ORIGINAL ARTICLE

Neuromuscular Electrical Stimulation Training: A Safe and Effective Treatment for Facioscapulohumeral Muscular Dystrophy Patients

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ABSTRACT. Colson SS, Benchortane M, Tanant V, Faghan J-P, Fournier-Mehouas M, Benaïm C, Desnuelle C, Sacconi S. Neuromuscular electrical stimulation training: a safe and effective treatment for facioscapulohumeral muscular dystrophy patients. Arch Phys Med Rehabil 2010;91:697-702.

Objective: To investigate the feasibility, safety, and effectiveness of neuromuscular electrical stimulation (NMES) strength training in facioscapulohumeral muscular dystrophy (FSHD) patients.

Design: Uncontrolled before-after trial.

Setting: Neuromuscular disease center in a university hospital and a private-practice physical therapy office.

Participants: FSHD patients (N=9; 3 women, 6 men; age 55.2±10.4y) clinically characterized by shoulder girdle and *quadriceps femoris* muscle weakness.

Interventions: Patients underwent 5 months of strength training with NMES bilaterally applied to the deltoideus, trapezius transversalis, vastus lateralis, and vastus medialis muscles for five 20-minute sessions per week.

Main Outcome Measures: Plasma creatine kinase (CK) activity; scores for pain and fatigue on visual analog scales (VAS), manual muscle testing (MMT), maximal voluntary isometric contraction (MVIC), 6-minute walking tests (6MWT), and self-reported changes in daily living activities.

Results: NMES strength training was well tolerated (CK activity and pain and fatigue scores on VAS were not modified). Most of the muscle functions (shoulder flexion and extension and knee extension) assessed by MMT were significantly increased. MVIC of shoulder flexion and abduction and the 6MWT distance were also improved.

Conclusions: In FSHD, NMES strength training appears to be safe with positive effects on muscle function, strength, and capacity for daily activities.

Key Words: Isometric contraction; Quadriceps muscle; Rehabilitation; Shoulder.

AUTOSOMAL DOMINANT facioscapulohumeral muscular dystrophy is one of the most common inherited myopathies.[1,2] It is associated with a deletion of an integral number of 3.3Kb tandem repeats, termed D4Z4, located on 4q35.[3] In unaffected persons, the D4Z4 array consists of 11 to 150 repeats, whereas FSHD patients carry 1 to 10 repeats. The extent of the D4Z4 repeat deletion has been roughly correlated with the clinical severity.[4]

The disease is typically characterized by selective and often asymmetric weakness of the facial and shoulder girdle muscles, eventually spreading to pelvic, abdominal, humeral, and anterior foreleg muscles.[5] The clinical phenotype varies considerably, but muscle weakness is generally not severe because only 10% to 20% of patients become wheelchair-bound, and life expectancy is almost normal.[6]

To date, no therapy is available for FSHD patients, mainly because of the uncertain pathophysiology of the disease.[7] However, nonpharmacologic interventions like physical exercise help to maintain and/or improve strength and limit functional losses. Indeed, FSHD patients tend to gradually reduce daily activities in response to their progressive muscle weakness, making these activities increasingly more difficult to carry out. This sedentary lifestyle can cause a "debilitative cycle," with cardiorespiratory and neuromuscular deconditioning aggravating the muscle deficiencies.[8] In the past, physical exercise and muscular strengthening were not recommended for patients with muscular dystrophies because of the hypothetical risk that overuse would induce rhabdomyolysis[9] and precipitate weakness. However, recent studies have indicated the safety of moderate aerobic training programs and the effectiveness of improving aerobic and muscular capacities in order to maintain patient autonomy.[10-14] These training programs improve global fitness but unfortunately have limited applicability because they cannot be followed by myopathic patients with more severe muscular weakness and are not designed to build strength in targeted muscles.

List of Abbreviations

CK	creatine kinase
ES	effect size
FSHD	facioscapulohumeral muscular dystrophy
MMT	manual muscle test
MVIC	maximal voluntary isometric contraction
6MWT	six-minute walk test
NMES	neuromuscular electrical stimulation
VAS	visual analog scales

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NMES may be particularly advantageous in such cases because it is a passive muscular training technique that can easily be adapted to stimulate a selected group of muscles. Moreover, its effectiveness has been demonstrated in sports medicine,[15] geriatric medicine,[16] and physical therapy[17] and in the prevention of muscle atrophy in spinal cord–injured patients.[18] Concerning the muscular dystrophies, several studies on Duchenne muscular dystrophy patients have shown the safety and efficacy of NMES training in stabilizing or even improving muscular weakness.[19-22] Similar results were reported in another study on NMES training in neuromuscular disorders, which included a few FSHD patients.[23] All these studies presented limitations (low number of patients, variability of methods, heterogeneity of diseases and clinical conditions, etc) and firm conclusions could not be drawn. Nevertheless, NMES strength training appears to be a very promising rehabilitation strategy for patients suffering from neuromuscular disorders.

Because we expected a positive effect of NMES training on muscle strength and function and the performance of daily activities, we investigated the feasibility, safety, and effectiveness of an NMES strength training program in patients affected by genetically confirmed FSHD.

METHODS

Participants

This study was a prospective uncontrolled before-after trial to assess the feasibility, safety, and effectiveness of NMES training of the shoulder girdle and quadriceps femoris muscles of FSHD patients. Patients were recruited through the Neuromuscular Disease Center of Nice (France). Nine eligible FSHD patients (6 men, 3 women; mean age 55.2y; range, 39–69y) volunteered and were included. The local Institutional Human Ethics Committee approved the study (CPP 07.046), and written informed consent was obtained from all subjects. Patients had typical facioscapulohumeral muscle involvement associated with quadriceps femoris muscle weakness and were still able to walk without help (Vignos scale $\leq$5).[24] The baseline characteristics of the 9 FSHD patients are summarized in table 1. Diagnosis had been established with routine methodology,[4] and the number of 4q35 D4Z4 repeats ranged from 5 to 9. A rough relationship between the repeat number and the degree of clinical involvement was observed, being patient FSHD7, who carried 5 D4Z4 repeats, the most affected. In line with the genetic heterogeneity, MMT reflected the variability in the patients' degree of muscle involvement. Upper-limb functions—in particular, shoulder horizontal extension—were the most affected, as typically seen in FSHD patients.

NMES Training Program

NMES training sessions were performed with a Compex 2 portable battery-powered stimulator.[a] The patients were seated on a physical therapy table with a trunk-thigh angle of 110°, the arms relaxed along the upper body, the knees flexed at 70° (0° corresponds to full knee extension), and the feet on the table. The patients were simultaneously stimulated bilaterally on the shoulder girdle and quadriceps femoris muscles. A 2-mm thick (5×5cm), elastomer-type, self-adhesive pair of electrodes[a] was used for each muscle. For the trapezius transversalis muscle, the negative electrode was placed midway between the medial border of the scapulae and the spine, at T3, with the positive electrode placed vertically as close as possible to the negative one. For the deltoideus muscle, the negative and positive electrodes were positioned over the posterior and anterior muscle bellies, respectively. For the quadriceps femoris, the electrode pairs were fixed around the motor point of the vastus lateralis and vastus medialis muscles.

The training program (35-Hz rectangular-wave pulse currents lasting 200μs) consisted of 20-minute sessions of NMES over a 5-month period, with 5 sessions per week. Seventy-five isometric contractions (rise time: 1.5s; steady tetanic stimulation time: 6s; fall time: 1.5s) were carried out during each training session. Each stimulated contraction was followed by a pause lasting 7 seconds (duty cycle: 56.25%). Training session intensity was monitored online and gradually increased (0–100mA) by the physical therapist during the first 5 minutes of the session to a level of maximally tolerated intensity, which was maintained for the rest of the training session. All the maximally tolerated intensities delivered during this study induced a tetanic contraction of the stimulated muscles. Each session was preceded by a standardized warm-up consisting of 2 minutes of submaximal electrostimulated contractions with the above-mentioned parameters. Then, the session was followed by a 3-minute relaxing period. The stimulation parameters of the present NMES training program were selected according to previous NMES studies, which have successfully used low-frequency NMES training protocols in patients with neuromuscular disease to increase muscle strength.[19-23] Indeed, because FSHD patients should have a greater proportion of slow twitch fibers, a low-frequency stimulation NMES program would optimize their recruitment and then, the strength gains.

Table 1: Baseline Patient Characteristics

Patients	Age (y)	Sex	D4Z4 (repeat number)	CK level (U/L)	Brooke Scale	Vignos Scale	Manual Muscle Testing (right/left)					
							SHE	SF	SE	KE	EF	EE
FSHD 1	63	W	9	231	2	3	3/3	6/7	6/7	7/7	9/8	7/8
FSHD 2	50	M	6	134	2	1	4/4	5/5	8/8	9/8	8/10	9/9
FSHD 3	39	W	8	369	2	2	4/5	7/8	7/6	8/8	10/10	10/10
FSHD 4	68	W	7	160	3	3	3/3	7/5	7/5	7/6	10/9	10/9
FSHD 5	60	M	7	336	1	2	7/7	7/7	7/7	7/7	10/10	10/10
FSHD 6	52	M	8	454	2	3	2/2	7/7	7/8	3/4	10/10	10/10
FSHD 7	44	M	5	359	3	3	2/2	2/2	5/5	3/4	5/5	2/2
FSHD 8	69	M	8	101	3	3	4/4	4/4	6/6	8/8	10/10	10/10
FSHD 9	52	M	8	469	1	1	7/7	8/8	10/10	5/5	10/10	10/10
Mean	55.2			290			4/4.11	5.89/5.89	7/6.89	6.33/6.33	9.11/9.11	8.67/8.67

Abbreviations: EE, elbow extension; EF, elbow flexion; KE, knee extension; M, man; SE, shoulder extension; SF, shoulder flexion; SHE, shoulder horizontal extension; W, woman.

Measurements and Experimental Procedure

Plasma CK was measured at M0 and then after 3 (M3) and 5 months (M5).

Blood samples were collected at the hospital at rest, before the testing sessions at M0 and M5, and before the first training session of the fourth month at M3. Serum CK activity was determined spectrophotometrically by an automatic analyzer using a test kit[b] (Roche/Hitachi Automated Clinical Chemistry Analyzer, Modular P-800).

Pain and fatigue were quantified by VAS[25]; a VAS score of 0mm indicated no pain and 100mm indicated unbearable pain; the same scale was used for fatigue. Muscle function, muscle strength, and functional capacity were assessed by MMT, MVIC, the 6MWT, and self-reported changes in the activities related to daily living.

MMT is used as a clinical measure of muscle strength, and a score was assigned according to the Medical Research Council Scale.[26] The following functions of both sides were assessed: shoulder flexion, extension and horizontal extension, knee extension, and elbow flexion and extension. Although the trapezius transversalis muscle was stimulated during NMES training sessions, its strength was not directly evaluated during MMT. Because FSHD patients have difficulty in stabilizing the scapula, the strength of a more global function (ie, horizontal extension of the shoulder) was preferred. The functional status of the upper- and lower-extremities was assessed with the Brooke and Vignos scales,[24,27] respectively, as previously reported in FSHD patients.[28] Briefly, the score range of the Brooke scale, which evaluates upper-limb function, is from 1 to 6. The Vignos scale is an ordinal scale ranging from 1 to 10 points, where 1 means that the patient is able to walk and climb stairs without assistance and 10 indicates that the patient is bed-bound.

MVIC tests were carried out with a Biodex 3 isokinetic dynamometer.[c] Because the tests were carried out in isometric conditions, the dynamometer speed for isokinetic testing was set at 0° per second and torque outputs were measured in Newton meters. The subjects were comfortably seated beside the dynamometer with a trunk-thigh angle of 120°. To minimize extraneous movement, straps were applied over the upper body and around the waist. The axis of the dynamometer was always aligned with the anatomic rotational axis of the joint. Left and right sides and the muscle functions (shoulder flexion, shoulder abduction, shoulder horizontal extension, elbow flexion, knee extension) were randomly assessed, and a 45-second rest was allowed between each contraction.

The 6MWT was conducted according to the American Thoracic Society recommendations.[29] Patients were instructed to cover the greatest possible distance in 6 minutes on a 20-m shuttle. During each session, the different tests (MMT, MVIC, 6MWT) were presented in random order with a 10-minute rest period between each one. At M5, all tests were performed at 3 ± 1 days after the last training session.

At the end of the training program (M5), patients graded changes in walking, muscle strength, endurance, activity level, fatigue, and pain using a standardized questionnaire. Self-reported changes were graduated as "worse," "unchanged," or "improved."[11]

Data Analysis

The CK activity was considered as a biologic marker of training-induced damage for each patient.[30] Pain and fatigue were considered to be clinically significant when the VAS score was greater than 40mm and/or when their variation during the study was greater than 13mm.[31] The duration and intensity of the electrostimulations were recorded by the physical therapists. During the monthly follow-up visits, the following were calculated: monthly average pain and fatigue scores, session durations and the tolerated electrostimulation intensities, the global patient participation rate, and the patient participation rate in the training sessions.

Criteria for not including patient data in the final analysis were (a) CK greater than 1000U/L at M1, M3, or M5; (b)

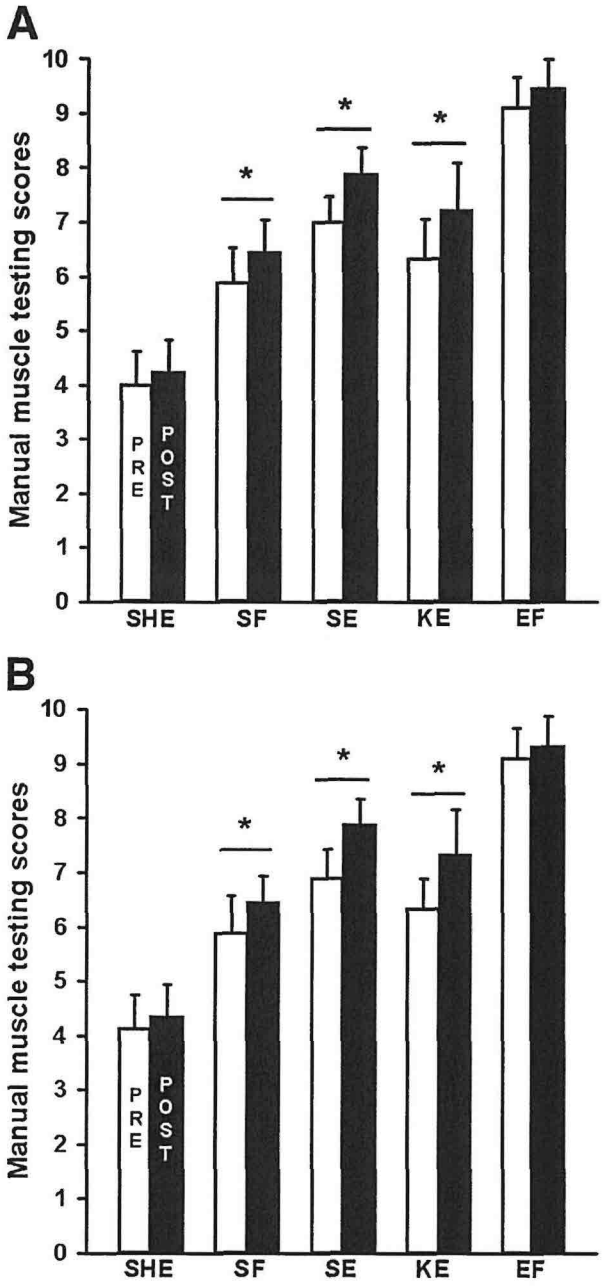

Fig 1. MMT before and after 5 months of NMES strength training in 9 FSHD patients. Pretraining and posttraining values of the right side (A) and the left side (B), respectively. Significant difference between pre- and posttraining values: *$P<.05$. Abbreviations: EF, elbow flexion; KE, knee extension; SE, shoulder extension; SF, shoulder flexion; SHE, shoulder horizontal extension.

monthly average pain or fatigue greater than 70mm; (c) monthly average session duration less than 15 minutes; and/or (d) patient participation rate at or below 50%. The study would have been interrupted if global patient participation rate was less than 50%.

The program feasibility was assessed by the patients' global patient participation rate and their rate of participation in the training sessions. Plasma CK activity, pain and fatigue VAS scores, average duration of NMES sessions, and average intensity used during the NMES sessions (clinic tolerance) were used to assess the safety of the NMES training program. The effectiveness was assessed by the following functional outcomes: MMT, MVIC (highest value), 6MWT, and self-reported changes in walking, strength, endurance, activity level, fatigue, and pain.

Statistics

Power: The study was designed to test the feasibility of NMES strength training by assessing patient tolerance and to detect a relative difference in functional outcomes between M0 and M5. Power analysis showed that 4 patients were needed (power 80%, α=.05, *t* tests, mean differences between 2 dependent variables). The minimum relative improvement as a result of NMES strength training was expected to be 108% with an SD ±56%.[23] We checked and confirmed the normality of the data by using the Kolmogorov-Smirnov test. Paired-sample Student *t* tests were calculated for within-group comparisons. The ES for each variable was calculated (Cohen *d*)[32] to assess the meaningfulness of pre- to posttraining changes. Significance was set at $P<.05$. Unless specified, numbers are means ± standard errors. Statistic analysis was performed by using Statistica 6.0 software.[d]

RESULTS

Program feasibility was evaluated by the patients' global patient participation rate, which was 100% every month. The individual patient participation rate in the training sessions was also very high and did not decrease significantly between M1 (88.9±3.7%) and M5 (80±5.2%).

Safety and tolerance were excellent. Plasma CK did not change significantly during the NMES program (290.33±46.02U/L at M0, 299.33±49.78U/L at M3, 245.33±24.62U/L at M5). Occasionally, skin redness related to the use of electrodes was noted, but it disappeared within 2 hours after the session.

Concerning clinic tolerance, the pain and fatigue VAS scores were reduced, respectively, from 1.7±0.7 and 1.7±0.9 at M1 to 0.8±0.4 and 1.3±0.6 at M5. All patients were able to complete every 20-minute NMES session. The monthly average of the tolerated NMES intensities globally increased during the training period, from 52.6±3.3mA to 55.5±5.6mA for the trapezius transversalis muscle, from 42.3±2.2mA to 43.9±3.6mA for the deltoideus muscle, and from 34.6±1.8mA to 39±3.4mA for the vastus lateralis and medialis muscles, between M0 and M5.

In terms of effectiveness, significant improvements were found by MMT assessment for shoulder flexion (right: +11.2±5.6%, $P<.05$, ES=.32 [fig 1A]; left +15.8±7.4%, $P<.05$, ES=.32 [fig 1B]), shoulder extension (right: +13.8±5.7%, $P<.05$, ES=.61 [see fig 1A]: left +16.3±4.4%, $P<.01$, ES=.65 [see fig 1B]), and knee extension (right: +14.3±5.5%, $P<.05$, ES=.37 [see fig 1A]: left +14±6.7%, $P<.05$, ES=.47 [see fig 1B]), whereas no significant modifications were observed for shoulder horizontal extension. Elbow flexion and extension remained unchanged and were considered as "control" functions, because these muscle groups were not stimulated.

MVIC was significantly increased for shoulder abduction (right: +45.5±20%, $P<.05$, ES=.65 [fig 2A]: left +42.5±13.2%, $P<.05$, ES=.79 [fig 2B]) and left shoulder flexion (+83.7±35.9%, $P<.05$, ES=.79 [see fig 2B]), whereas no significant changes were observed for right shoulder flexion, shoulder horizontal

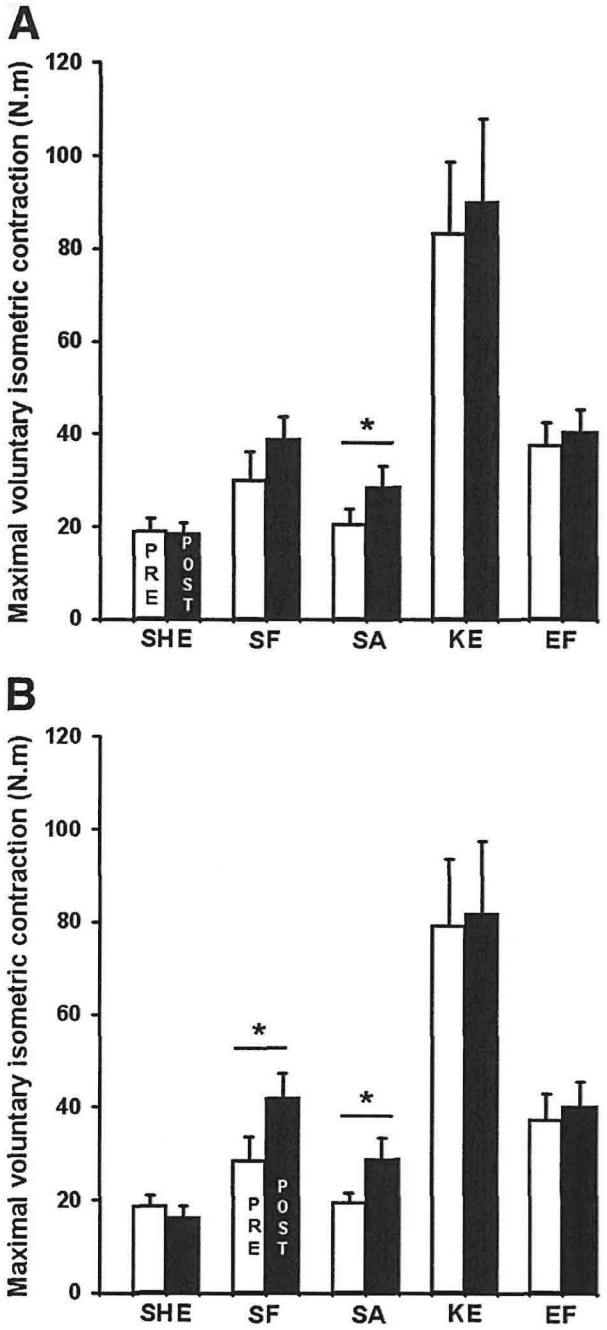

Fig 2. MVIC before and after 5 months of NMES strength training in 9 FSHD patients. Pretraining and posttraining values of the right side (A) and the left side (B), respectively. Significant difference between pre- and posttraining values: *$P<.05$. Abbreviations: EF, elbow flexion; KE, knee extension; SA, shoulder abduction; SF, shoulder flexion; SHE, shoulder horizontal extension.

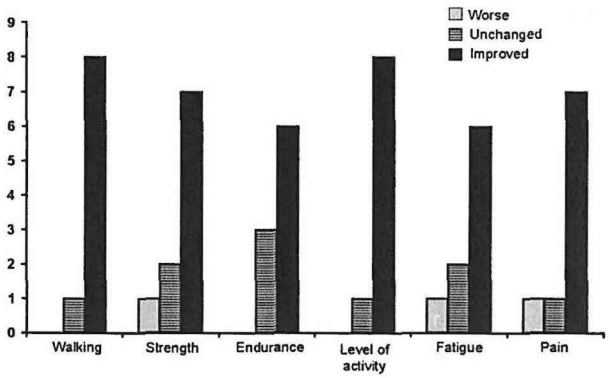

Fig 3. Self-reported changes in activities related to daily living in 9 FSHD patients after 5 months of NMES strength training. The y-axis represents the number of subjects.

extension, knee extension, or elbow flexion on either side. Distance covered for the 6MWT was also significantly increased (from 305.7±40.1m at baseline to 333.8±44.9m at M5; $P<.05$, ES=.22; data not illustrated). No correlation was noted between individual gains in the functional outcomes and the level of stimulation applied during the study. Finally, self-reported changes in the variables related to daily living (walking, strength, endurance, activity level, fatigue, pain) showed that a majority of patients felt improvement after the training period (fig 3).

DISCUSSION

In the 1990s, several trials showed that NMES training was harmless and well-tolerated by Duchenne muscular dystrophy patients and that it improved maximal voluntary strength and function in stimulated muscles.[19-22] Despite these encouraging results, NMES was progressively abandoned because of the difficulty in setting up long-term protocols, mainly related to the severe and generalized muscle involvement characterizing Duchenne muscular dystrophy patients and the technical problems with NMES devices (eg, size, management of stimulation parameters). Currently, NMES devices are easy to manage and transport. In addition, FSHD is characterized by a selective weakness of specific muscles that can be easily targeted by NMES strength training. In this study, we explored the feasibility, safety, and effectiveness of NMES training in 9 FSHD patients presenting with classic facioscapulohumeral involvement associated with quadriceps femoris weakness but who were still able to walk.

Concerning feasibility, all the patients finished the program and participated in more than 75% of the sessions planned for each month. No session was prematurely interrupted, and no side effects were reported during or after training. The pain and fatigue felt by the patients remained clinically not significant (mean VAS<2 throughout the protocol) and did not significantly increase during the study. No rhabdomyolysis was evident as a consequence of NMES training. CK activity did not increase, suggesting the absence of any significant damage to the integrity of the sarcolemmal membrane. These results agree with the reports in the literature on protocols for aerobic training and NMES in neuromuscular diseases,[9-14,19-22] all of which concluded that clinic and biologic tolerance were excellent.

We assessed the efficacy of NMES strength training in FSHD patients by MMT, MVIC, and the 6MWT. After the training program, MMT scores were significantly improved for shoulder flexion, shoulder extension, and knee extension on both right and left sides, whereas shoulder horizontal extension, elbow flexion, and elbow extension were not modified. The unchanged MMT scores of elbow flexion and elbow extension were expected because these muscle groups were not stimulated and were considered as control muscle groups. The absence of significant change in shoulder horizontal extension may be explained by the fact that the muscles mainly contributing to this function were too degenerated to show a significant change. Indeed, shoulder horizontal extension showed the lowest MMT score in all patients. This may explain the absence of MVIC modification in shoulder horizontal extension. Conversely, the other muscles were less affected, as confirmed by their higher basal MMT, and displayed an increase of 11% to 16% over the basal MMT score. Our observation is consistent with a previous report suggesting that strength gains are greatly influenced by disease severity and the rate of progression.[33] Both the literature and the present study thus suggest that the less the muscle is affected, the greater the benefit from NMES strength training will be.

Few studies have assessed the positive effects of NMES strength training on MVIC in the context of muscular dystrophies.[19-23,34] We demonstrated that MVIC was enhanced for shoulder flexion (left side) and shoulder abduction (right and left sides) after 5 months of training. However, surprisingly, we failed to observe any significant MVIC gains for knee extension, although the MMT scores were increased for this muscle group. It has been suggested that absolute gains in the muscle strength of dystrophic patients after strength training are probably dependent on preexercise muscle strength, and severely weakened muscles (<10% of normal strength) in general may not improve.[23] The quadriceps femoris of 6 of the 9 FSHD patients included in this study was only slightly affected, as suggested by the moderate MMT scores for knee extension (>6), while it was more affected in the remaining 3. This heterogeneity in muscle involvement may have contributed to reducing the significance of these results. Strength improvement is of little benefit if it does not enhance daily functional capacity. Interestingly, the 5-month NMES training protocol not only improved the knee extension MMT score, but it was also correlated with a significant improvement in the distance covered during the 6MWT and had an overall positive effect on the self-reported walking, strength, endurance, activity level, fatigue, and pain of these patients.

Study Limitations

Several limitations of our study are worth noting. First, this trial was not double-blinded, placebo-controlled, or randomized. To definitively dismiss a placebo effect, a control group should be included in further studies. Second, it has been reported that the use of NMES is more effective in rehabilitation settings when combined with voluntary contractions.[35] In our study, however, voluntary muscle contraction was not added to NMES contraction in order to avoid muscle breakdown, which could have been triggered by muscle overuse. Third, fatigue was evaluated by means of VAS and self-reported questionnaire. In future studies, physiologic muscle fatigue analysis should be added in order to gain knowledge on the effects of NMES strength training on that outcome. Fourth, the discrepancies between the MMT and MVIC gains could be partly ascribable to the specificity and sensitivity of the respective assessments. Although MMT explores an isolated muscle function, MVIC provides a global assessment of several muscles contributing to movement. Last, it was not possible to estimate the rate of gain for the benefits reported in this study because functional outcomes were only assessed at M0 and M5. An intermediate evaluation should be included in future investigations, as well as a follow-up to quantify the durability of the gains. On the basis of the results of this trial, NMES strength training

appears to be harmless for FSHD patients and may help the patients maintain their daily living activities. This type of training could be initially incorporated into regular physical therapy sessions under a clinician's supervision to monitor effects and prevent injuries, and then gradually continued at home.

CONCLUSIONS

Five months of daily NMES strength training of shoulder girdle and quadriceps femoris muscles appeared to be safe and well-tolerated by FSHD patients, and this protocol significantly improved MMT scores, the MVIC of several muscles, and the distance covered during the 6MWT. In addition, it had a positive effect on self-reported daily living activities. Our findings should be considered alongside the observation of Milner-Brown and Miller[23,33] that strength training is more effective in patients with neuromuscular disorders if initial muscle strength is greater than 15% of normal. Taken together, these studies draw attention to the importance of starting a strength training program as soon as the diagnosis is made to maximize the benefits to muscle. Finally, the efficacy of NMES training in FSHD patients should be tested in a multicenter randomized controlled study.

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Suppliers

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