S, Medicotest, Olstykke, Denmark) were placed with an inter-electrode distance of 2 cm. The reference electrode was placed between the active electrodes, approximately 10 cm away from each muscle, according to the manufacturer's specifications. All signals were acquired at a sampling frequency of 1kHz, amplified and converted from analog to digital. To acquire the surface EMG signals produced during exercise, an ME6000P8 (Mega Electronics, Ltd., Kuopio, Finland) biosignal conditioner was used. All records of myoelectrical activity (in microvolts) were stored on a hard drive for later analysis. Prior to the exercise performance described below, one MVIC of 5 sec was performed for each muscle. Participants performed a non-maximal practice trial to ensure that they understood the task. They were asked to exert progressive contraction during 2 seconds and 3 seconds of maximal contraction without reaching a pain intensity greater than 4 of 10 on a numerical pain rating scale. Verbal encouragement was provided to motivate all participants to achieve maximal muscle activity. Positions during the MVICs were based on standardized muscle testing

procedures for the biceps brachii and triceps brachii¹⁸ and for the upper trapezius and middle deltoid.¹⁹ All the MVICs were performed against a fixed immovable resistance (i.e., a fixed bar). Specifically, the MVIC positions were: forearm flexion and extension with elbows at 90° in a seated position with erect posture and no back support for the biceps brachii and triceps brachii respectively and deltoid abduction at 90° in a seated position with erect posture and no back support for the upper trapezius and middle deltoid.

Participants performed 2 exercises (shoulder abduction and elbow flexion) (Fig. 1) with 3 different conditions: 2 types of external resistance (elastic bands and free weights) and without external resistance (conventional). All the 6 conditions were randomly performed for each participant. Before starting each exercise, participants performed 6 light intensity reps to warm-up and then 2-3 additional sets of 3 reps (with EMG recording) and 1-min rest between sets were allowed until they rated a 6 on Borg's CR10 Scale.²⁰ Only the set where the participants reached the desired intensity was stored for later EMG analysis. This intensity was selected because it seems to correspond with the appropriate weight that allows performing 12 reps,²⁰ which is also equivalent to 67% of 1RM²¹ and considered a moderate intensity⁶. After each condition, participants were asked to rate how tolerable/not tolerated was each individual condition, according to the following scale: very tolerated, tolerated, neutral, little tolerated and not tolerated. The participants were positioned with feet at shoulder distance during the 2 exercises. To achieve adequate exercise intensity during the elastic-resisted conditions, the elastic bands were pre stretched to approx. 50% of the initial length (initial length, 1.9 m) and then different bands were added when needed to reach the desirable intensity. For this purpose, red, blue, black, silver

and gold elastic band colors were available (TheraBand CLX, The Hygenic Corporation, Akron, OH, USA), alone or combined in parallel. During the free-weight conditions, common iron adjustable dumbbells were used, with several available weight plates of 0.5Kg, 1Kg and 2Kg.

During the exercises, the participants stood upright holding the dumbbells or elastic bands to the side. In case of the shoulder abduction exercise, participants abducted the shoulder joint until the upper arm was slightly above horizontal¹⁰ while the elbows were static, with a slightly flexed position (approximately 5°) during the entire ROM. The exercises had to be performed with subject's available ROM, as close as possible to the original exercise technique. During the exercise performance, they were asked to use minimal lower body and trunk movement and to perform the exercise without sudden jerks or acceleration for 3 consecutive repetitions. A metronome was used to standardize movement velocity at 1.5-s rate for descent and 1.5-s rate for ascent and feedback was provided to correct the subjects if any variance was observed. A trial was discarded and repeated if participants were unable to perform the exercise properly. After finishing the EMG measurements, the TSK-11 was re-assessed.

Finally, 24 and 48 hours after the session, participants were asked by text message (sms) about possible adverse effects (bleedings, pain). In addition, they were asked to inform if any adverse event occurred during the following week.

Bayesian post hoc estimation of individualized pharmacokinetics values (half-life ($t_{1/2}$) and peak level) was obtained using the Web Accessible Population Pharmacokinetic Service for Hemophilia (WAPPS-Hemo tool).²²

[H2] Data analysis

EMG data processing was performed using custom-made algorithms implemented in MATLAB (The MathWorks, Inc., Natick, Massachusetts, USA, version R2015a) software. During later analysis, all raw EMG signals obtained during the exercises were digitally filtered, consisting of (1) high-pass filtering at 10 Hz and (2) a moving root-mean square (RMS). The RMS routine was performed using a smoothing filter/window of 500 ms (250 ms backwards and 250 ms forward from each data point) across the entire signal (i.e., across all contractions). For each individual muscle, peak RMS EMG of the 3 repetitions performed at each level was determined, and the average value of these 3 repetitions was then normalized to the maximal RMS EMG obtained during the MVICs collection.

An a priori power analysis was conducted in G*Power (3.1.9.2 version) software to calculate the sample size. With the present study design, assuming a medium effect size ($f = 0.30$), $\alpha = 0.05$, power = 0.80 and correlation among repeated measures of 0.50, the total sample size required is 11 participants.

[H3] Statistical analyses

A linear mixed model (Proc Mixed, SAS version 9.4, SAS Institute, Cary, NC, USA) was used to determine whether differences existed between conditions (conventional, elastic resistance, and free-weights) for each respective muscle. Normalized EMG was the dependent variable. Participant was included in the statistical model as a random factor. Values are reported as least square means (95% CI) unless otherwise stated. Normality of EMG and Kinesiophobia data was checked using the Shapiro-Wilk test and

pre-post differences in the total score of this outcome were evaluated using paired-sample *t* test. *P* values <.05 were considered statistically significant.

[H2] Role of the Funding Source

This study was supported by a grant (H15-29504) from Baxalta, now part of Shire. The funders played no role in the design, conduct, or reporting of the study.

[H1] Results

Five of the 12 participants (41.7%) received prophylactic treatment 3 times a week, 5 (41.7%) twice a week, one (8.3%) daily and one (8.3%) on demand treatment. Table 1 shows complete demographic and descriptive data of participants and Figure 2 depicts individualized pharmacokinetics values of participants with severe hemophilia A. Pharmacokinetics values of the participant with severe hemophilia B (patient #4) are: FIX dose = 56.0 IU/Kg, FIX peak = 44.3 IU/dL and half-life = 13.0 hours. Basal level of the participant with mild hemophilia A (patient #10) is 8 IU/dL. Regarding bleeding history, 11 participants reported an annual joint bleeding rate (AJBR) in elbows of 0, and only patient #6 showed an AJBR of 1 (in the left elbow).

When questioned about their leisure-time activity, two-thirds of participants reported exercising at least twice per week and only 2 had previous experience in strength training.

No adverse effects occurred at 24 and 48 hours following the sessions or during the week after the experimental session. All externally resisted conditions provided greater EMG activity than the conventional variation. During the elbow flexion exercise, the biceps brachii was similarly activated during the elastic resistance and

free-weight conditions and both variations provided greater activity than the conventional condition. The triceps brachii showed no differences during the different elbow flexion conditions. During the shoulder abduction movement, both middle deltoid and upper trapezius achieved comparable activity at the 2 externally resisted conditions, being different from the conventional variation. Complete results with numeric values are reported in Table 2.

The shoulder abduction exercise was equally considered “very tolerated” with elastic bands or with free weights (53.9%). In addition, 46.2% considered “tolerable” this exercise performed with free weights while the elastic band version was considered “tolerable” by 38.5% and “neutral” by 7.7% of the participants. The elbow flexion exercise was equally considered “very tolerated” by 46.2%, “tolerable” by 46.2% and “neutral” by 7.7% of participants. Figure 3 shows complete tolerability data. In regard of the kinesiophobia results, there were no statistical differences ($P = .9$) between the pre-session (mean: 26.8 [5.6]) and the post-session (mean = 26.7 [7.2]) measures.

[H1] Discussion

The main finding of the present study is that externally resisted exercise is both safe and efficient in activating upper-body muscles among PWH undergoing prophylactic treatment.

No other studies evaluating neuromuscular activity during upper-body exercises in PWH exist. Our findings are similar to previous literature in healthy subjects. For instance, a previous study showed that machine-based or free-weight exercises yielded greater lower extremity activity in the agonist muscles than conventional exercises in healthy adults.⁹ A more recent study in patients with chronic stroke also

found that machine-based exercises generally yielded greater activity in the leg muscles than other conventional body-weight exercises, either in the non-paretic leg or in the paretic leg.¹¹ Andersen et al.¹⁰ compared the use of free weights and elastic resistance during common shoulder rehabilitation exercises (with shoulder abduction exercise between others) and concluded that both training methods can be comparable in terms of muscle activity and perceived exertion in healthy women when intensity is adequately matched. This latter result in healthy adult women is comparable to the present result in PWH. Likewise, another study in healthy adults reported that elastic-resisted elbow flexion resulted in similar biceps brachii activity compared with a similar free-weight exercise.¹² Thus, results from studies using healthy subjects may also be valid for PWH, although more studies are needed to confirm this. It is also worth mentioning that during the elbow flexion exercise, the antagonist muscle (triceps brachii) showed comparable EMG values among the 3 conditions. Hence, it seems that the triceps muscle had greater efficiency during the externally resisted exercises, being equally relaxed during the agonist contraction in the 3 different conditions, but at the same time, allowing greater agonist force production and activity during the externally resisted conditions. In addition, the middle deltoid yielded greater activity during the elbow flexion exercise when was externally resisted, increasing its role as synergist. Something similar occurred with the upper trapezius, despite this muscle only showed statistical difference during the elbow flexion when the exercise was performed with elastic band in comparison with the conventional exercise mode. However, in any case any of these muscles reported a difference between the 2 externally resisted conditions during the elbow flexion. The same occurred regarding the assisting role of the biceps and triceps brachii during the

shoulder abduction exercise, where there was no difference between the externally resisted conditions and only the triceps brachii showed difference between the externally resisted and conventional conditions. This may have happened due to the triceps' attributed role in stabilizing the abducted glenohumeral joint by resisting inferior displacement of the humeral head.²³ Low intensities (e.g., 30%–50% of one-repetition maximum) are recommended to improve muscular endurance^{24,25} and can be effective in untrained participants for improving strength, whereas higher intensities maximize strength^{24,25} and neural adaptations.²⁴ Even though previous studies have considered that exercises should at least reach 60%MVIC to promote effective muscle strength gains,⁹ it is difficult to establish whether different EMG levels can be used to infer strength gains or hypertrophy.²⁶ However, it is usually accepted that greater neural drive would more effectively promote strength adaptations.^{9,10} Importantly, biomechanically similar exercises providing similar muscle activity have resulted in similar muscle strength gains after a training period.²⁷ Not in vain, agonist EMG was found to be the primary predictor of strength changes, accounting for more than half of the total variance after 12 weeks of training.²⁸

When designing proper exercise programs, a relevant aspect is to ensure adherence of patients. A variable linked with adherence is patient satisfaction.²⁹ In an exercise program, the perceived tolerability can indicate the level of satisfaction with the exercise, providing a relevant feedback to specialists in order to select the most optimal exercise for each individual case. This could be especially relevant for PWH due to the high degree of individualization required. Our results show that conventional exercises were the most tolerated, something that could be expected due to their lower intensity. However, both externally resisted methods were well

tolerated, with equal rates for the elbow flexion and almost equal for the shoulder abduction exercise. Accordingly, none of the participants rated the externally resisted exercises as "not tolerated". Nevertheless, we would like to encourage physical therapists to evaluate exercise tolerability of each individual patient, e.g. by using a simple tolerability-scale as in the present study.

Fear of movement to minimize discomfort or pain results in an avoidance behavior pattern which engages in a vicious cycle increasing muscle disuse, disability and probability of depression.³⁰ The consequences of muscle disuse due to fear could be especially relevant in PWH, where muscle atrophy and joint instability leads to chronic pain and a greater bleeding risk³¹ and accelerates joint degeneration, resulting in greater pain and functionality loss. Importantly, the practice of both externally resisted exercises did not result in greater fear of movement after the experimental session, which together with the absence of acute adverse effects after the experimental session supports the notion that training sessions in PWH at the prescribed intensity could be used. However, future long-term studies must be conducted to test this hypothesis.

A limitation in relation to generalizability of the current study is the small sample size, although the number of participants was sufficient in accordance with an a priori power analysis. Importantly, our study provides novel data about safety and efficiency of upper-body exercises commonly advised to PWH. The fact that adverse effects were only self-monitored by the participants could have limited finding subclinical bleeds or minor adverse events. However, it seems that performing the exercises 1-2 hours after prophylactic treatment (in the case of severe hemophilia), with a coverage factor near

the peak did not cause major adverse events. EMG cross-talk may be present, especially in the shoulder muscles, although electrode placement and EMG procedures were performed according to standardized guidelines which ensures reduced cross-talk. Another limitation could be the absence of familiarization with the participants before the experimental session. However, in view of the results, we could assume that PWH are able to match intensity between externally resisted exercises in only one session, which can increase applicability at the clinical practice. The general absence of resistance training experience in our participants could be considered a positive aspect of this study, providing greater generalizability since these individuals could have less tolerability and greater fear of movement during strength training as well as adverse events. Future studies should conduct longitudinal interventions using these exercises to assess their efficacy in improving physical function and work ability.

[H1] Conclusions

Greater agonist muscle activity can be achieved by using external resistance in comparison with conventional non-resisted elbow flexion and shoulder abduction, without difference between both external types of resistance. Patients with severe hemophilia undergoing prophylactic treatment can tolerate elbow and shoulder exercises with moderate resistance on the same day they receive their prophylactic dose without increasing fear of movement and without late adverse effects. Data provided can be used in prevention/rehabilitation programs targeting the elbow and shoulder joints in PWH, where either free weights or elastic resistance can be used to provide a greater neural drive to muscle than with conventional exercises. The use of

elastic resistance seems to be a promising alternative to other practices in PWH due to their portability and to avoid possible impacts.

Author Contributions and Acknowledgments

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The authors thank the participants for their contribution to the study.

Ethics Approval

The study conformed to The Declaration of Helsinki and was approved by the University of Valencia Ethical Committee (H1461147538087). All participants were informed in advance about the purpose and content of the investigation. Written informed consent was obtained from all individual participants included in the study.

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Disclosures and Presentations

The authors completed the ICJME Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

Data reported in the present study are part of a research project investigating muscle activity during different exercises in people with hemophilia. This article adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

References

- 1 Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1–e47.
- 2 Stephensen D, Tait RC, Brodie N, et al. Changing patterns of bleeding in patients with severe haemophilia A. *Haemophilia*. 2009;15:1210–1214.
- 3 van Vulpen LF, Mastbergen SC, Lafeber FP, Schutgens RE. Differential effects of bleeds on the development of arthropathy: basic and applied issues. *Haemophilia*. 2017;23:521–527.
- 4 Manco-Johnson MJ, Pettersson H, Petrini P, et al. Physical therapy and imaging outcome measures in a haemophilia population treated with factor prophylaxis: current status and future directions. *Haemophilia*. 2004;10 Suppl 4:88–93.
- 5 Strike K, Mulder K, Michael R. Exercise for haemophilia. *Cochrane Database Syst Rev*. 2016;12:CD011180.
- 6 Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43:1334–1359.
- 7 Lobet S, Lambert C, Hermans C. Stop only advising physical activity in adults with haemophilia... prescribe it now! The role of exercise therapy and nutrition in chronic musculoskeletal diseases. *Haemophilia*. 2016;22:e554–e556.
- 8 Mulder K. *Exercises for People With Hemophilia*. Montreal, Quebec, Canada: World Federation of Hemophilia; 2006.

- 9 Andersen LL, Magnusson SP, Nielsen M, Haleem J, Poulsen K, Aagaard P. Neuromuscular activation in conventional therapeutic exercises and heavy resistance exercises: implications for rehabilitation. *Phys Ther.* 2006;86:683–697.
- 10 Andersen LL, Andersen CH, Mortensen OS, Poulsen OM, Bjørnlund IB, Zebis MK. Muscle activation and perceived loading during rehabilitation exercises: comparison of dumbbells and elastic resistance. *Phys Ther.* 2010;90:538–549.
- 11 Vinstrup J, Calatayud J, Jakobsen MD, et al. Electromyographic comparison of conventional machine strength training versus bodyweight exercises in patients with chronic stroke. *Top Stroke Rehabil.* 2017;24:242–249.
- 12 Aboodarda SJ, Hamid MS, Muhamed AM, Ibrahim F, Thompson M. Resultant muscle torque and electromyographic activity during high intensity elastic resistance and free weight exercises. *Eur J Sport Sci.* 2013;13:155–163.
- 13 Kerr ZY, Collins CL, Comstock RD. Epidemiology of weight training-related injuries presenting to United States emergency departments, 1990 to 2007. *Am J Sports Med.* 2010;38:765–771.
- 14 Hilliard P, Funk S, Zourikian N, et al. Hemophilia joint health score reliability study. *Haemophilia.* 2006;12:518–525.
- 15 Tkachuk GA, Harris CA. Psychometric properties of the Tampa Scale for Kinesiophobia-11 (TSK-11). *J Pain.* 2012;13:970–977.
- 16 Kurtze N, Rangul V, Hustvedt BE, Flanders WD. Reliability and validity of self-reported physical activity in the Nord-Trøndelag Health Study: HUNT 1. *Scand J Public Health.* 2008;36:52–61.
- 17 Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G. Development of recommendations for SEMG sensors and sensor placement procedures. *J Electromyogr Kinesiol.* 2000;10:361–374.
- 18 Kendall FP, McCreary EK, Provance PG, Rodgers MM, Romani WA. *Muscles: Testing and Function With Posture and Pain.* 5th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005.
- 19 Ekstrom RA, Soderberg GL, Donatelli RA. Normalization procedures using maximum voluntary isometric contractions for the serratus anterior and trapezius muscles during surface EMG analysis. *J Electromyogr Kinesiol.* 2005;15:418–428.
- 20 Buckley JP, Borg GA. Borg's scales in strength training; from theory to practice in young and older adults. *Appl Physiol Nutr Metab.* 2011;36:682–692.
- 21 Haff G, Triplett NT. *Essentials of Strength Training and Conditioning.* 4th ed. Champaign, IL: Human Kinetics; 2016.

- 22 Iorio A, Keepanasseril A, Foster G, et al. Development of a web-accessible population pharmacokinetic service-Hemophilia (WAPPS-Hemo): study protocol. *JMIR Res Protoc*. 2016;5:e239.
- 23 Moore KL, Dalley AF, Agur AM. *Clinically Oriented Anatomy*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins Health; 2014.
- 24 Jenkins ND, Miramonti AA, Hill EC, et al. Greater neural adaptations following high- vs low-load resistance training. *Front Physiol*. 2017;8:331.
- 25 Schoenfeld BJ, Peterson MD, Ogborn D, Contreras B, Sonmez GT. Effects of low- vs high-load resistance training on muscle strength and hypertrophy in well-trained men. *J Strength Cond Res*. 2015;29:2954–2963.
- 26 Vigotsky AD, Halperin I, Lehman GJ, Trajano GS, Vieira TM. Interpreting signal amplitudes in surface electromyography studies in sport and rehabilitation sciences. *Front Physiol*. 2017;8:985.
- 27 Calatayud J, Borreani S, Colado JC, Martin F, Tella V, Andersen LL. Bench press and push-up at comparable levels of muscle activity results in similar strength gains. *J Strength Cond Res*. 2015;29:246–253.
- 28 Balshaw TG, Massey GJ, Maden-Wilkinson TM, et al. Changes in agonist neural drive, hypertrophy and pre-training strength all contribute to the individual strength gains after resistance training. *Eur J Appl Physiol*. 2017;117:631–640.
- 29 Weingarten SR, Stone E, Green A, et al. A study of patient satisfaction and adherence to preventive care practice guidelines. *Am J Med*. 1995;99:590–596.
- 30 Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*. 2000;85:317–332.
- 31 Hilberg T, Czepa D, Freialdenhoven D, Boettger MK. Joint pain in people with hemophilia depends on joint status. *Pain*. 2011;152:2029–2035.





Figure 1. Illustrative example of the 2 exercises performed with elastic resistance: 1a and 1b show the initial/final phases of the elbow flexion exercise, whereas 1c and 1d show the initial/final phase of the shoulder abduction exercise.

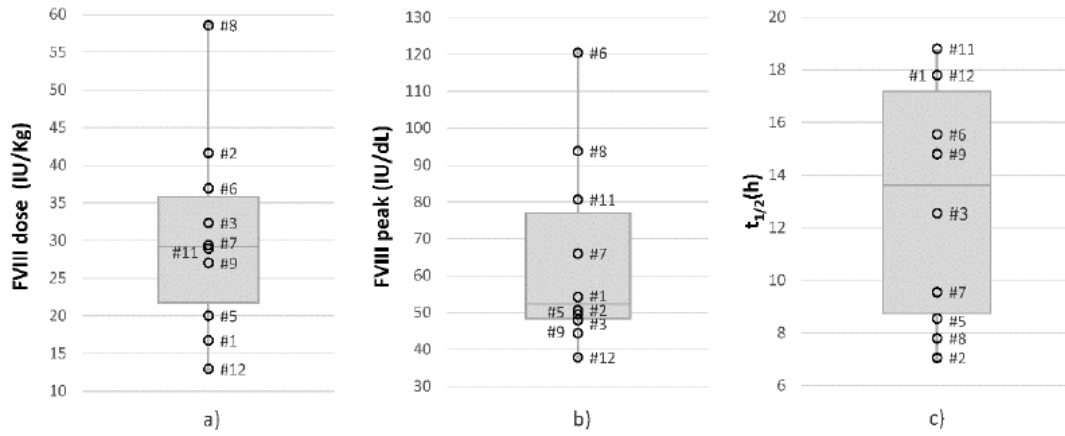


Figure 2. Boxplots of pharmacokinetics variables for people with severe hemophilia A: (a) FVIII dose, (b) FVIII peak, and (c) half-life ($t_{1/2}$).

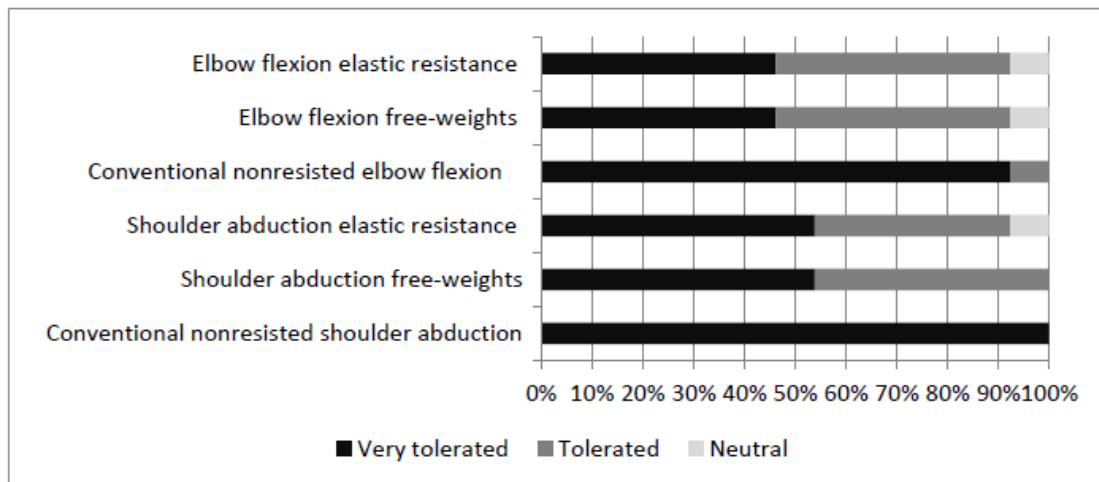


Figure 3. Participant tolerability during each exercise and condition.

Table 1. Demographic and Descriptive Data.^a

	Mean	SD	Minimum	Maximum
Age (years)	35.2	8.8	21.0	47.0
Height (cm)	172.8	8.6	157.0	187.0
Body mass (kg)	76.7	17.5	51.1	116.6
HJHS dominant	3.0	4.1	0.0	11.0
HJHS nondominant	5.0	4.8	0.0	13.0
Pettersson dominant	3.8	4.7	0.0	11.0
Pettersson nondominant	5.2	4.8	0.0	13.0

^a HJHS = Hemophilia Joint Health Score.

Table 2. Least Square Means and 95% CI of Normalized Electromyography Signals

Muscle		Mean	95% CI		Between-Exercise Differences ^a
Biceps brachii	1. Conventional nonresisted elbow flexion	24	0	49	2, 3
	2. Elbow flexion free weights	60	35	85	1
	3. Elbow flexion elastic resistance	50	25	75	1
	4. Conventional nonresisted shoulder abduction	11	1	20	-
	5. Shoulder abduction free weights	20	10	30	-
	6. Shoulder abduction elastic resistance	23	13	33	-
Triceps brachii	1. Conventional nonresisted elbow flexion	12	5	18	-
	2. Elbow flexion free weights	12	6	19	-
	3. Elbow flexion elastic resistance	17	11	24	-
	4. Conventional nonresisted shoulder abduction	11	3	19	5, 6
	5. Shoulder abduction free weights	23	15	31	4
	6. Shoulder abduction elastic resistance	27	19	35	4
Middle deltoid	1. Conventional nonresisted elbow flexion	3	1	7	2, 3
	2. Elbow flexion free weights	9	5	13	1
	3. Elbow flexion elastic resistance	10	6	14	1
	4. Conventional nonresisted shoulder abduction	33	18	48	5, 6
	5. Shoulder abduction free weights	68	53	83	4
	6. Shoulder abduction elastic resistance	73	58	88	4

Upper trapezius	1. Conventional nonresisted elbow flexion	6	3	15	3
	2. Elbow flexion free weights	18	9	27	-
	3. Elbow flexion elastic resistance	21	12	30	1
	4. Conventional nonresisted shoulder abduction	22	7	37	5, 6
	5. Shoulder abduction free weights	52	37	67	4
	6. Shoulder abduction elastic resistance	54	39	69	4

^aNumbers denote statistical differences between the exercises for the same muscle.