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Enhanced neural drive after maximal strength training in multiple sclerosis patients

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Abstract Multiple sclerosis (MS) patients suffer from impaired muscle activation and lower limb strength. Strength training enhances muscle activation and muscle strength, but neural adaptations to strength training remain unexplored in MS patients. The hypothesis was that maximal strength training (MST) using high loads and few repetitions would improve central neural drive and thus strength capacity of MS patients. 14 MS patients staying at a national MS rehabilitation center were randomly assigned to a MST group or a control group (CG). Both groups received "today's treatment". In addition, the MST group trained 4 × 4 repetitions of unilateral dynamic leg press and plantar flexion 5 days a week for 3 weeks. Neural adaptations of the soleus muscle were assessed by surface electromyography (EMG) activity, and by superimposed H-reflexes and V-waves obtained during maximum voluntary isometric plantar flexor contractions (MVCs). H-reflexes and V-waves were normalized by the M-wave (H_{SUP}/M_{SUP}, V/M_{SUP}, respectively). In the MST group, MVC increased by 20 ± 9% ($P < 0.05$). Soleus EMG activity and V/M_{SUP} ratio increased by 40 and 55%, respectively, in the MST group compared to the CG ($P \leq 0.05$). The H_{SUP}/M_{SUP} ratio remained unchanged. No change was apparent in the CG. MST group subjects were able to complete all training sessions. No adverse effects were reported. This randomized study provides evidence that MST is effective of augmenting the magnitude of efferent motor output of spinal motor neurons in MS patients, alleviating some neuromuscular symptoms linked to the disease.

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Introduction

Multiple sclerosis (MS) is a disease affecting the central nervous system, leading to destruction of myelin, oligodendrocytes and axons (Noseworthy et al. 2000). As a consequence, MS patients are neither able to fully activate muscles in the lower limbs (de Haan et al. 2000; Ng et al. 2004; Rice et al. 1992; Sharma et al. 1995) nor to drive active motor units at high firing frequencies (rate coding) (Rice et al. 1992). Accordingly, the muscle strength of MS patients is 30–70% lower compared to healthy control subjects, stating that muscle weakness is a common symptom of MS (Ng et al. 2004; Rice et al. 1992; Sharma et al. 1995).

Strength training has been shown to increase the neuromuscular activity in skeletal muscles through the use of surface electromyography (EMG) (Aagaard et al. 2002b; Del Balso and Cafarelli 2007; Fimland et al. 2009a; Hakkinen et al. 1998; Hortobagyi et al. 1996; Scaglioni et al. 2002; Suetta et al. 2004). Twitch interpolation techniques have demonstrated increased muscle activation in response to strength training (Knight and Kamen 2001; Scaglioni et al. 2002). Intramuscular EMG recordings have demonstrated increased motor neuron firing frequency in healthy subjects after a period of strength training (Kamen and Knight 2004; Van Cutsem et al. 1998). Studies investigating resistance training effects in MS patients have reported enhanced muscle strength (Dalgas et al. 2009, 2010; de Souza-Teixeira et al. 2009; DeBolt and McCubbin 2004; Gutierrez et al. 2005; Romberg et al. 2005; Taylor et al. 2006; White et al. 2004) but to date neural adaptations in response to strength training remain unexplored in MS patients.

Recent studies have employed electrically evoked spinal reflexes, namely H-reflex and V-wave, to reveal changes in the central nervous system (Aagaard et al. 2002b; Del Balso and Cafarelli 2007; Duclay et al. 2008; Fimland et al. 2009a, b, 2010; Gondin et al. 2006). The H-reflex comprises a monosynaptic connection between the group Ia afferent and the α-motor neuron (Schieppati 1987) and has been reported to increase following strength training during muscle activation in some studies, but not at rest (Aagaard et al. 2002b; Holtermann et al. 2007; Lagerquist et al. 2006). Increased H-reflex responses following strength training have been interpreted as increased motor neuron excitability and/or reduced pre- and post-synaptic inhibition (Aagaard 2003).

The V-wave, which is an electrophysiological variant of the H-reflex, can be evoked when a stimulus sufficient to evoke a maximal M-wave is delivered to a motor nerve during a voluntary contraction. It is assumed that the peak-to-peak amplitude of the V-wave reflects the magnitude of central descending neural drive to spinal motor neurons (Aagaard et al. 2002b; Upton et al. 1971), although spinal factors (motor neuron excitability, pre/post-synaptic inhibition) may also be involved (Aagaard 2003). Augmented V-wave responses have been observed after strength training in healthy subjects (Aagaard et al. 2002b; Del Balso and Cafarelli 2007; Fimland et al. 2009a, b; Sale et al. 1983), but have never been reported in a diseased population.

As MS is linked to decreased central neural drive from the nervous system to the lower limb muscles whereas strength training has been demonstrated to enhance neural drive, the main hypothesis is that MS patients performing 3 weeks of maximal strength training (MST) + standard rehabilitation will show enhanced efferent drive from spinal motor neurons to soleus muscle fibers compared to patients receiving only standard rehabilitation.

Methods

Patients

14 MS patients, free from any other known disease, were recruited while attending a rehabilitation program at a national MS rehabilitation center. The volunteers were pretested and randomized to an MST group ($n = 7$, age range 33–65 years) or to a control group (CG, $n = 7$, age range 48–60 years) (see Fig. 1). Patient characteristics are depicted in Table 1. Both groups took part in the conventional rehabilitation program at the center. The expanded disability status scale (EDSS) (Gaspari et al. 2002) was employed by the same neurologist to assess the severity of neurological impairment among the subjects before and after training (MST group range 3.0–6.5; CG range 2.0–6.0, Table 1). These EDSS values correspond well with the target patient groups for the rehabilitation center which are persons with mild and moderate disabilities due to MS. The study was approved by the regional ethics committee and conformed to the standards set by the latest revision of the Declaration of Helsinki. Patients gave informed written consent prior to participation.

Study overview

This randomized study assessed the hypothesis that MST using high loads and few repetitions in combination with

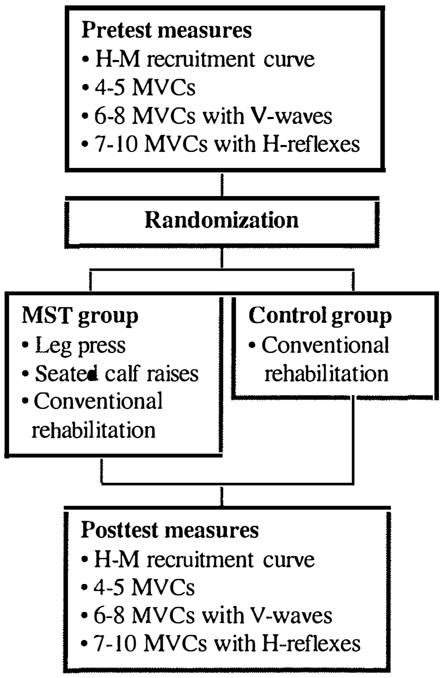

Fig. 1 Overview of the study design. *H-M* H-reflex/M-wave, *MVCs* maximum voluntary isometric plantar flexor contractions, *MST* maximal strength training

Table 1 Subject characteristics

Variables	MST group ($n = 7$)	Control group ($n = 7$)
Female/male	3/4	3/4
Age (years)	53 ± 4	54 ± 2
Height (cm)	172 ± 4	170 ± 2
Body weight (kg)	74.8 ± 9.6	76.8 ± 5
BMI	24.7 ± 2.3	26.5 ± 1.8
EDSS	4.6 ± 0.4	3.5 ± 0.5
Years since diagnosed	8 ± 1	8 ± 1
Daily use of facilitating aids		
Wheelchair	1	1
Orthosis	1	0
Rollator	0	1
Crutches/cane	4	2

Data are presented as mean ± SE

BMI body mass index, *EDSS* expanded disability status scale

conventional rehabilitation would improve efferent neuronal outflow to the lower limbs more than conventional rehabilitation alone.

Muscle strength, EMG recordings and stimulation

Isometric force was recorded by a force transducer (Model 363-D3-50-20P1, Revere Transducers, Tustin, CA, USA) attached to the custom-made ankle dynamometer. The force signal was sampled at 1 kHz and digitally low-pass filtered (10 Hz). Force was multiplied with the moment arm length to attain torque.

After preparation of the skin to obtain interelectrode impedance < 5 kΩ, pairs of bipolar Ag/AgCl surface electrodes (Ambu M-00-S, Ballerup, Denmark) were placed on the soleus along the mid-dorsal line of the leg, ~5 cm distal to the gastrocnemius. For the tibialis anterior and vastus lateralis muscles, electrodes were placed according to the recommendations by SENIAM (Hermens et al. 2000). Measurements were made on the right leg and with an interelectrode distance of 25 mm. Subjects performed preliminary contractions, and the shape of the M-waves and H-reflexes was monitored to ensure proper placement of the stimulating and recording electrodes. EMG was sampled (ME6000 Biomonitor, Mega Electronics LTD, Kuopio, Finland) at 2 kHz, CMRR: 110 dB, amplified and band-pass filtered (8–500 Hz) prior to being stored on a personal computer.

Soleus H-reflexes, V-waves and M-waves were evoked by 1-ms square wave stimuli delivered by a constant-current stimulator (DS7, Digitimer, Welvyn Garden City, UK) via gel-coated bipolar felt pad electrodes (8 mm diameter, 25 mm between tips; Digitimer, Welvyn Garden City, UK) to the posterior tibial nerve. The cathode was medial to the anode to avoid anodal block (Pierrot-Deseilligny and Burke 2005).

Experimental procedure

The protocol to obtain electrophysiological measurements and maximum voluntary isometric plantar flexor contractions (MVCs) was similar to previous reports (Fimland et al. 2009a, b, 2010). Patients were seated slightly reclined in a chair mounted on a solid wooden platform with their right foot placed in a custom-made isometric ankle dynamometer made of steel and plexiglass. The foot-plate axis of rotation was aligned with the anatomical axis of the ankle. Rigid straps secured the heel and forefoot to the foot-plate with the ankle at 90°. The thigh, hip and back were secured with broad velcro-straps and held the subject in a constant position. For the tested (right) limb, the knee was flexed at 80° from full extension and the hip was at 90°. The opposite leg rested on a chair.

Prior to the main testing, patients were familiarized with percutaneous electrical pulses in the tibial nerve and practiced voluntary isometric contractions of the plantar flexors. Patients attended an experimental session before and after the 3-week period (Fig. 1). The following measurements were obtained: (1) resting H-reflex/M-wave recruitment curve (1 mA increments, 0.2 Hz stimuli frequency), (2) MVCs, (3) V-waves and concomitant maximal superimposed M-waves (M_{SUP}) (see Fig. 3), (4) H-reflexes superimposed on MVCs (H_{SUP}; see Fig. 3). To evoke H_{SUP}, the stimulus intensity was adjusted to evoke the maximal peak-to-peak amplitude H-reflex. The H-reflex/M-wave recruitment curve provided a starting point for H_{SUP} stimulation. In some subjects, it was difficult to elicit consistent H-reflex responses from the resting soleus muscle; however, this was usually not a problem when subjects performed weak (5–10% MVC) plantar flexor contractions. For these patients, H-reflexes were elicited during weak contractions to provide a starting point for H_{SUP} stimulation. 200% of the stimulus intensity needed to evoke the maximal M-wave was employed to obtain V-wave and concomitant M_{SUP} responses. MVCs were performed at a rate of one per minute. MVCs performed to determine torque lasted 3 s and MVCs with superimposed H-reflexes or V-waves lasted until the subject had received the V-wave or H_{SUP} stimulus (~2 s). To optimize performance during MVCs, the criteria proposed by Gandevia (2001) related to practice, instruction, visual feedback and standardized verbal encouragement were followed.

Training intervention

The MST group performed a 3-week training regime (15 sessions) supervised by an exercise physiologist. The

MST consisted of horizontal leg press exercise (Super Gym, Taiwan) and seated calf raises (Gymleco, Haninge, Sweden). Both exercises consisted of four sets of four repetitions (~85–90% 1RM), and were performed unilaterally to account for limb variations in strength. A 1–2 min pause was given between sets. The load was increased when the patients were able to complete 4 × 4 repetitions. It was emphasized that the weight should be lowered in a controlled manner, short pause and maximal mobilization of force in the concentric phase as described previously (Fimland et al. 2009a; Hoff et al. 2007; Husby et al. 2009; Karlsen et al. 2009; Storen et al. 2008; Wang et al. 2009). Seated calf raises were trained in the full range of motion of the plantar flexors, with the knee joint at ~90°. The leg press exercise was trained from full extension to 90° in the knee joint. Both groups participated in the conventional rehabilitation exercises (e.g. aqua gymnastics, stretching, physiotherapy, relaxation techniques).

Data analysis

To calculate voluntary activation levels, the EMG signal was converted to the root mean square (RMS) values of a 500-ms epoch coinciding with peak force (250 ms on each side). The best MVC (highest peak force) was considered for analysis. To assess tibialis anterior co-activity and vastus lateralis EMG activity during MVC, absolute EMG_{RMS} was assessed at the pre- and post-test at the same time point as soleus EMG (described above). H-reflex excitability was determined by averaging the three H_{SUP} responses with the highest peak-to-peak amplitude and normalizing to the M_{SUP} evoked in the V-wave protocol in the same session. The size of the evoked responses was assessed by peak-to-peak amplitudes, and the peak-to-peak amplitudes were used to calculate ratios. For one patient in the MST group, we were not able to obtain consistent H-reflexes, V-waves and M-waves, thus $n = 6$ for all variables obtained with electrical stimulation in the MST group, $n = 7$ for all other variables. To determine the level of efferent neural drive, V-waves were obtained in the soleus during MVC and normalized by the corresponding M_{SUP}. To ensure that measurement conditions were stable, only V-waves with a corresponding $M_{SUP} > 90\%$ of the highest M_{SUP} were included. EMG and force data were synchronized and analyzed using commercial software (MegaWin, Mega Electronics LTD, Kuopio, Finland).

Statistical analysis

Pre- to post-test changes were assessed by the Wilcoxon signed-rank test for paired samples and change scores between groups were assessed by the Mann–Whitney *U* test (both two-tailed). Data are expressed as mean ± SE. $P \leq 0.05$ was considered statistically significant. SPSS v16.0 (SPSS Inc., Chicago, USA) was used for all statistical analyses.

Results

There were no differences between the groups in any of the pretest measures. All patients in the MST group were able to complete 15 MST sessions during the 3-week period.

Isometric strength and EMG_{RMS} activity

MVC torque increased by 20.1 ± 9.0% (Table 2, $P < 0.05$) and was accompanied by a 36 ± 16% increase (Fig. 2a, $P < 0.05$) in soleus EMG_{RMS} activity in the MST group. The change in EMG_{RMS} activity was different from the change in the CG (+40%, $P < 0.05$). No changes were observed for tibialis anterior co-activity or vastus lateralis EMG_{RMS} activity obtained during MVC (Table 2). No changes occurred in the CG (Fig. 2a; Table 2).

Table 2 Torque and EMG_{RMS} recordings

	Maximal strength training group		Control group	
	Pre	Post	Pre	Post
MVC (N m)	88 ± 18	101 ± 18*	88 ± 10	91 ± 12
V-wave (μV)	1,051 ± 228	1,603 ± 124*	978 ± 222	832 ± 195
M_{SUP} (μV)	6,702 ± 1,167	6,997 ± 1,013	7,069 ± 1,168	6,820 ± 881
H_{SUP} (μV)	3,024 ± 729	3,327 ± 961	3,380 ± 599	3,325 ± 367
TA EMG_{RMS} (μV)	39 ± 10	35 ± 5	32 ± 6	25 ± 5
VL EMG_{RMS} (μV)	20 ± 9	18 ± 4	22 ± 5	25 ± 9

Data are presented as mean ± SE

MVC maximum voluntary isometric plantar flexor contraction, *TA* tibialis anterior, *VL* vastus lateralis

* $P < 0.05$, from pre- to post-test

Evoked responses

The CG did not change in any of the evoked potentials or normalized ratios from pre- to post-test (Fig. 2; Table 2). In response to MST, the H_{SUP}/M_{SUP} ratio remained unchanged (Fig. 2b) with no changes observed in the small M-waves accompanying the H_{SUP} stimuli expressed relative to M_{SUP} (pre: 0.18 ± 0.04; post: 0.16 ± 0.02). The level of voluntary torque at the onset of H_{SUP} stimuli, relative to MVC on the same day, was similar between sessions in the CG (pre: 88 ± 2%, post: 88 ± 3%) and MST groups (pre: 80 ± 7%, post: 83 ± 6%).

The V/M_{SUP} ratio increased from 0.17 ± 0.04 to 0.25 ± 0.03 ($P < 0.05$, Fig. 2c) in the MST group, which corresponded to a mean percentage change of 81 ± 35%. This was also significantly different from the CG change (+55%, $P = 0.05$). The level of voluntary torque at the onset of V-wave and M_{SUP} stimuli, relative to MVC on the same day, was similar between sessions in the CG (pre: 91 ± 1%, post: 93 ± 1%) and MST groups (pre: 93 ± 1%, post: 95 ± 1%). Raw EMG traces of evoked V-wave and H_{SUP} responses are presented in Fig. 3.

EDSS

No changes were observed for the EDSS between groups (Table 1). The EDSS score remained unchanged in all subjects from pre- to post-test.

Discussion

This randomized study demonstrated for the first time that training increased the magnitude of efferent motor outflow from spinal motor neurons to the lower limb muscles in MS patients, as evidenced by increased soleus EMG activity and V/M_{SUP} ratio accompanying isometric strength gains of the plantar flexors. No exacerbations of MS symptoms were observed in response to MST.

MVC and EMG_{RMS} activity

A mean percentage increase of 20% in MVC was observed after 3 weeks of MST. This is very similar to what has been reported in healthy subjects after specific strength training (i.e. isometric training and isometric testing) of similar duration (Del Balso and Cafarelli 2007; Holtermann et al. 2007) and demonstrates the vast potential for improvements in strength and neural drive with strength training for MS patients.

Increases in EMG activity in response to strength training have been reported by many previous investigations (Aagaard et al. 2002a; Del Balso and Cafarelli 2007;

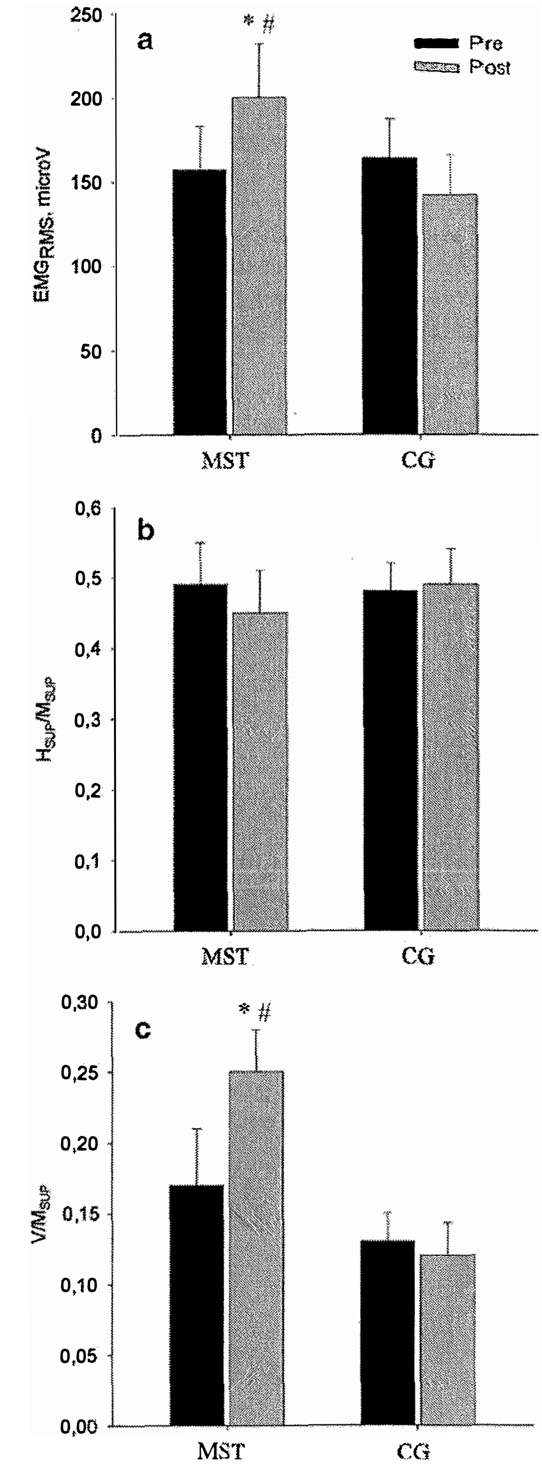

Fig. 2 Soleus **a** EMG_{RMS} activity, **b** superimposed H-reflexes normalized by the superimposed M-wave (H_{SUP}/M_{SUP}), and **c** V-wave normalized by the corresponding M-wave (V/M_{SUP}) obtained during maximum voluntary isometric plantar flexor contraction before and after training in the maximal strength training group (MST) and the control group (CG). *$P < 0.05$, from pre- to post-test. $^{\#}P \leq 0.05$, different from control group change. Mean ± SE

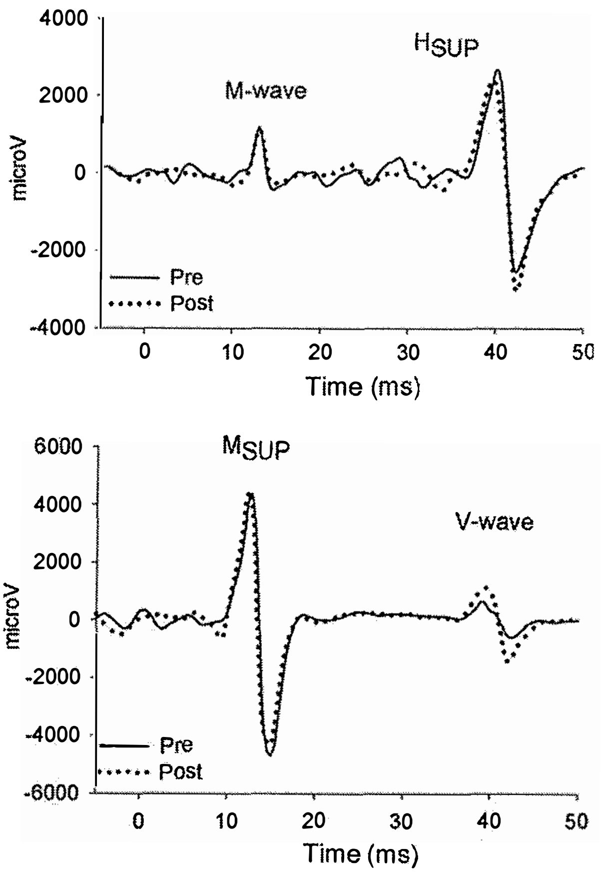

Fig. 3 Recordings of evoked H_{SUP} (mean of three trials) and V-wave (mean of four trials) with accompanying M-waves for one male patient before and after 4 weeks of maximal strength training

Fimland et al. 2009a, b; Hakkinen et al. 1998; Hortobagyi et al. 1996; Suetta et al. 2004). In the present study, the mean soleus EMG_{RMS} activity obtained during MVC increased by 36% from pre- to post-test in the MST group. There was no significant change in the M_{SUP}, indicating that the efficacy and sensitivity of the EMG recording procedures remained unchanged. Therefore, it can be assumed that changes in EMG_{RMS} are mainly related to neural adaptations. This suggests enhanced neural drive after strength training in MS patients for the first time. The increase in EMG_{RMS} activity is probably explained by increased motor neuron recruitment and/or rate coding, although enhanced synchronization has been observed after strength training (Milner-Brown et al. 1975), that can also increase the EMG amplitude (Keenan et al. 2005; Yao et al. 2000).

H-reflex responses

No change in H-reflex excitability was evident in the current study after 15 sessions of MST. Great effort was taken to minimize the extraneous factors that affect H-reflex measurements such as posture, movement, noise and lighting (Zehr 2002). No change in the small concomitant M-waves normalized by M_{SUP} could be observed, indicating that the same fraction of the soleus α-motor neuron pool was depolarized by the stimuli at the pre- and post-test.

In contrast to the present findings, Aagaard et al. (2002b) reported a 19% increase in normalized H-reflex responses during MVC after 14 weeks of heavy multi-exercise strength training. Muscle hypertrophy is usually not observed until the eighth week of training (Akima et al. 1999; Narici et al. 1989). 3 weeks of MST in the present study probably induced minimal hypertrophy
flexors, whereas 14 weeks of training likely induced substantial hypertrophy that the central nervous system would have to adapt to. In line with the size principle (Henneman et al. 1965), the H-reflex volley relies primarily on the pool of small motor neurons (Pierrot-Deseilligny and Burke 2005; Schieppati 1987). 14 weeks of a 4–12 repetition, multi-exercise intervention of the entire lower limb may have affected the recruitment and/or rate coding of the smaller motor neurons activated by the H-reflex afferent volley to a larger extent than 3 weeks of MST. This could also be the case in the study by Gondin et al. (2006), in which neuromuscular electrical stimulation (NMES) training was performed. NMES activates greater motor units before smaller motor units (Paillard 2008), which may explain why no H-reflex change after NMES training was observed during MVC by Gondin and co-workers. Based on the above-mentioned studies, it can be speculated that hypertrophy of slow-twitch muscle fibers may be necessary to observe changes in H_{SUP}/M_{SUP}.

Another methodological issue is that different stimulation intensities may be employed to evoke H-reflexes. Aagaard et al. (2002b) evoked H-reflexes at a stimulation intensity corresponding to 17.5–22.5% of M_{SUP}. The present study and Gondin et al. (2006) employed stimulus intensities that evoked concomitant M-waves $\sim$10–18%. The larger M-wave associated with H-reflex stimulation in the study by Aagaard et al. (2002b) also implies that a greater afferent volley was evoked, which would reflexively activate larger motor neurons that may be more important in strength training.

Nevertheless, no change was observed in H_{SUP}/M_{SUP} during MVC in the current study which indicates that spinal motor neuron responsiveness was not affected in MS patients after MST.

V-wave responses

A substantial increase in the V/M_{SUP} ratio reflects increased voluntary motor output (enhanced motor neuron recruitment and/or firing frequency) from the spinal motor neurons innervating the soleus muscle. This enhanced efferent neural drive can be measured due to the proportional removal of antidromic impulses evoked by the supramaximal stimulus (M_{SUP}) travelling in the α-motor neuron axons, permitting a larger part of the evoked reflex volley of action potentials to pass to the muscle, resulting in a greater V-wave amplitude (Aagaard 2003; Aagaard et al. 2002b).

Longitudinal strength training studies employing healthy volunteers have reported large V-wave enhancements in the soleus muscle. Aagaard et al. (2002b) reported a 55% enhancement in the normalized V-wave response after 14 weeks of heavy dynamic strength training. Similarly Del Balso and Cafarelli (2007) reported a 57% increase in the V/M_{SUP} ratio after 4 weeks of isometric strength training. Fimland et al. (2009a) observed a 53% increase in the V/M_{SUP} ratio after 8 weeks of leg press MST. This is similar to the present result for MS patients.

The current study is the first to employ the V-wave method for investigating neural adaptations in a disease population. As MS is a disease resulting in impaired central neural drive to the lower limb muscles, this technique might be a useful and non-invasive tool to investigate the neural adaptations following resistance training in this population. Aagaard et al. (2002b) suggested that enhanced V-wave amplitude after a period of strength training in healthy subjects was due to augmented descending drive from higher centers mediating increased motor neuron firing frequency. In healthy subjects, the upper level of motor unit recruitment is ~85% of MVC, and increasing force above this level should only be possible by changes in rate coding (Duchateau et al. 2006). However, it seems very unlikely that the descending drive of MS patients that are not fully ambulatory (EDSS $\geq$ 5) is adequate to ensure full motor neuron recruitment. Nonetheless, it was previously suggested that MS patients are not capable of attaining the same motor neuron discharge rates as healthy counterparts (Rice et al. 1992). For MS patients, enhanced motor unit recruitment or elevated motor neuron firing frequency may translate to greater muscle strength and improved functional capacities, thus it seems that strength training can reverse some of the neurological symptoms linked to the disease.

Prior to MST, the mean soleus V/M_{SUP} ratio was 0.17 in the MST group and increased to 0.25 post-training. In other investigations, the average V/M_{SUP} ratio has been reported to be between 0.22 and 0.40 before training and between 0.38 and 0.63 after training (Aagaard et al. 2002b; Del Balso and Cafarelli 2007; Fimland et al. 2009a, b; Gondin et al. 2006). Unsurprisingly, this indicates lower motor output from the spinal motor neurons to the soleus muscle of MS patients compared to healthy subjects. It is interesting to note that the post-training values of the current study were similar to pre-training values reported by Fimland et al. (2009b) and Gondin et al. (2006), despite the fact that the present study included MS patients aged 33–65 and the studies by Fimland, Gondin and co-workers included recreationally active young participants. Thus, the present MS patients involved in MST appeared to become normalized in terms of maximal efferent motor neuron outflow when compared to untrained healthy individuals.

Conclusions

This randomized study provides evidence that MST in combination with standard rehabilitation is effective of augmenting the efferent motor drive from spinal motor neurons to lower limb muscles, alleviating some of the neuromuscular symptoms in patients with mild and moderate disabilities due to MS.

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