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Extra Forces induced by wide-pulse, high-frequency electrical stimulation: Occurrence, magnitude, variability and underlying mechanisms

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HIGHLIGHTS

- The percentage of responders showing “Extra Forces” to wide-pulse, high-frequency (WPHF) neuromuscular electrical stimulation has been previously over-estimated.
- Force output evoked by WPHF shows markedly high inter- and intra-individual variability.
- In the responder group only, H-reflex is depressed immediately after WPHF indicating a significant central contribution to “Extra Forces”.

ABSTRACT

Objective: In contrast to conventional (CONV) neuromuscular electrical stimulation (NMES), the use of “wide-pulse, high-frequencies” (WPHF) can generate higher forces than expected by the direct activation of motor axons alone. We aimed at investigating the occurrence, magnitude, variability and underlying neuromuscular mechanisms of these “Extra Forces” (EF).

Methods: Electrically-evoked isometric plantar flexion force was recorded in 42 healthy subjects. Additionally, twitch potentiation, H-reflex and M-wave responses were assessed in 13 participants. CONV (25 Hz, 0.05 ms) and WPHF (100 Hz, 1 ms) NMES consisted of five stimulation trains (20 s on–90 s off).

Results: K-means clustering analysis disclosed a responder rate of almost 60%. Within this group of responders, force significantly increased from 4% to 16% of the maximal voluntary contraction force and H-reflexes were depressed after WPHF NMES. In contrast, non-responders showed neither EF nor H-reflex depression. Twitch potentiation and resting EMG data were similar between groups. Interestingly, a large inter- and intrasubject variability of EF was observed.

Conclusion: The responder percentage was overestimated in previous studies.

Significance: This study proposes a novel methodological framework for unraveling the neurophysiological mechanisms involved in EF and provides further evidence for a central contribution to EF in responders.

1. Introduction

Neuromuscular electrical stimulation (NMES) is commonly used to enhance muscular performance (Gondin et al., 2011b)

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and to maintain contractile activity in paralyzed or immobilized muscles (Sheffler and Chae, 2007). Electrically-evoked contractions are generated by a combination of peripheral mechanisms (i.e., the direct activation of motor axons under the stimulation electrodes) and central mechanisms (i.e., the depolarization of sensory axons producing a "reflex" response). It has been recently suggested that the relative contribution of peripheral and central factors to force production might be modulated by pulse duration, pulse frequency and stimulation intensity with the aim of generating contractions with a better resistance to fatigue (Collins, 2007; Dean et al., 2008; Bergquist et al., 2011b).

The conventional (CONV) form of NMES typically applied in clinical settings involves the utilization of short stimulus pulses (50–400 μs) delivered at high current intensities and as intermittent low-frequency trains (15–40 Hz) (Hainaut and Duchateau, 1992). These parameters generate contractions predominantly *via* peripheral pathways due to both the preferential activation of motor axons and the large antidromic transmission along them (Bergquist et al., 2011b). Thus, even though being a key component in training and rehabilitation, the major and commonly accepted drawback of CONV is the rapid onset of muscular fatigue due to a non-physiological recruitment of motor units (i.e., random, spatially limited and temporally synchronous) (Vanderthommen et al., 2003; Gregory and Bickel, 2005; Maffiuletti, 2010).

It has recently been suggested that the central contribution to motor unit recruitment could be enhanced when delivering the stimulation at low current intensities and with long pulse duration (Collins, 2007). Low current intensities minimize the antidromic collision in motor axons, thereby allowing orthodromically transmitted signals to descend from spinal circuits. In addition, the use of relatively long pulse durations (0.5–1 ms) favors the recruitment of sensory axons having a longer strength-duration and lower rheobase as compared to motor axons (Veale et al., 1973). Interestingly, the use of wide-pulse (1 ms), high-frequency (>80 Hz) (WPHF) and low-current-intensity NMES has been shown to produce up to three times higher isometric forces than CONV (Collins et al., 2002; Lagerquist et al., 2009). For a given stimulation intensity, this progressively increasing force output that arises in addition to what would be expected from the direct response to motor axon stimulation has been referred to as "Extra Forces" (EF) (Collins et al., 2001, 2002). Based on the fact that a peripheral nerve block abolished the EF phenomenon in some previous studies (Collins et al., 2001; Lagerquist et al., 2009) and that WPHF-induced EF was associated with enhanced H-reflex and/or asynchronous activity (Bergquist et al., 2011a), central mechanisms are likely to be involved in EF generation. Moreover, similar EF patterns have been observed at high frequency tendon vibration. Based on increases in the soleus V/F wave amplitude, vibration-induced EF was attributed to an increased motoneuron excitability (Magalhaes et al., 2013). On that basis, it has been suggested that the central contribution to force production might minimize muscle fatigue due to the preferential recruitment of fatigue-resistant motor units according to the Henneman size principle (Binder-Macleod and Scott, 2001; Gregory et al., 2007), thereby providing a prospective advantage of WPHF over the CONV stimulation pattern for clinical use. However, the central origin hypothesis of EF has been recently challenged by the findings of Frigon et al. suggesting that EF could essentially result from intrinsic muscle properties (Frigon et al., 2011). In the latter study, anesthetic nerve block experiments in human subjects and nerve transection in decerebrate cats failed to abolish EF, instead muscle length changes significantly affected EF. Accordingly, peripheral mechanisms such as length-dependent changes in Ca^{2+} release, sensitivity, and phosphorylation of the myosin light chain have been proposed as underlying mechanisms for EF (Binder-Macleod and Kesar, 2005; Frigon et al., 2011). Another finding that challenges the hypothesis of an enhanced central contribution involved in WPHF is that neuromuscular fatigue was even increased for repeatedly evoked WPHF contractions (Neyroud et al., 2014).

Previous studies reported that WPHF-induced EF occurs in 85–100% of healthy individuals, classified as responders for nerve (Baldwin et al., 2006; Klakowicz et al., 2006) and muscle belly stimulation (Collins et al., 2001; Baldwin et al., 2006; Dean et al., 2007). However, this large proportion has been observed when small sample sizes were tested (i.e., ranging from 5 to 15 subjects). Moreover, the hitherto existing classification approach suffers from methodological limitations given that no comparative analysis has been performed between WPHF and CONV to determine EF occurrence. This is surprising given that force production can also slightly increase in response to CONV, e.g. due to staircase potentiation (Rassier and MacIntosh, 2002). The mechanisms that may account for the differences in force response between subjects and NMES protocols remain to be determined.

In the present study, we investigated, in a first instance, the occurrence of EF in a large cohort of subjects by using a clustering method previously applied for quantifying the inter-individual variability to resistance training (Bamman et al., 2007; Gondin et al., 2011a). In addition to EF occurrence, we studied the magnitude and variability of EF in response to WPHF in order to estimate the protocol's effectiveness and its potential beneficial use. Considering that NMES-induced strength gains are correlated with the electrically-evoked force (i.e., the magnitude of EF) (Maffiuletti, 2010; Gondin et al., 2011b), information regarding both the between- and within-subject variability are of importance in the context of rehabilitation. To account for EF occurrence, magnitude and variability, we investigated, for a subset of responders and non-responders, the potential underlying neuromuscular mechanisms by evaluating twitch potentiation, H-reflex and M-wave. We hypothesized that the responder subjects would exhibit a higher twitch potentiation and a higher resting H-reflex excitability as compared to the non-responders.

2. Methods

The study is divided into two experiment sections (Fig. 1). The first sub-study addresses the EF phenomenon in terms of occurrence and magnitude on a large cohort of subjects. The second sub-study investigates the central and peripheral factors for EF generation by using a smaller sample. The entire study was approved by the Local Human Research Ethics Committee Sud Méditerranée I (n° 2012-A01265–38) and was conducted in conformity with the Declaration of Helsinki.

2.1. Sub-study 1 – EF occurrence and magnitude

2.1.1. Subjects

42 healthy volunteers (20 men, 22 women; age: 28 ± 6 years, weight: 64 ± 10 kg, height: 171 ± 10 cm, mean ± SD) devoid of neurological and musculoskeletal impairment participated in the study after providing written informed consent. All subjects reported to be occasionally but not regularly active in recreational sports. Before testing, subjects were asked to avoid any strenuous exercise 48 h prior to the protocol to minimize possible residual fatigue.

2.1.2. Experimental design

The testing session included: (1) a warm-up period consisting of 5–7 submaximal plantar flexion contractions of 3–5 s, (2) assessment of isometric maximal voluntary contraction (MVC) force; (3) adjustment of NMES intensity by using 2-s testing trains and