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Intra-rater reliability of motor unit number estimation and quantitative motor unit analysis in subjects with amyotrophic lateral sclerosis

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HIGHLIGHTS

- Decomposition-enhanced spike-triggered averaging (DE-STA) motor unit number estimation (MUNE) was found to be highly reliable in subjects with amytrophic lateral sclerosis (ALS).
- Comparison of the results in subjects with ALS to control data demonstrated the ability of the technique to detect MU loss.
- The upper trapezius (UT) was found to be a suitable proximal muscle for application of the technique.

ABSTRACT

Objectives: To assess the intra-rater reliability of decomposition-enhanced spike-triggered averaging (DE-STA) motor unit number estimation (MUNE) and quantitative motor unit potential analysis in the upper trapezius (UT) and biceps brachii (BB) of subjects with amyotrophic lateral sclerosis (ALS) and to compare the results from the UT to control data.
Methods: Patients diagnosed with clinically probable or definite ALS completed the experimental protocol twice with the same evaluator for the UT ($n = 10$) and BB ($n = 9$).
Results: Intra-rater reliability for the UT was good for the maximum compound muscle action potential (CMAP) (ICC = 0.88), mean surface-detected motor unit potential (S-MUP) (ICC = 0.87) and MUNE (ICC = 0.88), and for the BB was moderate for maximum CMAP (ICC = 0.61), and excellent for mean S-MUP (ICC = 0.94) and MUNE (ICC = 0.93). A significant difference between tests was found for UT MUNE. Comparing subjects with ALS to control subjects, UT maximum CMAP ($p < 0.01$) and MUNE ($p < 0.001$) values were significantly lower, and mean S-MUP values significantly greater ($p < 0.05$) in subjects with ALS.
Conclusions: This study has demonstrated the ability of the DE-STA MUNE technique to collect highly reliable data from two separate muscle groups and to detect the underlying pathophysiology of the disease.
Significance: This was the first study to examine the reliability of this technique in subjects with ALS, and demonstrates its potential for future use as an outcome measure in ALS clinical trials and studies of ALS disease severity and natural history.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the selective death of upper and lower motor neurons that typically affects middle-aged to older adults (Rowland and Shneider, 2001). Degeneration of lower motor neurons results in denervation of skeletal muscle fibers and a corresponding decline in the number of functioning motor units (MUs) of a given muscle. Collateral reinnervation (the compensatory process whereby new nerve sprouts from surviving nerve axons supply orphaned muscle fibers) is eventually outpaced by MU loss, leading to progressive muscle atrophy and weakness (Hansen and Ballantyne, 1978).

Highly relevant for application to this disease population, motor unit number estimation (MUNE) was developed by McComas et al.

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(1971a) as a quantitative, electrophysiological method for estimating the number of functioning MUs within a muscle or group of muscles.

ALS clinical trials aimed at finding treatments to alter the natural history of the disease frequently employ outcome measures that assess function and muscle strength. However, as a result of collateral reinnervation, these measures may remain relatively stable until MU loss has surpassed a critical threshold. In contrast, MUNE takes into account the effects of collateral reinnervation (McComas et al., 1971b). The subsequent ability of MUNE to quantify underlying disease progression (MU loss as well as collateral reinnervation) makes it a valuable addition as an outcome measure for use in ALS clinical trials (Bromberg and Brownell, 2008; Rashidipour and Chan, 2008).

First described as a method of MUNE by Boe et al. (2004), a key advantage of decomposition-enhanced spike-triggered averaging (DE-STA) over many other MUNE techniques is its ability to study proximal muscles. It also improves upon other techniques in its collection of not only surface, but also intramuscular electromyographic (EMG) data, allowing for quantitative motor unit potential (MUP) analysis. Incorporation of a series of computer-based algorithms for intramuscular EMG signal decomposition (termed decomposition-based quantitative electromyography [DQEMG]) (Stashuk, 1999) gives DE-STA MUNE a number of specific advantages over conventional spike-triggered averaging MUNE, which have been previously described (Bromberg and Brownell, 2008; Doherty et al., 1995).

In evaluating the potential utility of DE-STA MUNE as an outcome measure for use in ALS clinical trials, the muscle to which it will be applied is an important consideration. The role of the upper trapezius (UT) as an accessory muscle of respiration may make it particularly relevant to study in ALS, given that respiratory failure is generally the cause of death (Gregory, 2007). The UT aids with inspiration in the presence of impaired diaphragmatic function, as occurs with progressive denervation in ALS (Gregory, 2007). Quantification of the number and characteristics of MUs associated with a muscle related to respiratory function may offer insight into the severity and progression of the disease, as well as the potential efficacy of interventions. In addition to the UT, the current study examined the biceps brachii (BB). Application of the technique to multiple muscles representing different segmental levels of innervation is relevant given the highly variable distribution and progression of muscle involvement associated with the disease (Bromberg and Brownell, 2008).

In order for a measurement technique to be useful, its results must be reproducible in the hands of the same evaluator at two or more points in time (intra-rater reliability) (Portney and Watkins, 2008). Among other muscle groups, the intra-rater reliability of DE-STA MUNE has been studied in the BB (Boe et al., 2006) and UT (Ives and Doherty, 2012) in control subjects. In addition, the intra- and inter-rater reliability of the analysis of data collected using DQEMG (not including MUNE) has been assessed in various muscle groups (Boe et al., 2010; Calder et al., 2008). However, despite being applied to the study of subjects with ALS in the BB (Boe et al., 2007, 2008, 2009), and to a single subject in the UT (Lewis, 2009), the intra-rater reliability of DE-STA MUNE has yet to be examined in these or any other muscle groups in this patient population.

In addition to reliability, a critical property of any outcome measure is its validity. In the absence of a gold standard technique, or normative anatomical data with which to compare the results of DE-STA MUNE, the ability of the technique to detect the underlying pathophysiology of the disease can be evaluated by comparing the results between subjects with ALS and control subjects, as was previously done in the BB and first dorsal interosseous (Boe et al., 2007).

Thus, the objectives of this study were twofold. First, to assess the intra-rater reliability of DE-STA MUNE and quantitative MUP analysis in the UT and BB of subjects with ALS. Second, to compare the results of DE-STA MUNE and quantitative MUP analysis in the UT of subjects with ALS to data obtained previously in control subjects in the same muscle (Ives and Doherty, 2012).

2. Methods

2.1. Subjects

In total, 14 patients diagnosed with clinically probable or definite ALS as defined by the revised El Escorial criteria (Brooks et al., 2000) were recruited from the Motor Neuron Diseases Clinic at University Hospital, London Health Sciences Center to participate in this study. Patients were included if they were between the ages of 18–90, were within 10 years of symptom onset, and were judged as having sufficient upper extremity (UE) strength to perform the degree of scapular elevation and/or elbow flexion required for the MUNE protocol. Patients were excluded if they had evidence of other neuromuscular or musculoskeletal disease.

Each subject completed testing in one or both of the muscles of interest (not all 14 subjects were willing and/or able to participate in testing in both muscle groups for various reasons), with 10 subjects participating in the UT portion of the study and 9 subjects participating in the BB portion of the study. All subjects gave written, informed consent in accordance with The University of Western Ontario Health Sciences Research Ethics Board, which approved this study.

2.2. Electromyographic data collection and analysis

EMG signals were acquired using DQEMG (version 3.2) and Acquire EMG software on a Neuroscan Comperio (Neuroscan Medical Systems, El Paso, TX). Self-adhering Silver Mactrode® electrodes (GE Medical Systems, Milwaukee, WI) were used to detect surface signals, and 25 mm × 30 gauge disposable concentric needle electrodes (TECA™ elite, CareFusion, Middleton, WI) were used to detect intramuscular signals, with bandpass settings of 5 Hz to 5 kHz and 10 Hz to 10 kHz, respectively (Boe et al., 2004; Doherty and Stashuk, 2003).

Testing was conducted unilaterally on the arm identified by the subject as having less weakness. If the patient was unable to determine which arm was stronger, the right arm was selected. For the UT, subjects were seated upright in a straight back chair or wheelchair, and for the BB, subjects were supine on an examination table or, if this was not tolerated, positioned in a semi-reclined or seated position. For the BB, the arm being tested was supported in partial abduction with the forearm supinated.

Surface electrodes were cut in strips (1 cm × 3.5 cm) for use as the active and reference electrodes, with a full-sized electrode serving as a ground. For both muscle groups, the skin was cleansed with isopropyl alcohol and surface electrodes positioned appropriately. For the UT, the active electrode was positioned transversely over the belly of the muscle, approximately midway between the acromion process and C7 spinous process, with the reference electrode placed over the acromion process, and the ground electrode over the deltoid (Ives and Doherty, 2012; Lewis, 2009). For the BB, the active electrode was again positioned transversely over the belly of the muscle, with the reference electrode placed over the tendon at the elbow and the ground electrode over the forearm just distal to the elbow crease (Boe et al., 2006).

A handheld bipolar stimulator was used in order to elicit a maximum compound muscle action potential (CMAP), with the spinal accessory nerve stimulated posterior to the sternocleidomastoid