

Chapter 18

Motor unit number estimates, quantitative motor unit analysis and clinical outcome measures in amyotrophic lateral sclerosis

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1. Introduction

Clinical outcome measures currently used in the assessment of patients with amyotrophic lateral sclerosis (ALS) have proven valuable due to their ability to predict survival and document the course and natural history of the disease (McGuire et al., 1996; Cedarbaum et al., 1997; De Carvalho et al., 2005; Kaufmann et al., 2005; Kimura et al., 2006; Schmidt et al., 2006). However, given the global nature of these measures, their ability to represent the underlying pathophysiology of ALS is limited, as they do not directly measure the changes occurring within the motor unit (MU) pool resulting from the disease. Insight into these changes, however, has been previously accomplished using

electrophysiological techniques including measuring the size of the evoked maximal M wave and standard needle electromyography (EMG). Unfortunately, both of these techniques have limitations that diminish their capacity to represent changes occurring at the level of the MU. For instance, size-related parameters of the maximum M wave may remain within normal limits, despite a substantial decline in MU number as a result of collateral reinnervation (McComas et al., 1971; Brown, 1973). Limitations associated with the recording characteristics of needle electrodes and the qualitative nature of the standard needle EMG examination reduces its capacity to accurately represent MU size, particularly in longitudinal studies (Nandedkar et al., 1988, 1990).

Decomposition-based quantitative electromyography (DQEMG) was recently shown to be useful in obtaining electrophysiological data from a group of patients with ALS. In this study, motor unit number estimates (MUNEs) and quantitative indices of MU size were obtained and found

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to be representative of changes occurring within the MU pool (Boe et al., 2007). Although these initial results support the use of DQEMG in the assessment of patients with ALS (Boe et al., 2007), further investigation into its ability to represent the degree of MU loss and subsequently the severity and course of the disease process in comparison to previous measures is warranted. Thus, this study sought to compare the results of DQEMG analysis with several clinical outcome measures to determine the value of DQEMG in the assessment of ALS.

2. Methods

2.1. Subjects

Nine patients (52 ± 12 years) with clinically probable or definite ALS as defined by the revised El Escorial criteria (Brooks et al., 2000) and ten healthy subjects (27 ± 4 years) volunteered to participate in the study. Two of the nine ALS patients were unable to perform the first dorsal interosseous (FDI) portion of the study due to severe atrophy of this muscle and had non-detectable M waves. All subjects gave informed consent and our institutional review board approved the study.

2.2. Electrophysiological data collection

DQEMG was applied to the FDI and biceps brachii (BB) muscles as previously described (Boe et al., 2006, 2007). Briefly, maximal M waves were acquired using supramaximal electrical stimulation of the ulnar nerve at the wrist (FDI) and the musculocutaneous nerve in the axilla (BB). Following acquisition of the maximal M wave, DQEMG was used to extract needle-detected motor unit potential (MUP) trains from the composite EMG signal during 30-s voluntary isometric contractions, and decomposition-enhanced spike-triggered averaging was used to obtain the surface-detected MUP (S-MUP) associated with each of these trains. Size parameters of the needle-detected MUPs (peak-to-peak

voltage) and S-MUPs (negative-peak amplitude) were measured and recorded. Additionally, MUNEs were derived by dividing the mean negative-peak amplitude of the S-MUPs of a given subject into the negative-peak amplitude of the corresponding maximum M wave.

2.3. Force measurement

Isometric maximal voluntary contractions (MVCs) were obtained for the FDI and BB muscles for each of the subjects using custom-made force dynamometers designed to isolate the action of the muscles of interest (Boe et al., 2006, 2007). In addition to these MVCs, a modified form of the isometric strength testing portion of the Tufts Quantitative Neuromuscular Exam (TQNE) was completed for each of the patients with ALS. In total, six movements were tested bilaterally according to standardized criteria (Andres et al., 1986), including three in the upper limb (elbow flexion, shoulder extension and grip strength), and three in the lower limb (hip flexion, knee extension and ankle dorsiflexion). An average raw score for each subject was determined for both the upper and lower limb by averaging the six scores for the upper (three muscles bilaterally) and lower (three muscles bilaterally) limbs independently. Using regression equations from the National Isometric Muscle Strength Database Consortium (National Isometric Muscle Strength Database, 1996), we were able to determine an estimate of the expected pre-morbid strength for each patient for each muscle tested. Using these data, we calculated for each patient the percentage of predicted force that their raw score represented for each of the muscles tested (i.e., elbow flexion raw score/elbow flexion predicted score $\times 100$). These percentage values were then averaged for the upper and lower limbs independently, with the resultant values representing the percentage of residual isometric strength compared to an age-, gender-, height- and weight-matched control population. Lastly, megascores were calculated for both the upper and lower limbs

for each patient using standardized methodology (Andres et al., 1988) to facilitate comparison of strength values obtained using the TQNE with that of the ALS population mean.

2.4. ALS functional rating scale-revised (ALSFRS-R)

The ALSFRS-R is a disease-specific questionnaire containing 12 items rated from 0 (complete dependence) to 4 (normal function) for a total possible score ranging from 0 to 48. The items contained in the ALSFRS-R represent 4 categories, including bulbar, fine motor, gross motor, and respiratory function, with each category represented by 3 items. Completion of the ALSFRS-R in the current study was performed according to standardized criteria previously reported (ALS CNTF Treatment Study, 1996; Cedarbaum et al., 1999).

2.5. Forced vital capacity (FVC)

FVC testing was completed according to standards established by the American Thoracic Society (Miller et al., 2005). Briefly, three trials were performed per patient; in order for a test to be considered valid, variability of less than 5% was required between trials. The maximal effort of the three trials was used as the FVC

and is presented throughout both as a raw score (L) and as a percentage of the predicted FVC determined using regression equations.

2.6. Statistics

Mean values along with their standard deviations are presented throughout unless specified otherwise. Where indicated, differences between groups were determined using either a standard one-way analysis of variance (ANOVA) or a Kruskal-Wallis one-way ANOVA (non-parametric data, SPSS v.14.0 Graduate Student Package, Chicago, IL) with an alpha level of $P < 0.05$ denoting significance. In order to illustrate differences between groups, the patients' values have been expressed as a percentage of the control subjects, with the exception of the TQNE and FVC values, which were expressed as a percentage of predicted values calculated using regression equations (see specific methodology for details).

3. Results

3.1. Maximal force, FVC and ALSFRS-R

Maximal voluntary contraction values differed between control subjects and patients with ALS for the FDI and BB muscles ($P < 0.05$, Table 18.1,

TABLE 18.1

MEAN MAXIMAL FORCE VALUES AND ELECTROPHYSIOLOGICAL DATA FOR BOTH CONTROL SUBJECTS AND PATIENTS WITH ALS IN THE FDI AND BB MUSCLES

	MVC (N)		M wave NpAmp (μ V)		S-MUP NpAmp (μ V)		MUNE		Needle-detected MUP P-P vol (μ V)	
	FDI	BB	FDI	BB	FDI	BB	FDI	BB	FDI	BB
ALS	17.8 (10.7)	132.6 (78.8)	8.7 (3.7)	4.6 (2.1)	197.3 (110.2)	238.2 (451.4)	65 (39)	101 (126)	669.2 (183.7)	494.7 (132.4)
Controls	27.1 (5.4)	349.3 (56.2)	14.3 (3.1)	12.2 (2.2)	124.1 (46.6)	58.0 (20.7)	144 (42)	271 (125)	463.1 (120.6)	398.9 (124.5)

MVC = maximal voluntary contraction; NpAmp = negative-peak amplitude; P-P vol = peak-to-peak voltage; μ V = microvolt. Parentheses indicate standard deviation.

Figs. 18.1 and 18.2). For the upper limb portion of the TQNE, patients were able to produce on average 18.0 ± 9.7 kg, which represented $67.8 \pm 35.8\%$ of the predicted force output of matched controls. As expected, lower limb raw scores were higher

than those observed in the upper limb, with patients producing an average of 31.4 ± 7.1 kg; however, this value represents a lower percentage of the force output predicted for matched controls ($59.9 \pm 16.8\%$) compared to the corresponding

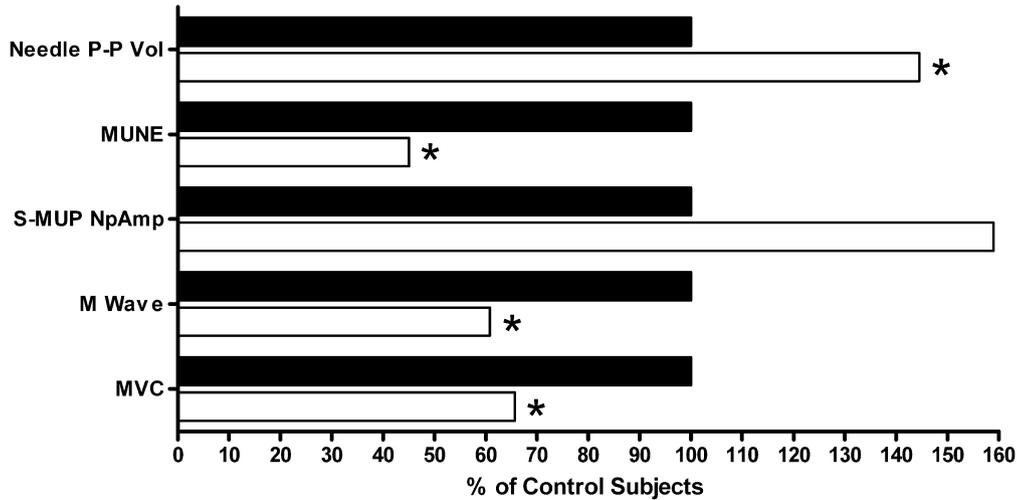


Fig. 18.1 Maximal force and electrophysiological data for the FDI. The ALS patients' values (open bars) have been expressed as a percentage of values obtained for the healthy control subjects (solid bars).* Indicates a significant difference ($P < 0.05$).

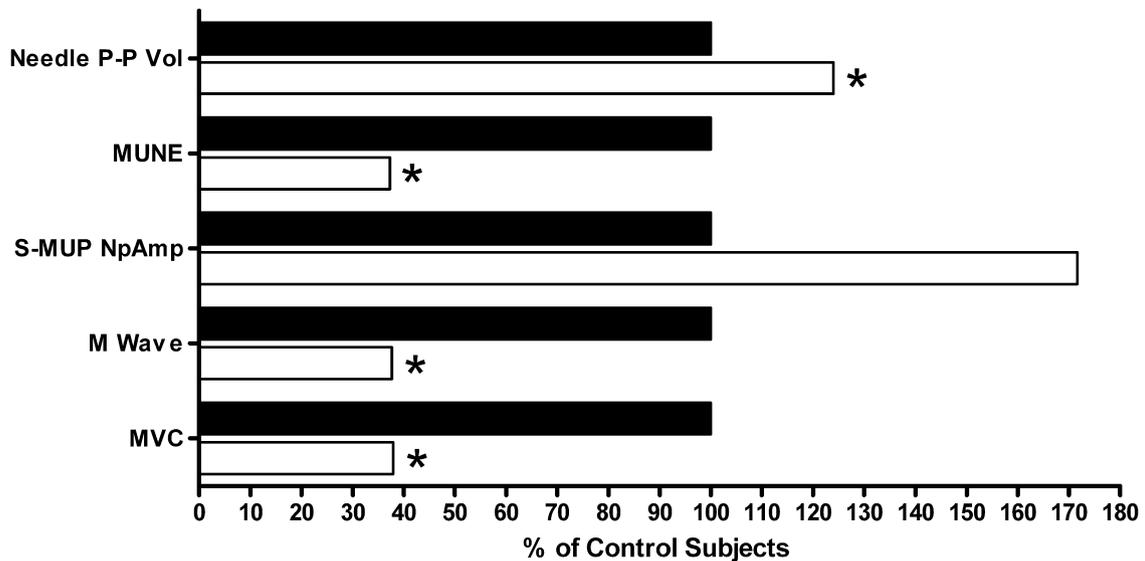


Fig. 18.2 Maximal force and electrophysiological data for the BB. The ALS patients' values (open bars) have been expressed as a percentage of values obtained for the healthy control subjects (solid bars). For illustrative purposes, one patient's mean S-MUP value ($1415 \mu\text{V}$) was not included.* Indicates a significant difference ($P < 0.05$).

value for the upper limb. The values observed for both the upper and lower limb portion of the TQNE display a considerable range, highlighting the variability in this group of patients with ALS. For instance, upper limb raw scores ranged from 7.1 to 35.5 kg, with a similar range observed for the lower limb (11.7–32.3 kg). Pulmonary function as measured via FVC was relatively well preserved in this patient group, with an average FVC of 3.6 ± 0.9 l, which corresponds to $90.4 \pm 15.5\%$ of predicted values; however, similar to the TQNE, a range of values was present (2.4–5.0 l or 73–122%). Lastly, on average, the patients with ALS scored 36.9 ± 6 out of a possible 48 on the ALSFRS-R with a range of 27–45.

3.2. Electrophysiology

Maximum M wave values differed significantly between groups for both the FDI and BB muscles (Table 18.1, Figs. 18.1 and 18.2). Unlike maximal M-wave values, S-MUP amplitude did not differ significantly between control subjects and the patients with ALS, despite a considerable difference in mean values for both the FDI and BB muscles (Table 18.1, Figs. 18.1 and 18.2). Despite this non-statistical finding, comparison of MUNE values between groups revealed significant differences for both muscles (Table 18.1, Figs. 18.1 and 18.2). Lastly, needle-detected MUP peak-to-peak voltage was found to differ between the two groups for both the FDI and BB muscles ($P < 0.05$; Table 18.1, Figs. 18.1 and 18.2).

4. Discussion

It is generally well accepted that muscle weakness, atrophy and fatigue observed in patients with ALS are due to both the lower (decrease in the number of MUs) and upper motor neuron component of the disease, although the contribution of the upper motor neuron component is less readily measured (Strong et al., 1988; Bromberg, 1998; Kent-Braun et al., 1998; Mills, 2003). Previous studies examining the lower motor neuron

component of ALS have suggested that the relationship between decreased strength and reduced MU number is not linear, but rather there is a relative preservation of strength despite substantial MU loss (Wohlfart, 1957, 1958; McComas et al., 1971; Brown, 1973). This non-linear relationship has been attributed to the process of collateral reinnervation, whereby denervated muscles fibers are reinnervated by surviving motor neurons, thus resulting in fewer but larger MUs and the resultant maintenance of strength. The implications of this process with regard to clinical outcome measures, including those utilized in the current study are that patients may score relatively high on tests that are more functional in nature despite considerable changes in the number of functioning MUs. This observation is certainly not intended as a criticism of these clinical tests, given that preserved respiratory and functional independence are ultimately the goals of any patient (and treatment), and in light of the evidence supporting these tests as valid predictors of disease course and severity (Andres et al., 1986, 1988; Munsat et al., 1988; ALS CNTF Treatment Study, 1996; Eisen et al., 2001; Cudkowicz et al., 2004). Rather, the observation is intended to suggest that quantitative electrophysiological data derived using DQEMG may provide unique information pertaining to the course of the disease and its severity that is reflective of changes at the level of the MU that are currently not accessible with these clinical outcome measures.

The results of the current study support this notion of preserved functional performance in the face of reduced MUNE and increased MU size (Figs. 18.1 and 18.2). Fig. 18.3 shows the results for patients with ALS as a percentage of the healthy control subject's values for the clinical outcome measures and MUNE values. Both the FDI and BB MUNE values display considerably lower percentages (reductions of 54.9% and 62.7%, respectively) compared to the clinical outcome measures, with the lowest of these measures (TQNE lower and upper limb) displaying reductions of 40.9%

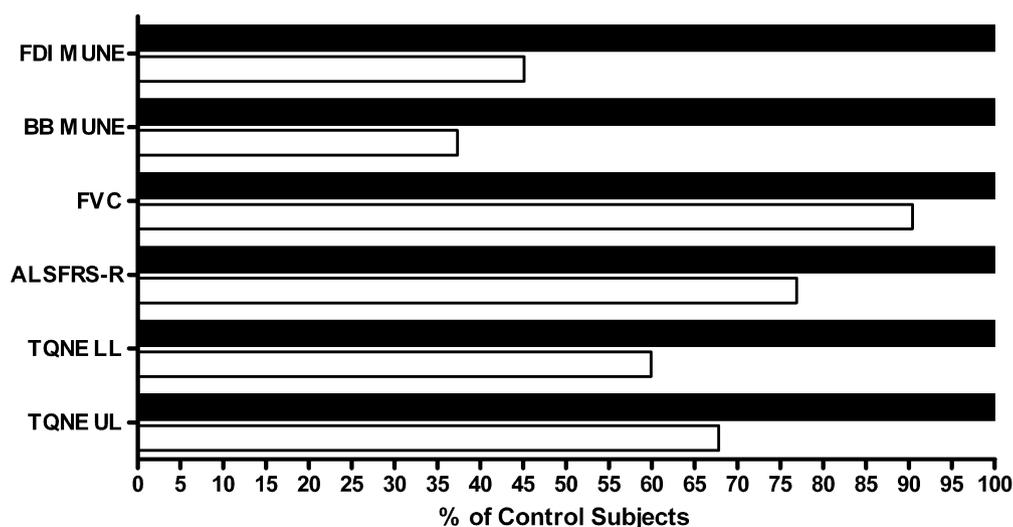


Fig. 18.3 MUNE and clinical outcome measures. The ALS patients' values (open bars) have been expressed as a percentage of the values obtained for the healthy control subjects (closed bars). The percentage decrease relative to that of the control subjects is greatest for the FDI and BB MUNE values. TQNE LL, UL = Tufts Quantitative Neuromuscular Exam lower limb, upper limb.

and 32.2% (Fig. 18.3). Conversely, ALSFRS-R scores, which provide a more global impression of function, were reduced by only 23.1% with pulmonary function the best preserved with a reduction of only 9.6% (Fig. 18.3).

As highlighted in the Results section, S-MUP amplitude, which may provide the best representation of MU size (Stålberg, 1980; Stålberg et al., 1982; Boe et al., 2007), was increased in patients compared to the healthy controls. The relative magnitude of this difference was considerable for both the FDI (59%) and BB (71.6%, Figs. 18.1 and 18.2) and, coupled with MUNE, further supports the notion that DQEMG derived quantitative data can provide additional information with regard to disease severity and if performed serially, possibly insight into its course and natural history.

With regard to ALSFRS-R scores and their corresponding level of functional independence, a previous study (Cedarbaum et al., 1997) documented a median score of 35 for patients who reported complete independence. Additionally, 90% of patients who reported being able to independently manage a household had scores

above 26. In this study, the average ALSFRS-R score was 36.9 ± 6 , suggesting that these patients displayed a relatively high degree of functional independence. In a similar fashion, the upper and lower limb megascores, which provide an indication of upper and lower limb strength compared to the ALS population mean, were 1.3 and 0.8 units respectively. These values are approximately 1 SD greater than the ALS population mean for these measures, supporting the notion that these patients were functioning at a relatively high level. These findings further underscore the point that clinical outcome measures providing an indication of gross function may not accurately represent the pathophysiological changes associated with the disease, but rather may provide the most comprehensive overview of the disease process if coupled with quantitative EMG data.

Overall, the results of this study provide evidence to support the use of quantitative data obtained using DQEMG as an indication of the degree of disease involvement and severity. This conclusion is based on the aforementioned results which show that DQEMG derived data,

including MUNE, provide unique insight into the changes occurring at the level of the MU that are greater than those observed for the clinical outcome measures assessed.

Abbreviations

ALS = amyotrophic lateral sclerosis
 ALSFRS-R = amyotrophic lateral sclerosis functional rating scale (revised)
 BB = biceps brachii
 DQEMG = decomposition-based quantitative electromyography
 EMG = electromyography
 FDI = first dorsal interosseous
 FVC = forced vital capacity
 MU = motor unit
 MUP = motor unit potential
 MUNE = motor unit number estimate
 MVC = maximal voluntary contraction
 S-MUP = surface-detected motor unit potential
 TQNE = Tufts Quantitative Neuromuscular Exam

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