

ORIGINAL ARTICLE

Neural and muscular mechanisms of electrically induced fatigue in patients with spinal cord injury

M Papaiordanidou^{1,2}, A Varray¹, C Fattal³ and D Guiraud⁴**Study design:** Intervention study.**Objectives:** The present study aimed at examining whether spinal and/or peripheral alterations are in the origin of neuromuscular fatigue development induced by intermittent neuromuscular electrical stimulation (NMES) in subjects with complete spinal cord injury (SCI).**Setting:** Neurological Rehabilitation Center CMN Propara, Montpellier, France.**Methods:** Thirteen volunteers with complete SCI participated in the study. The right *triceps surae* muscle was fatigued using a 30-Hz NMES protocol (2 s ON–2 s OFF) composed of three series of five trains. Spinal excitability (assessed by the H-reflex), muscle excitability (assessed by the M-wave), muscle contractile properties (assessed by mechanical response parameters) and torque evoked by NMES were tested before and after each five-train series.**Results:** NMES-evoked torque significantly decreased throughout the protocol ($P < 0.001$). This decrease was accompanied by a significant increase in M-wave amplitude ($P < 0.001$), whereas H-reflex and the H_{max}/M_{max} ratio were not significantly modified. The amplitude of the mechanical response was significantly decreased at the end of the protocol ($P < 0.05$).**Conclusion:** The results indicate significant fatigue development, which was attributed to impaired cross-bridge force-generating capacity, without modification of spinal excitability nor muscle excitability.*Spinal Cord* (2014) **52**, 246–250; doi:10.1038/sc.2013.172; published online 21 January 2014**Keywords:** muscle excitability; spinal excitability; contractile properties; paraplegia

INTRODUCTION

Spinal cord injury (SCI) leads to major muscle adaptations below the level of injury. Muscle atrophy associated with the conversion of muscle fibers toward a more glycolytic profile¹ lead to increased fatigability in patients with SCI.² Neuromuscular electrical stimulation (NMES) is one of the most used techniques to contract paralyzed muscles. This technique is used in rehabilitation settings to supplement for lost functions and can partially counteract the deleterious adaptations that skeletal muscles undergo after SCI.³ The motor unit recruitment pattern under NMES being different from that observed in voluntary contractions,⁴ metabolic stress is sharply increased,⁵ leading to marked and early fatigue development. Clinicians are seeking to develop efficient stimulation strategies in order to delay and minimize fatigue and thus improve its application.

It is well acknowledged that NMES-induced fatigue does not involve only muscular mechanisms, but also changes taking place at the neural level. When muscle contraction is electrically evoked, intramuscular axonal branches are activated,⁶ and hence muscle fibers are recruited both directly, by activation of the efferent motor axon, and indirectly, by activation of spinal loops⁷ through afferent pathways. Moreover, during fatigue development, activation of muscle afferents, sensitive to activity-dependent intramuscular chemical changes, would convey signals to spinal and/or supraspinal centers, altering in that way their output toward the muscle.⁸

Despite these phenomena, studies on electrically induced fatigue in persons with SCI have generally assessed fatigue by analyzing only muscular mechanisms (muscle excitability and contractile properties).^{9–12} However, although supraspinal control is absent, spinal circuitry below the lesion is still functional, and spinal excitability after SCI is known to increase. This is generally attributed to a loss of regulation of the presynaptic inhibition of Ia afferents from descending supraspinal pathways to motoneurons and interneurons.^{13,14} The only study to our knowledge examining neural implications in electrically induced fatigue in persons with SCI reported decreased motoneuron excitability, as assessed by analysis of F-waves, during a supramaximal fatiguing protocol.¹⁵ It is thus evident that spinal activity can be modified under fatigue conditions and this may affect muscle response to NMES. For a given electrical input at the spinal level, force output can vary according to the state of spinal excitability. Unfortunately, although presenting results on muscular parameters, this study¹⁵ did not focus on interpretation of peripheral fatigue components responsible for the decreased force. As a consequence, it is still impossible to know which processes are mainly involved in NMES-induced fatigue. Analyzing peripheral fatigue components in tandem with spinal excitability is thus called for and relevant to uncovering the physiological mechanisms responsible for fatigue development under NMES in subjects with SCI. Indeed, without a clear understanding of this

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Received 15 July 2013; revised 19 December 2013; accepted 23 December 2013; published online 21 January 2014

phenomenon, it is impossible to promote relevant means to counteract it.

The aim of the present study was to examine neuromuscular fatigue development at both peripheral and spinal levels under intermittent NMES in persons with complete SCI. Taking into consideration the muscle weakness and changes in the spinal circuitry occurring after SCI, we hypothesized that spinal as well as peripheral alterations would be implicated in the neuromuscular fatigue development.

MATERIALS AND METHODS

Subjects

Thirteen patients with SCI volunteered to participate in the study (Table 1). Inclusion criteria were: complete motor and sensory loss below the level of injury (American Spinal Injury Association (ASIA) Impairment Scale A), age between 18 and 65 years, neurological stability >6 months, complete range of motion for the hip and knee joints without any associated pathology, stimulation thresholds for the studied muscles <100mA, no cardiovascular or respiratory problems, no pressure ulcers and no pregnancy. The study was approved by the ethics committee for human protection in Nîmes, France (2008-A00068-47/1). All subjects were informed of the objectives and risks inherent to the study and signed the written consent form.

Experimental design

Subjects visited the research laboratory for two sessions, separated by 2–3 days. The first visit was a familiarization visit, whereas during the second one the experimental protocol was performed.

Data collection

Torque measurement. Torque of the right plantar flexors evoked by NMES and tibial nerve stimulation was measured by means of an isokinetic dynamometer (Biodex 3, Shirley Corporation, NY, USA). Subjects were seated on the dynamometer chair with their right foot strapped to a pedal, while straps were applied to the chest, pelvis and the right mid-thigh to secure positioning. The ankle and knee joints were at 90° and 120° (180° full extension), respectively. The dynamometer axis was aligned with the anatomical ankle plantar- and dorsi-flexion axis (Figure 1a).

Electromyographic measurement. Electromyographic (EMG) activity of the soleus muscle was recorded bipolarly by silver chloride surface electrodes with a recording diameter of 9 mm (Contrôle Graphique Medical, Brie-Compte-Robert, France) and with an inter-electrode distance of 20 mm. In order to minimize impedance, the skin was shaved. Recording electrodes were placed along the mid-dorsal line of the leg, about 5 cm distally to the insertion point

of the two *gastrocnemii* to the Achilles tendon. Electrode position was secured after verification of an appropriate M-wave acquisition (single response and highest amplitude for a given intensity). The ground electrode was placed on the contralateral patella. EMG signals were amplified (gain = 500) and recorded at a sampling frequency of 4096 Hz (Biopac MP100, Biopac Systems Inc., Santa Barbara, CA, USA) coupled with the isolation unit INISO).

Experimental procedures

First (familiarization) session. During the first session, a M-wave and H-reflex recruitment curve was established. The tibial nerve was stimulated using a constant-current stimulator (DS7AH, Digitimer Ltd, Hertfordshire, UK) delivering rectangular, monophasic pulses of 500- μ s duration. The cathode (a silver chloride electrode, Contrôle Graphique Medical) was fixed on the popliteal fossa and the anode (a rectangular electrode) was placed beneath the patella. Stimulation intensity was progressively increased (10-mA increments) until no further increase in the M-wave amplitude was evident. The intensity at which M_{max} was observed was increased 10% further in order to reach supramaximal intensity (I_{SM}). Parallel to the M-wave recruitment curve, the H-reflex was also recorded. Subsequently, the intensity where the maximum H-reflex was observed was carefully sought (I_{Hmax}) using 2-mA increments.

During this first session, the intensity at which maximum torque was evoked by NMES (I_{Tmax}) was also determined. The procedure for T_{max} has been previously described.² The *triceps surae* was stimulated using a portable stimulator (Cefar Physio 4, Cefar Medical AB, Lund, Sweden) that delivered constant-current, rectangular, symmetric biphasic pulses. Two rectangular electrodes (10 × 5 cm) were placed over the *triceps surae* muscle, one positioned 3 cm beneath the popliteal fossa and the other beneath the insertion point of the two *gastrocnemii* muscles to the Achilles tendon and just above the EMG recording electrodes. For T_{max} identification, each stimulation train (30 Hz, 450 μ s, 1 s duration) was delivered every 10 s. Stimulation intensity was progressively increased (10-mA increments) until torque evoked by stimulation reached a plateau.

At the end of this first session, electrodes placement (NMES, neural stimulation and EMG electrodes) was marked with indelible ink in order to ensure a consistent and reproducible electrode position between sessions.

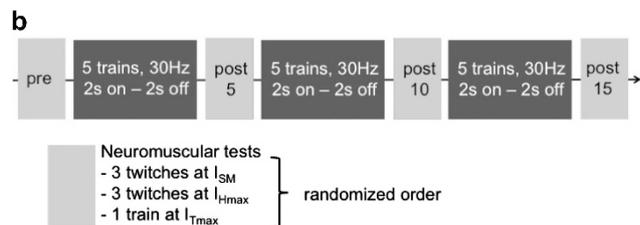
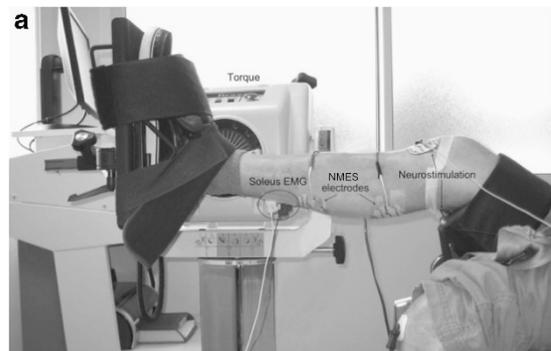


Figure 1 (a) Experimental setup. Torque and EMG activity of the soleus muscle were continuously acquired. NMES electrodes were used to induce T_{max} and to fatigue the muscle, whereas the technique of neurostimulation was used to assess neuromuscular fatigue components. (b) Experimental protocol. The *triceps surae* muscle was fatigued by NMES (three series of five stimulation trains). Neuromuscular tests were performed before and after each series of five trains.

Table 1 Characteristics of the subjects participating in the study

Subject	Sex	Age (years)	Years after injury	Level of injury
S1	M	39	3	T6
S2	M	46	14	T10
S3	M	22	2.5	C7
S4	M	21	1.5	C5
S5	F	25	1	C7
S6	M	26	3	T6
S7	M	45	14	T6
S8	M	37	12	T6
S9	M	32	0.6	C5
S10	M	45	1.5	C5
S11	M	48	1.5	T6
S12	M	53	4	T6
S13	F	60	37	T10

Sex: M (male) and F (female); Level of injury: T (thoracic) and C (cervical). All subjects were ASIA A (motor and sensitive complete spinal cord injury).

Second (experimental) session. The experimental session started with verification of I_{SM} , I_{Hmax} and I_{Tmax} . Then the fatiguing protocol and neuromuscular tests took place. Neuromuscular tests consisted of one train at I_{Tmax} , three twitches delivered at I_{SM} and three twitches at I_{Hmax} . These twitches were delivered every 10 s. Neuromuscular tests were performed before (pre) and immediately after every 5-train series (post5, post10 and post15, respectively). They lasted for ~ 90 s (Figure 1b).

Intermittent NMES protocol. The *triceps surae* muscle was fatigued by means of an intermittent NMES protocol bearing the following characteristics: 30 Hz, 450 μ s, 2 s on–2 s off, at an intensity evoking 50% of T_{max} . Three series of five trains were used to induce fatigue. Current was delivered through the same electrode placement used to evoke T_{max} and with the same stimulator.

Data analysis

Electrophysiological response. The EMG activity associated with the three twitches elicited at I_{SM} and I_{Hmax} were averaged for the analysis. M_{max} was analyzed for peak-to-peak amplitude and duration. The peak-to-peak amplitude of H_{max} was also calculated and then normalized with respect to the M_{max} amplitude (H_{max}/M_{max} ratio).

Mechanical response. The mechanical response associated with the three twitches at I_{SM} was recorded and averaged for the analysis. The following parameters were calculated: peak twitch (Pt), defined as the maximum value of torque production in response to a twitch; contraction time, the time from the beginning of the contraction to Pt and half-relaxation time, the time required for the torque to decrease by 50%.

The torque recorded during the train eliciting T_{max} was analyzed for its maximum value. The torque elicited during the fatiguing protocol was also analyzed. For each series, the mean torque of the five trains was calculated and compared with the torque value of the first train of the first series (pre-value).

Statistical analysis. Normality of the distributions was verified with the Shapiro–Wilk test. For parameters without normal distribution, a non-parametric Friedman analysis of variance (ANOVA) was performed. Variables with a normal distribution recorded before, during and after the NMES protocol were tested using a one-way repeated measures ANOVA (time as within-subject factor with four replications: before NMES (pre), after five trains (post5), after 10 trains (post10) and after 15 trains (post15)). When time had a significant effect on the variables ($P < 0.05$), the LSD Fisher *post hoc* test was used. Data are reported as means \pm s.e.m. Statistical analyses were performed using Statistica software (StatSoft, Inc., version 7.1, Tulsa, OK, USA). ANOVA F ratios are given with degree of freedom as subscript (F_3).

Statement of ethics

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

RESULTS

We managed to obtain an H-reflex response in eight of the 13 subjects in the study. In order to ensure that no bias in the statistical analysis was added because of the five ‘non-H’ subjects, we performed a complementary statistical analysis considering two sub-groups (‘H’ and ‘non-H’). This two-way ANOVA showed no significant interaction or sub-group effect for any of the studied parameters (F ratios ranged from 0.36 to 1.53 with associated P -values ranging from 0.22 to 0.77).

Torque during trains of stimulation and T_{max}

The torque developed during the stimulation trains used to induce fatigue significantly decreased throughout the protocol ($F_3 = 23.96$, $P < 0.001$). This decrease was significant from post5 ($P < 0.05$) and continued for the entire NMES session. From the initial value of 11.1 ± 1.71 Nm, observed at the first train of the first of the three five-train series, torque declined to 8.31 ± 1.35 Nm at post15. This represented a decrease of 28% at post15 compared with the initial values (Figure 2a).

T_{max} decreased throughout the experimental session ($F_3 = 25.04$, $P < 0.001$). The decrease was significant from the first train bout ($P < 0.001$) and persisted for the entire NMES protocol. From the pre-value of 20.56 ± 2.93 Nm, T_{max} declined to 17.62 ± 2.58 Nm at post15, representing a 16% decrease compared with pre-value (Figure 2b).

Electrophysiological parameters

M_{max} amplitude increased significantly during the protocol ($F_3 = 20.54$, $P < 0.001$, Table 2), whereas its duration showed no significant changes ($F_3 = 0.74$, $P = 0.53$).

For the subjects showing an H-reflex response ($n = 8$), the amplitude of H_{max} was not significantly modified ($F_3 = 0.26$, $P = 0.84$). In tandem, the H_{max}/M_{max} ratio was not statistically modified throughout the session ($F_3 = 1.64$, $P = 0.2$, Table 2), although a trend for reduction could be observed from post5. Figure 3 shows characteristic recordings of the electrophysiological parameters for one subject during the experimental protocol.

Muscle contractile properties

Pt significantly decreased during the protocol ($F_3 = 10.7$, $P < 0.05$). The decrease was only significant at post15. Contraction time significantly decreased from pre-values ($P < 0.05$), whereas half-relaxation time was not significantly modified by the NMES protocol (Table 3).

DISCUSSION

The aim of the study was to examine electrically induced fatigue in muscles paralyzed by SCI. We tested the hypothesis that fatigue could

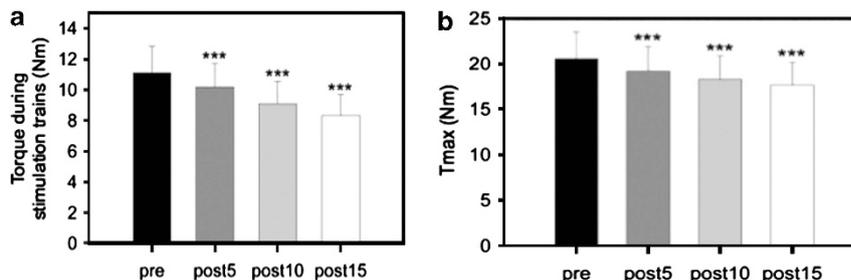


Figure 2 Torque evolution during the NMES protocol. (a) Torque evoked by the stimulation trains. The decrease was significant from post5 and continued throughout the protocol. (b) Decrease in the maximal torque evoked by NMES during the fatiguing protocol. *** $P < 0.001$, significantly different from pre-values.

Table 2 Electrophysiological responses during the experimental session

	pre	post5	post10	post15
M-wave (mV)	2.52 ± 0.43	2.58 ± 0.43**	2.64 ± 0.44***	2.68 ± 0.44***
(n = 13)	(1.57, 3.46)	(1.64, 3.52)	(1.67, 3.59)	(1.71, 3.63)
H-reflex (mV)	1.59 ± 0.37	1.57 ± 0.38	1.62 ± 0.35	1.62 ± 0.35
(n = 8)	(0.7, 2.48)	(0.66, 2.48)	(0.79, 2.46)	(0.79, 2.45)
H_{max}/M_{max}	0.63 ± 0.12	0.56 ± 0.08	0.56 ± 0.07	0.56 ± 0.07
(n = 8)	(0.34, 0.91)	(0.36, 0.75)	(0.39, 0.73)	(0.39, 0.73)

Values are means ± s.e.m. 95% confidence intervals are presented for each parameter at each stage of the experimental protocol. ** $P < 0.01$ and *** $P < 0.001$, significant differences from pre-values.

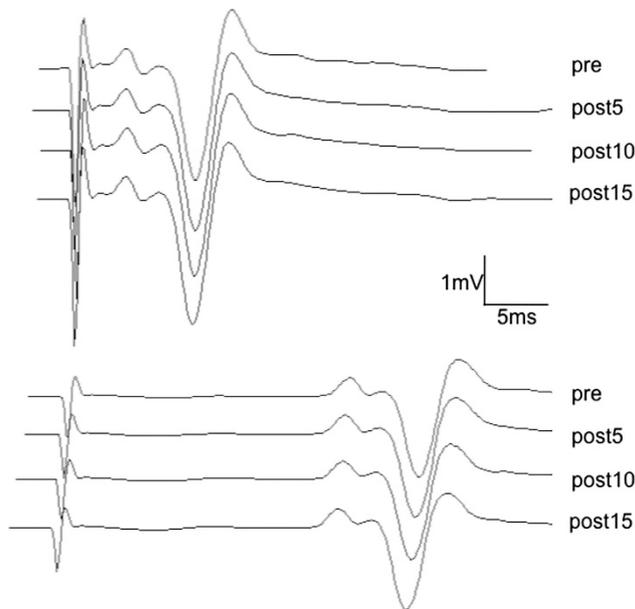


Figure 3 Electrophysiological parameters of a representative subject at all stages of the experimental protocol. In the upper panel, evolution of M_{max} is presented. M_{max} amplitude significantly increased from the first five trains and throughout the NMES protocol, whereas M-wave duration remained unchanged for the entire experimental session. In the lower panel, representative recordings of the H-reflex are depicted. H_{max} was not significantly modified throughout the NMES protocol. Accordingly, H_{max}/M_{max} ratio remained unchanged during the fatiguing protocol.

be attributed to both neural and muscular factors. Main results showed rapid fatigue development associated with alterations in muscle contractile properties, despite enhanced muscle excitability, while spinal excitability was not modified.

The decrease in T_{max} and torque evoked during the fatiguing trains (30% torque loss at the end of the stimulation protocol) is consistent with previous results in persons with SCI.⁹ It was accompanied by an increase in M_{max} amplitude, showing enhanced muscle excitability. This enhancement was most probably related to enhanced activity of sodium-potassium pumps¹⁶. The potentiation of M_{max} agreed with previous observations⁹ that reported M-wave potentiation at the initial phase of a 4-min NMES protocol. Other authors¹² reported unchanged M-wave amplitudes during a 2-min fatiguing protocol applied to paralyzed muscles and concluded that fatigue development in persons with SCI could be attributed to mechanisms distal to the muscle membrane. Present results corroborate this conclusion, as the enhanced muscle excitability could not have been at the origin of the torque decrease.

Table 3 Contractile properties during the experimental session

	pre	post5	post10	post15
Pt (Nm)	9.57 ± 1.05	9.54 ± 1.11	9.45 ± 1.11	9.33 ± 1.1*
	(6.98, 11.57)	(6.88, 11.72)	(6.81, 11.65)	(6.54, 11.71)
CT (ms)	89 ± 4.49	87 ± 4.49	85 ± 4.32*	85 ± 3.9*
	(78, 98)	(77, 97)	(75, 94)	(77, 94)
HRT (ms)	78 ± 5.29	80 ± 6.2	81 ± 6.5	78 ± 6.97
	(66, 89)	(66, 94)	(66, 95)	(63, 93)

Abbreviations: Pt, peak twitch; CT, contraction time; HRT, half-relaxation time. Values are means ± s.e.m. with 95% confidence intervals presented in the parenthesis. * $P < 0.05$, significantly different from pre-values.

The amplitude of the mechanical response associated to M_{max} (Pt) was decreased, giving evidence of impaired cross-bridge force-generating capacity at the end of the protocol. Despite the early torque decrease induced by stimulation over the *triceps surae*, the Pt decrease became significant only at post15. This suggests that the NMES torque decrease at post5 and post10 could not be attributed to contractile impairment, but was most probably because of changes taking place at the stimulation site over the muscle. Activity-dependent hyperpolarization of motor axons under the stimulating electrodes, leading to changes in the excitability threshold of motor units, would result in fewer motor units being recruited¹⁷ and could have been at the origin of the NMES torque decrease. Another possible explanation of the temporal mismatching between Pt and NMES torque evolution during the first two train bouts could be the potentiation phenomenon. Indeed, the effects of fatigue on a simple twitch can be masked by potentiation, as these phenomena with opposing effects on muscle mechanical response appear concomitantly.¹⁸ The observed transient preservation can be attributed to the combined effect of potentiation and fatigue, despite electrically evoked torque reduction from the beginning of the protocol.

Given the potentiation phenomenon, isometric twitches have been widely used to identify cellular mechanisms of muscle fatigue. They are associated with molecular events of the cross-bridge cycle and particularly with Ca^{2+} dynamics. Increased inorganic phosphate is thought to be one of the major causes of peripheral fatigue.¹⁹ Although its direct effect on cross-bridge function is probably rather small at physiological temperatures, increased inorganic phosphate can reduce filament sensitivity to Ca^{2+} and hence impact force production.¹⁹ In the present study, the Pt decrease was consistent with reduced myofibrillar Ca^{2+} sensitivity.

The preserved H_{\max}/M_{\max} ratio throughout the experimental session indicated that decreased spinal excitability could not be responsible for the fatigue development. However, the trend for a decrease of this parameter from the first five-train bout, gives evidence of NMES-induced changes at the spinal level. Spinal excitability was assessed by analyzing the H-reflex. H-reflex is considered to represent motoneuron response through activation of Ia afferents, although its amplitude is not only influenced by intrinsic motoneuron properties, but by supraspinal and peripheral modulations as well.²⁰ As mentioned above, the observation of preserved H_{\max}/M_{\max} did not exclude modifications taking place at the spinal level. Indeed, Butler and Thomas¹⁵ assessed motoneuron excitability in SCI using F-waves and demonstrated a reduction in their persistence and amplitude during stimulation of the median nerve, giving evidence of alterations in motoneuron excitability for paralyzed thenar muscles. Therefore, the preservation of the H_{\max}/M_{\max} ratio in the present study can reflect overlapped depressed motoneuron excitability by modulating mechanisms mediating spinal excitability not assessed by the F-wave analysis.²⁰ As descending tracts are interrupted in SCI and supraspinal control of motoneurons and interneurons is absent, afferent input acting at the spinal level to cover an eventual motoneuron failure appears the most probable mechanism explaining the unchanged H_{\max}/M_{\max} ratio.

In conclusion, present results provide information on the time course of neural adaptations during electrically induced fatigue applied to persons with SCI, which is added to the already well-studied muscular fatigue adaptations. We showed that NMES induced substantial fatigue, involving alterations in contractile properties and more precisely impaired cross-bridge force-generating capacity, while muscle and spinal excitability were preserved. Characterizing neuromuscular fatigue in persons with SCI can help clinicians to develop rehabilitation strategies to optimally stress their musculoskeletal system. Considering that contractile properties are the most affected parameter under intermittent NMES, future strengthening programs should be designed to enhance muscle contractile quality. Concerning the substantial fatigue development, it has been suggested that it could be partly counteracted by enhancing afferent input to the spinal level using large pulse widths and high frequencies of stimulation.⁷ Testing this hypothesis is a promising perspective to complete our study by analyzing new stimulation strategies to minimize fatigue in SCI patients under NMES.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We would like to thank Christine Azevedo-Coste, Patrick Benoit, Mitsuhiro Hayashibe, Qin Zhang and Mourad Benoussaad for their help during the experiments and Catherine Carmeni and Bénédicte Clément for English corrections of the manuscript.

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