Journal of Electromyography and Kinesiology 45 (2019) 41–45

Contents lists available at ScienceDirect

Journal of Electromyography and Kinesiology

journal homepage: www.elsevier.com/locate/jelekin

Motor unit recruitment in myopathy: The myopathic EMG reconsidered

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ARTICLE INFO

Keywords:
Motor units
Myopathy
Neurophysiology
Recruitment rate
Upper motor neuron

ABSTRACT

Motor unit recruitment is abnormal in myopathies. We have addressed this subject by recording motor unit potentials (MUPs) using a standard concentric needle electrode in tibialis anterior muscles of clinically normal strength in a group of patients with myopathy (15 with myositis and 4 with facioscapulohumeral muscular dystrophy Type 1). In each recording site, a minimal voluntary contraction was sought in order to activate only 2 MUPs. At least 5 pairs of MUPs were recorded in each muscle. We analysed the recruitment rate of the first activated MUP and the mean consecutive difference (MCD) of firing frequency between the individual MUPs of each recruited pair. Results were compared with 30 healthy control subjects. In myopathy the first recorded MUs fired at similar rates to controls (8.2 vs 8.0 Hz, respectively), but the MCD of the firing rate difference between the first two recruited MUPs was less than in controls (median difference 1.78 Hz vs median difference 2.47 Hz, $p = 0.02$). This change suggests increased lower motor neuron excitability as a functional adaptation, since muscle strength was normal in the studied muscles. These findings are consistent with spinal cord adaptation to the functional changes associated with myopathic muscle disease, although a primary muscle fibre feedback sensing mechanism could also be involved.

1. Introduction

Concentric needle EMG studies in myopathies reveal motor unit (MU) action potentials (MUPs) of increased complexity, shortened duration and reduced amplitude (Fuglsang-Frederiksen, 2006). In addition, there is greater recruitment of MUs at low effort (Dietz et al., 1975; Petajan, 1974; Halonen et al., 1981), firing at shorter MUP intervals, producing a full interference pattern at less than maximal voluntary contraction force, features suggesting disruption of Henneman's size principle of orderly recruitment (Petajan, 1974, 1991). Petajan (1974, 1991) thought that abnormal MU recruitment in myopathies could be explained by mismatch between force generated in weak myopathic muscles and central motor programming in the brain, but this EMG abnormality during recruitment in myopathies occurs even in strong muscles.

The pattern of altered MUP recruitment in myopathies has been studied using several different techniques. Halonen et al. (1981) reported that MUP firing frequency was higher in patients with myopathy than in controls (Dietz et al., 1975; Petajan, 1974) but the interval variability of MUPs was found to be similar to controls (Petajan, 1974; Dorfman et al., 1989). Fuglsang-Frederiksen and Smith (1987) described normal MUP firing rate frequency and variability in patients with myopathy, during contraction at 10% of maximal force. On the other hand, increased variability of inter-MUP intervals has been reported in both peripheral and central neurogenic disorders (Petajan, 1974; Halonen et al., 1981; Dorfman et al., 1989).

We have previously explored the variability of MUP firing during very mild contraction of the tibialis anterior muscle (TA) by calculating mean consecutive differences (MCD) of the firing rate of pairs of the recruited MUPs (de Carvalho et al., 2017). Using this novel method, we observed reduced MCD (lower MU firing rate variability) in patients with spasticity in leg muscles associated with spinal cord lesions, and in amyotrophic lateral sclerosis (ALS) (de Carvalho et al., 2017), confirming previous observations (Floeter et al., 2005; de Carvalho et al., 2012). Here we extend these observations to myopathic muscle.

2. Subjects and methods

We studied two groups of subjects. There were 30 normal control subjects, without neurological disease, referred for evaluation of non-specific muscle and limb pain in whom all investigations, including blood creatine kinase and inflammatory markers were normal, and in

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https://doi.org/10.1016/j.jelekin.2019.02.005
Received 24 July 2018; Received in revised form 16 February 2019; Accepted 18 February 2019

whom the EMG analysis was also normal. The second group consisted of 19 patients with myopathy, in whom there was proximal muscle weakness. These 19 patients all had EMG studies as part of their diagnostic work-up. Four (2 men and 2 women aged 38–64 years) had facioscapulohumeral muscular dystrophy Type 1, confirmed by genetic analysis as associated with mutational expansion of D4Z4 at C4q35. The remaining 15 patients (11 women and 4 men) aged 36–76 years had idiopathic chronic myositis confirmed by increased blood CK levels and by muscle biopsy. All of them were responsive to steroids. These 15 patients were routinely monitored during weaning from steroid therapy, which included neurophysiological assessment to identify signs of active denervation (Desmedt and Borenstein, 1975), but none were found. Typical 'myopathic' changes in motor unit morphology were noted in the 'Multi-MUP analysis' program on a Medtronic Keypoint-Net EMG machine. The protocol was approved by the local Ethics Committee and informed consent was obtained from all individual participants included in the study.

2.1. Neurophysiological methods

MUP morphology and MU recruitment was studied in the TA muscle in each subject using conventional disposable concentric needle electrodes (CNEMG); recording area 0.07 mm^2, linked to the EMG machine. All the studied muscles were of normal strength (MRC5). For reasons of convenience we preferred to study the right side. The skin temperature was maintained greater than 32 °C.

For MUP firing rate analysis using the 'Multi-MUP analysis" program, the filter settings were 5 Hz–10 KHz, gain 200 mV/div and sweep speed 5 ms/div. The CNEMG electrode was inserted into the superficial layer of the TA muscle. Each subject was asked to initiate a slight, steady contraction, without applied resistance (de Carvalho et al., 2017), using auditory feedback provided by the loudspeaker of the EMG machine, in order to recruit a single motor unit, and then to recruit a second unit. The second unit almost always closely followed the first, but did not fire at exactly the same frequency (Fig. 1). An initial period of unstable contraction was usually followed by a steady firing rate. The subject was asked to continue the muscle contraction for up to 2 min (de Carvalho et al., 2017). All recordings accepted for analysis were made in this stable phase. Recordings from subjects unable to maintain a stable contraction, and those unable to produce a steady contraction sufficient to recruit a second motor unit, were rejected. With this technique, 5–6 pairs of motor units were acquired in up to 5 different recording sites in the TA muscle, at different depth, each estimated as > 1 cm apart. At least 25 recorded discharges from each motor unit were required for analysis at each site (Fig. 1). Using this protocol, fatigue is not an important consideration (de Carvalho et al., 2012, 2017).

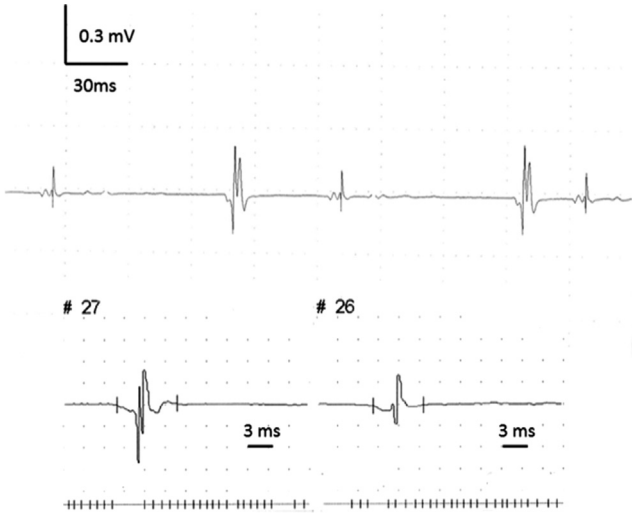

Fig. 1. In the top panel two small motor units of short duration have been recruited by very slight contraction of the tibialis anterior in a patient with myositis. In the bottom panel two myopathic motor units fire regularly at very similar firing rates.

2.2. Data analysis

The MUP analysis was done off-line. In each group, we compared the amplitude, area, area/amplitude ratio and number of phases between first and second recruited MUP in the pair by applying Student's paired *t*-test (175 × 2 MUPs in controls and 109 × 2 MUPs in patients with myopathy). Data between control group and patients with myopathy were explored with an unpaired *t*-test. The p-value was corrected for multiple comparisons (0.05/4 = 0.0125).

The mean firing rate for each motor unit in each pair of recorded units, and the MCD between firing rates in each pair recorded in each sequence were calculated. For MCD calculation we adapted the conventional formula for "jitter" calculation (Ekstedt et al., 1974): $MCD = [FR\_MU_1 - FR\_MU_2] + [FR\_MU_3 - FR\_MU_4] + [FR\_MU_{n-1} - FR\_MU_n]/[n - 1]$ (where FR is firing rate, MU is motor unit). The Shapiro-Wilk test rejected normality in the data distribution. The Mann-Whitney test was therefore applied to test differences between the two groups. This procedure was applied to the MCD analysis and to the study of the firing frequency of the first motor unit in a pair (Table 1). The threshold for statistical significance was defined as $p < 0.25$ (0.05/2).

3. Results

A total of 568 MUPs were analysed in both groups (350 in the control group and 218 in the group of patients with myopathy). In the group of patients with myopathy, comparing the first and second MUP in each pair did not disclose differences for amplitude (509.9 ± 370.1 vs 527.3 ± 382.8 mV, respectively, p = 0.7), area (537 ± 409.6 vs 604.13 ± 424.6 mV·ms, respectively, p = 0.2), area/amplitude ratio (1.09 ± 0.40 vs 1.23 ± 0.50, respectively, p = 0.2) and mean number of phases (3.72 ± 1.08 vs 3.47 ± 1.29, respectively, p = 0.5). The same holds true for the control group, amplitude (581.6 ± 369.2 vs 490.2 ± 302.7 mV, respectively, p = 0.14), area (739.4 ± 562.7 vs 650.1 ± 443.7 mV·ms, respectively, p = 0.08), area/amplitude ratio (1.31 ± 0.45 vs 1.34 ± 0.46, respectively, p = 0.40) and mean number of phases (3.28 ± 1.1 vs 3.47 ± 1.3, respectively, p = 0.44). Comparing the two groups, patients with myopathy and controls, MUP amplitude (518.6 ± 375.8 vs 535.9 ± 340.9 mV, respectively, p = 0.57) was similar, but MUP area (566.4 ± 413.4 vs 694.7 ± 508.0 mV·ms, respectively, p = 0.002) and area/amplitude ratio (1.16 ± 0.46 vs 1.33 ± 0.46, respectively, p < 0.001) were smaller in the group with myopathy (Fig. 2). In addition, the mean number of phases was greater in the myopathy group (3.08 ± 1.78 vs 3.38 ± 1.19, respectively, p = 0.001) (Fig. 2).

In both normal and myopathic subject groups the first recruited MUPs fired at the same median frequency (8.2 vs 8.0 Hz, respectively). However, the MCD of the MU firing rates of the first and second MU's was significantly shorter in the group of patients with myopathy (median difference of 1.78 Hz between 1st and 2nd recruited motor unit) compared with controls (median difference of 2.47 Hz, p = 0.02) – (Table 1 and Fig. 3).

4. Discussion

Our studies of MU recruitment in tibialis anterior (TA) muscles of normal power (MRC 5) in patients with myopathy were made at minimal voluntary activation, without imposed resistance. In all the myopathic TA muscles MUP analysis was consistent with myopathy, as supported by MUP area, area/amplitude area and number of phases.

Table 1
Results.

Subject groups [Males/Females]	Median age [1st–3rd IQR]	Number of MUs analysed	Median MCD of MU firing frequency – 1st and 2nd potentials [1st–3rd IQR]	Median firing frequency [Hz] of 1st MU [1st–3rd IQR]
Normal subjects [16/14]	62.0 [48.0–69.0]	350	2.47 Hz [2.00–2.82]	8.20 Hz [6.90–9.60]
Myopathy [6/13]	57.5 [45.8–65.0]	218	1.78 Hz [1.12–2.20]	8.0 Hz [7.13–8.90]
P value	0.44		**0.02**	0.49

MCD – mean consecutive difference; IQR – interquartile range; FR – firing rate; MU – motor unit. $p < 0.05$ was considered as significant [bold].

MUP duration was not specifically analysed as MUP area is directly derived from duration and amplitude of the recorded potential. We investigated the variability between the frequencies of the recruited MUPs in each MUP pair, using a calculation originally described to estimate neuromuscular junction jitter (Ekstedt et al., 1974; de Carvalho et al., 2017). In myopathy we found that the first recorded MUPs fired at the same frequency as in control subjects, but the mean consecutive difference (MCD) between the first and second recruited MUPs was decreased (Table 1 and Fig. 3), indicating that the firing rate of the second recruited MU was less variable than that of the first recruited MU, measured in consecutive discharges.

High-density EMG analysis is a more novel and powerful technology in EMG analysis, which would permit to investigate multiple MUs per contraction, allowing to study MUPs integration and the propagated muscle fibre conduction velocity of the individual muscle fibre components of MUs. In utilising this technique the relation of neural drive to EMG features, based on EMG spectral analysis and the average conduction velocity of action potentials might be of interest in inferring recruitment strategies (Farina et al., 2016; del Vecchio et al., 2017, 2018). However, it would be difficult to address the firing rate interplay between the first and the second recruited MU during minimal voluntary force.

Myopathies are primary disorders of muscle. Spinal cord circuitry is undamaged, and adaptable to muscle weakness. Petajan (1974, 1991) suggested that in myopathies there is a mismatch between the reduced force generated by a weakened muscle and the central program in the brain and spinal cord required for force generation in the muscle, as signalled by feedback from muscle, joint and cutaneous afferents. The normal 'efference feedback' relationship is therefore disrupted leading to re-ordering of the recruitment pattern of individual motor units. A similar mismatch is present in neurogenic disorders but, in some of these, e.g., motor neuron disease, there is disruption of sensory input from muscle receptors at a spinal level as well as to the gamma efferent innervation of muscle spindles (Swash and Fox, 1974; Dietz et al., 1975; Halonen et al., 1981) leading to marked variability in MU firing rates (Dietz et al., 1975; Halonen et al., 1981) in these disorders.

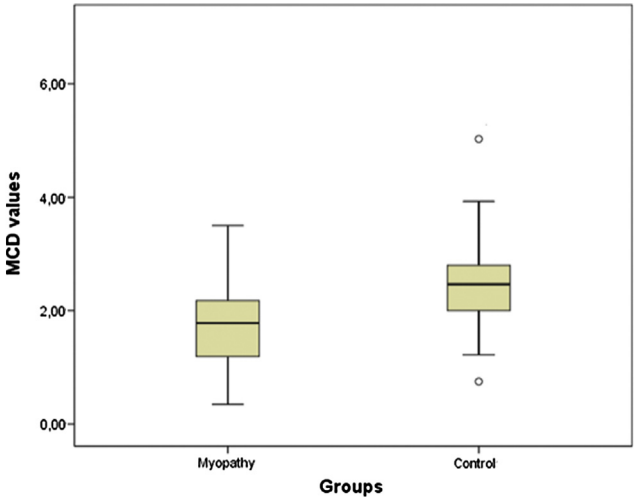

Fig. 3. Box-plot representation of the mean consecutive differences [MCD] of the firing rate of pairs of motor units in patients with myopathy and in controls.

During minimal activation of a muscle in normal subjects the first recruited MUs are Type 1, slow-firing MUs, as predicted by the Henneman principle. Muscle spindle and tendon organ activity (Swash and Fox, 1974; Dietz et al., 1975; Hagbarth and Vallbo, 1969; Calancie et al., 1993) and spinal interneurons (Pierrot-Deseilligny and Burke, 2005) are important in the regulation of low-rate firing, tonic alpha MU excitability. Modulation between the firing rates of the first and second recruited MUs in our recordings is unlikely given the slow firing rates recorded at minimal voluntary activity (de Carvalho et al., 2017). In degenerative motor neuron disorders, in which the neurons and their connexions in the anterior horns are directly damaged, MU firing rate variability tends to be more marked (Halonen et al., 1981; Fuglsang-Frederiksen and Smith, 1987; de Carvalho et al., 2012). In contrast to previous electrophysiological studies of myopathy, using different techniques (Petajan, 1974; Fuglsang-Frederiksen and Smith, 1987;

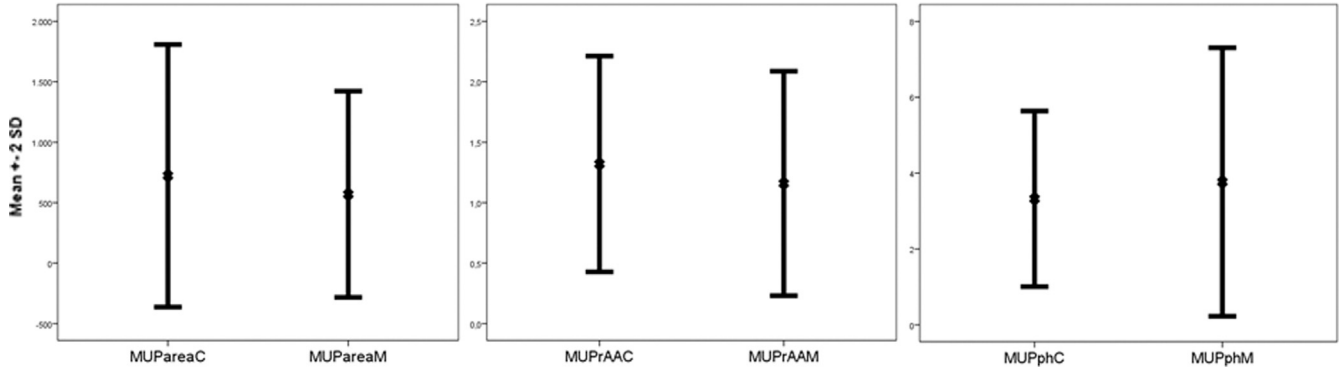

Fig. 2. Error bars with mean values and 2SD of the MUP measurements for controls and patients, amplitude (MUPamplC and MUPamplM, respectively), area (MUPareaC and MUPareaM, respectively), area/amplitude ratio (MUPrAAC and MUPrAAM, respectively) and number of phases (MUPphC and MUPphM, respectively), showing differences for area, area/amplitude ration and number of phases, but with large overlap.

Dorfman et al., 1989), we found a lower variability (smaller MCD) in patients with myopathy. Tonic motor unit activity is physiologically slightly irregular (Andreassen and Rosenfalk, 1980; Petajan, 1991) during slow motor unit firing. This has been attributed to threshold spontaneous oscillations of the lower motor neuron membrane due to "synaptic noise" from inconstant presynaptic inflow (Stålberg and Thiele, 1973). The reduced MU firing rate variability observed in myopathies is likely to reflect an adaptive increased motor neuron excitability, as also described in patients with upper motor neuron lesion (Floeter et al., 2005; de Carvalho et al., 2012). This probably involves a change in the after-hyperpolarisation potential (Andreassen and Rosenfalk, 1980) related to abnormal activation of persistent inward currents (Gorassini et al., 2002; Floeter et al., 2005), that act to smooth force output during a motor task (Broman et al., 1985).

The classical description of the 'myopathic EMG' pattern has been criticised as not specific to primary muscle disease since atrophic or hypoplastic muscle fibres, and neurogenic loss of axonal end-twigs could also cause increased MU potential activation in relation to effort, characteristic of the myopathic EMG (Engel, 1975). However, the typical myopathic EMG is a universal feature of primary muscle disorders, whether metabolic, endocrine, inflammatory, structural or dystrophic. Simulation studies have suggested that increased complexity of MU action potential waveforms in myopathy is due to increased variability of muscle fibre diameter, rather than loss of muscle fibres (Nandedkar and Sanders, 1989), but this hypothesis does not account for the early EMG changes in metabolic myopathies, such as thyrotoxic myopathy. Petajan (1974, 1991) noted the increased recruitment and firing rate of MUs in myopathies both at onset of minimal activity and during increasing voluntary force, while also commenting on the lack of correlation of abnormal MU potential morphology with fibre necrosis or metabolic change. In myopathy weakness may be subclinical, undetected by simple clinical assessment of voluntary force. In metabolic and endocrine myopathy, without structural change in muscle fibres, weakness reflects an energy gap, causing altered excitation-contraction coupling. The relationship between energy liberated during isometric contraction and force was established by Fenn (1924), including its variation during shortening and lengthening contraction, leading to refutation of the then-pervasive visco-elastic theory of muscular contraction (Rall, 1982). The sliding filament theory (Huxley and Hanson, 1943) has required modification to take account of the role of titin, a prominent muscular elastic protein which can store energy released at the actin-myosin cross-bridges, providing a mechanistic explanation of the Fenn effect. Titin binds to actin in the presence of released calcium. Thus, disruption of the action of titin by disturbed calcium homeostasis in muscle fibres offers a possible explanation of muscle fibre weakness in non-structural myopathies (Nishikawa et al., 2012). In addition to neural mechanisms, force production in muscle fibres may be modified by intrinsic muscle signalling involving a focal adhesion kinase associated with the titin complex at the sarcomeric M-band (Durieux et al., 2009). The complex mechanisms governing mechanochemical transduction and changes in MU firing rate, and in variability of firing rate, have not been closely explored in neuromuscular disease, although this aspect of central motor system adaptation to neuromuscular disease is important in maintenance of functional capacity (Swash, 2017).

Conflict of interest

The authors report no conflict of interest.

Acknowledgements

This research was supported by UID/BIM/50005/2019, project funded by Fundação para a Ciência e a Tecnologia (FCT)/Ministério da Ciência, Tecnologia e Ensino Superior (MCTES) through Fundos do Orçamento de Estado (Portugal).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelekin.2019.02.005.

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