The Promising Application of a New Ulnar Nerve Compound Muscle Action Potential Measurement Montage in Amyotrophic Lateral Sclerosis

Yixuan Zhang  
Peking University Third Hospital

Jingyue Ma  
Peking University Third Hospital

Shuo Zhang  
Peking University Third Hospital

Zhou Yu  
Peking University Third Hospital

Dongsheng Fan (✉ dsfan2010@aliyun.com)  
Peking University Third Hospital  https://orcid.org/0000-0002-3129-9821

Research

Keywords: compound muscle action potential, ulnar motor nerve conduction, proximal E2 electrode, amyotrophic lateral sclerosis

Posted Date: January 4th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1185620/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Objective

Detecting peripheral nerve damage by electrophysiology examination accurately and sensitively is important for the follow-up evaluation of amyotrophic lateral sclerosis (ALS). In this study, we applied a new proximal E2 electrode in the ulnar motor nerve conduction study with E1 on abductor digiti minimi (ADM), and investigated its effect on the compound muscle action potential (CMAP) of the ulnar nerve.

Methods

We included 64 ALS patients and 64 age- and sex-matched controls. Patients characteristics were collected for phenotype, symptom duration and site of onset. The revised ALS Functional Rating Scale (ALSFRS-R) was evaluated at the time of administration to assess the severity of ALS. The ulnar nerve CMAP was recorded using an E1 electrode on the muscle belly and an E2 electrode on distal tendon (traditional montage, CMAP-dE2) and proximal tendon (new montage, CMAP-pE2) respectively.

Results

The waveform of CMAP-pE2 was steadier presenting a uniform unilobed pattern. In the controls, there were no significant differences between the amplitudes of CMAP-dE2 and CMAP-pE2 ($p=0.96$). In ALS patients, the amplitude of CMAP-pE2 was significantly lower than that of CMAP-dE2 ($p<0.01$), especially for patients with ADM spontaneous activity and muscular atrophy. Using the new method, the damaged axons were more likely to be stratified into more severe decreased levels. Furthermore, the decline of CMAP-pE2 was significantly correlated with ALSFRS-R ($p<0.01$).

Conclusions

The new electrode configuration in the ulnar nerve conduction test could reflect the degree of axonal injury much more sensitively after the presence of ulnar nerve degeneration and was more suitable for the evaluation of disease progression.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the degeneration of both upper and lower motor neurons. Peripheral nerve injury is an important process in disease progression (1). Imai et al. (2) reported that motor nerve compound muscle action potential (CMAP) amplitude had the strongest influence on disease prognosis outside the onset site. Therefore,
accurately and sensitively detecting peripheral nerve damage by electrophysiology examination is important for the follow-up evaluation of ALS.

In the motor nerve conduction study (NCS), CMAP is recorded by the ‘belly-tendon’ montage, which was introduced by Harvey and Masland(3) in 1941. The CMAP is recorded using three electrodes: the recording (or active) electrode (E1), reference electrode (E2) and ground electrode (E0). The E0 is used to reduce background noise and interference. The E1 electrode is placed over the muscle belly. The E2 is always at the distal muscle tendon or even further distal to the E1, in order to reduce the stimulus artifact, particularly when motor conductions were originally described and recording equipment was more prone to artifact(4, 5). Potentials are recorded by a differential amplifier. Hence, the displayed signals are the difference of activity between E1 and E2(6). Under ideal conditions, E2 is supposed to be electrically quiet or "inactive"; thus, CMAP can primarily represent the electrical activity at E1. However, in actual practice, the E2 electrode records significant voltage from other muscles innervated by the stimulated nerve(6-8), especially in ulnar motor NCS recorded from the abductor digiti minimi (ADM)(9).

When E2 is placed distally, the CMAP produced by ulnar nerve stimulation shows two distinct peaks. Due to the contribution of the interosseous muscles, the unintended peak of E2 coincides with the ulnar nerve CMAP peak used for amplitude measurements(4, 9, 10). Hence, the hypothenar CMAP cannot truly reflect the amplitude of the innervated ulnar nerve branch. McGill KC et al.(10) has proposed that using a different electrode configuration can reduce the interosseous muscle contribution. Nandedkar SD(4) et al. applied a “proximal E2 site” at the centre of the dorsal wrist that was just distal to the ulnar styloid process. In modern amplifiers, the proximal E2 position gave high quality recordings with good separation between the CMAP and stimulus artifact(4). Electrophysiological analysis has demonstrated the proximal E2 site to be electrically inactive; thus, greater sensitivity may be achieved(4).

This study was based on the proximal E2 electrode configuration proposed by Nandedkar SD et al.(4), and applied to ALS patients to explore the clinical value of this method in detecting ulnar nerve damage in ALS.

**Materials And Methods**

**Subjects**

This study was conducted at Peking University Third Hospital. All study procedures were reviewed and approved by the Ethical Committee of our institution (approval No. M2017198). The subjects provided their written informed consent to participate in this study. We included 64 ALS patients who met the revised El Escorial diagnostic criteria(11) and 64 one-to-one age- and sex- matched controls. The exclusion criteria for the controls were any comorbidities that may involve motor neurons of the upper limbs, such as ALS, neuromuscular diseases, autoimmune diseases, tumours, and other conditions. The characteristics of the patients were collected for demographic details, symptom duration, phenotype and
site of onset. The ALS Functional Rating Scale (ALSFRS-R) was evaluated at the time of administration to assess the severity of ALS.

**Neurophysiological examinations**

Clinical neurophysiologic examinations were performed by an experienced electromyography technologist, using a Keypoint four-channel electromyography evoked potentiometer (Medtronic, USA). The skin temperature was maintained >33°C. In our study, the ulnar-abductor digiti minimi (ADM) combination was used for CMAP recording. The stimulation site was the wrist, and the E1 electrode was placed over the muscle belly. Under usual practice, we placed E2 at the distal tendon of the ADM, the fifth metacarpophalangeal joint, which is called the “traditional montage”; in the “new montage”, we placed E2 at the proximal tendon (at the centre of the dorsal wrist) according to the study of Nandedkar et al.(4) (Fig. 1)

Each subject was tested three times for the “traditional” and “new” montages on the ulnar nerve bilaterally, and the average amplitudes were taken. The stimulus intensity was supramaximal. We recorded the CMAP amplitudes and waveforms measured by each method for subsequent analysis. Furthermore, all patients underwent concentric needle EMG in bilateral ADM. We recorded spontaneous activity with the muscle at rest. Fibrillation potentials (fibs) and positive sharp waves (PSWs) were used to assess the spontaneous activity. We defined the muscle without fibs/PSWs as EMG (–) and muscles with any degree of fibs/PSWs as EMG (+).

**Statistical analysis**

The statistical analyses were performed using SPSS 22.0. The CMAP amplitudes obtained by both methods were normally distributed (Shapiro-Wilk test for normality $p>0.05$). For the same patient, a paired t-test was used to compare the CMAP amplitudes obtained in two methods. The Wilcoxon test was used for the comparison of the stratification levels of the CMAP amplitude. Partial correlation analysis was conducted to detect the correlation between the CMAP amplitude and disease progression. $P<0.05$ was considered significant.

**Results**

**Demographic and clinical data of ALS and controls**

A total of 64 sporadic ALS patients and 64 one-to-one age- and sex- matched controls underwent EMG examination. According to the revised El Escorial criteria, we included 9 definite (14.1%), 15 probable (23.4%), 19 laboratory-supported probable (29.7%) and 21 possible (23.4%) ALS patients. The control group included 41 with lumbar spondylosis, 15 with peroneal nerve injury, 4 with facial palsy, and 4 healthy controls. The demographics and general clinical characteristics of the patients and controls were summarized in Table 1.

**Ulnar nerve CMAP in the controls**
CMAP waveform patterns

First, we compared the CMAP waveforms obtained by the traditional montage (CMAP-distal E2, CMAP-dE2) and new montage (CMAP-proximal E2, CMAP-pE2). CMAP-dE2 could be subclassified into three patterns: the first was bilobed, with a lower peak followed by a higher peak (low-high) waveform, which was the most common pattern, accounting for 64% of the cases, and the posterior higher peak was used for measurement; the second was bilobed, with a higher peak followed by a lower peak (high-low) waveform, accounting for 20% of the cases, and the anterior higher peak was used for measurement by default. The third pattern was unilobed, accounting for 19%. Waveform examples are shown in Table 2.

However, CMAP-pE2 had a unified unilobed waveform, which was a negative peak followed by a lower repeated amplitude (Fig. 2).

CMAP amplitudes comparison

In the controls, the amplitude of CMAP-dE2 was 7.69±1.82 mV, which was 7.70±1.87 mV by the new method, without a significant difference ($p=0.96$).

We further subdivided the CMAP-dE2 according to the waveform pattern. The amplitude of the first pattern (bi-lobed, "low-high" waveform) was 7.83±1.86 mV, which was significantly higher than that obtained by the new method (7.46±1.76 mV, $p<0.01$); the amplitude of the second pattern (bilobed, “high-low” waveform) was 6.98±1.61 mV, which was significantly lower than that obtained by the new method (7.77±2.02 mV, $p<0.01$); however, for the unilobed waveform, there was no significant difference between the values measured by the two methods ($p=0.16$). (Table 2)

Ulnar nerve CMAP in ALS patients

CMAP amplitudes comparison

CMAP-dE2 became unified with ulnar nerve injury, mainly presenting a unilobed pattern. However, in CMAP-pE2, the waveform consistently presented a unilobed pattern, regardless of the decline in CMAP amplitude (Fig. 2).

Next, we compared the CMAP measurements obtained by the traditional and new methods. The amplitude of CMAP-dE2 was 4.97±2.30 mV, which was 4.53±2.51mV by the new method and was significantly lower ($p<0.01$). The ALS patients were subdivided into the EMG (-) and EMG (+) groups. In the EMG (-) group, there were no significant differences in CMAP amplitude between the traditional and new methods ($p=0.285$), but in the EMG (+) group, the amplitude of CMAP-pE2 was significantly lower ($p<0.01$). The ALS patients were also grouped according to their clinical characteristics into “with ADM muscular atrophy [ADM atrophy (+)]” and “without ADM muscular atrophy [ADM atrophy (-)]”. We found that for the ADM atrophy (-) patients, the CMAP amplitudes were not significantly different between the two groups ($p=0.724$), while in the ADM atrophy (+) group, the amplitude of CMAP-pE2 was significantly lower ($p<0.01$) (Table 3).
CMAP amplitudes stratification

The amplitudes of CMAP measured by these two methods were stratified into four levels according to the normal range of healthy controls: normal (≥ the lower limit of normal, LLN), mild decrease (<LLN but ≥ 50% of LLN), moderate decrease (<50% but ≥ 30% of LLN), and severe decrease (<30% of LLN) (Table 4).

The amplitude level of CMAP-pE2 was significantly higher than that of CMAP-dE2 ($p<0.01$) (Table 5). Among the amplitudes of CMAP-dE2, there were 42 data points classified into a more severely decreased groups, while 13 data points were classified into less damaged groups when measured by the new method. These level changes mainly occurred in the normal and mildly decreased groups (Fig. 3A).

For EMG (-) patients, their amplitudes obtained by the two methods all belonged to the normal group. Nevertheless, in the EMG (+) group, the amplitude stratification of CMAP-pE2 was significantly more advanced ($p<0.01$). There were 39 data points classified into more severely decreased groups, and 10 of them were in the normal group when using the traditional method (Fig. 3B).

In the ADM atrophy (-) group, there was no significant difference in stratification by using two methods. In the ADM atrophy (+) group, the level of CMAP-pE2 was significantly higher ($p<0.01$). There were 27 amplitudes still within the normal range when measured by the traditional method, while they were transformed into the decreased group when using the new method (Fig. 3C).

Correlation between CMAP amplitudes and disease progression

The partial correlation analysis adjusting for confounding effects of sex, age and onset site confirmed a significant inverse correlation between the amplitude of CMAP-pE2 and disease duration ($r=-0.31$, $p=0.014$). The amplitude of CMAP-pE2 also declined significantly with ALSFRS-R ($r=0.47$, $p=0.006$). However, the amplitude of CMAP-dE2 did not show any significant correlation between ALSFRS-R ($p=0.080$) or disease duration ($p=0.449$) (Fig. 4).

Discussion

In this study, we compared the CMAP waveforms of the ulnar nerve obtained by the traditional and new methods in ALS patients. A previous study demonstrated that the CMAP amplitudes obtained by the traditional muscle-tendon montage were not sensitive enough to detect ulnar nerve damage of in the early phase of ALS(12). After Nandedkar et al.(4) proposed the “proximal E2” montage, this study firstly applied this strategy to ALS patients in different stages. We found that compared with the traditional method, CMAP-pE2 was steadier. Before the involvement of ulnar nerve, the CMAP amplitudes obtained by the two methods were consistent. However, CMAP-pE2 could reflect the degree of axonal injury much more sensitive after the presence of ulnar nerve degeneration and was more suitable for the evaluation of disease progression.
We found that the CMAP-dE2 had three patterns: “low-high” and “high-low” bilobed waveforms, and unilobed waveforms, which were all presented in previous studies(9, 13). In contrast, these waveforms all manifested as unilobed when measured by the new method. CMAP-pE2 showed a large negative peak followed by a low amplitude wave contributed by the reference electrode, consistent with the previous study(4). The uniformity of the waveforms across different laboratories suggests that the new montage has better stability and is more suitable for clinical and scientific applications.

The difference in the waveform patterns between the two methods could be explained by the electrophysiological mechanism. The distal E2 potential of the ulnar nerve was not electrically inactive but registered a negative (N1)–positive (P1)–negative (N2) triphasic waveform comprised of an initial N1, a steep P1 and a bi-lobed N2, which was basically stable in previous studies(4, 7, 9, 14). These reference potentials are far-field potentials produced by interosseous (or other deep motor branch–innervated) muscles: the N1 is generated by second and third dorsal interosseous muscles; P1 by second and third palmar interosseous muscles, and by third and fourth dorsal interosseous muscles to a lesser extent; early N2 by third palmar interosseous muscle, and late N2 by ADM(7, 9, 14). Since the E1 electrode has a shorter onset latency than distal E2, this time difference results in the bilobed CMAP in the traditional montage. When the onset latencies approach each other, the waveform will become unilobed. In ALS patients, the distal E2 potential decreased with the neurogenic injury to the interosseous muscles; thus, the waveform became unilobed as the disease progressed. In contrast, the proximal E2 position recorded a lower volume conducted signal and yielded a CMAP that was more representative of the E1 electrode is placed. Therefore, in both healthy controls and patients in the early or advanced stage of ALS, CMAP-pE2 was unilobed.

Generally, the CMAP amplitude did not differ between the two methods in healthy controls. However, in early-stage ALS patients with ADM spontaneous activity or muscular atrophy, the amplitudes of CMAP-pE2 were significantly lower than those of CMAP-dE2 and tended to be stratified into more advanced levels. Furthermore, the decline of CMAP-pE2 was significantly correlated with ALS disease progression.

Nandedkar et al.(4) found that the negative peak of ulnar nerve CMAP coincided with the positive peak of the signal recorded by the distal E2 electrode, meaning that the initially negative E2 signal will cancel the first negative potential from the E1 electrode, and the steep P1 will add to the negativity of the E1 signal by virtue of differential amplification. In the “low-high” bilobed waveform, we measured the posterior high peak that overlayed the P1 amplitude from E2. In the “high-low” bilobed waveform, we measured the first high peak that subtracted the N1 amplitude from E2. However, the CMAP amplitude measured by the new method was mainly contributed by the E1 potential. Thus, the amplitude of the “low-high” CMAP was higher than that of the new method, but the “high-low” CMAP was lower.

When the ulnar nerve was mildly impaired in ALS patients, the interosseous muscles innervated by deep motor branches were also involved. In this state, the N1 and N2 peaks decreased in the distal E2 signal, presenting a one-way wave dominated by the P1 peak, which would conceal the decline in E1 potential. As the disease progressed, atrophy of the interosseous muscles led to a further decline in E2 potential,
and its interference with CMAP was also reduced. Therefore, in the severely decreased group, the main component of CMAP was the E1 potential in both methods, and the stratification of CMAP damage was consistent.

This study has several limitations. First, the sample size of the patients was limited, which might lead to selection bias. A large-sample multicentre validation study is still needed. Second, this study focused on the clinical application of the new ulnar nerve examination method, but lacked further study on the electrophysiological mechanism. A combination of surface motor unit potentials (SMUPs) and motor unit number estimation (MUNE) was suggested to provide more underlying mechanism of the far field potential in ALS patients.

**Conclusion**

In conclusion, the traditional method cannot accurately reflect the decrease of ulnar nerve CMAP amplitude in the early stage ALS due to the electrical activity in the distal E2. In some ALS patients who have presented with ADM weakness and muscular atrophy, their ulnar nerve CMAP amplitudes were still in the normal range. But the new method reduced this reference potential by changing the position of E2, resulting in a more accurate CMAP of ulnar nerve and was more suitable for the evaluation of the disease progression.

**Declarations**

**Ethics approval and consent to participate**

All study procedures were reviewed and approved by the Ethical Committee of Peking University Third Hospital (approval No. M2017198). The subjects provided their written informed consent to participate in this study.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

**Funding**
This study was supported by the National Natural Science Foundation of China (81873784, 82071426) and Clinical Cohort Construction Program of Peking University Third Hospital (BYSYDL2019002).

**Competing interests**

The authors declare that they have no competing interests.

**Authors' contributions**

JY M, YX Z, and DS F designed the research. YX Z and JY M wrote the main manuscript text. JY M and YX Z performed data analysis and interpreted the findings. JY M and Z Y contributed to the recruitment and evaluation of patients. S Z contributed to the acquisition of imaging data. All of the authors read the draft, made contributions, and approved the final manuscript.

**Acknowledgements**

Not applicable

**References**


### Tables

#### Table 1. The demographics and general clinical characteristics of patients and controls.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ALS (n = 64)</th>
<th>Healthy controls (n = 64)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>58.34 ± 10.76</td>
<td>56.80 ± 12.04</td>
<td>0.445</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>40 (62.5%)</td>
<td>38 (59.4%)</td>
<td>0.865</td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>40.08 ± 6.64</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Disease duration (mo)</td>
<td>14.00 ± 8.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease onset location</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar</td>
<td>6 (9.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal-upper</td>
<td>39 (60.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal-lower</td>
<td>19 (29.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic level</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>9 (14.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td>15 (23.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory-supported probable</td>
<td>19 (29.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>21 (32.8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Table 2. The amplitude and waveform patterns of ulnar nerve CMAP obtained by the traditional (distal E2) and new (proximal E2) montages in the controls.

#### Table 3. Subgroup comparison of CMAP amplitude.
<table>
<thead>
<tr>
<th>Traditional montage</th>
<th>Waveform patterns</th>
<th>Traditional montage</th>
<th>New montage</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Amplitude (mV)</td>
<td>Amplitude</td>
<td></td>
</tr>
<tr>
<td>Overall analysis</td>
<td>-</td>
<td>7.69±1.82</td>
<td>7.07±1.87</td>
<td>0.96</td>
</tr>
<tr>
<td>Subgroup analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilobed Low-high (n=75)</td>
<td></td>
<td>7.83±1.86</td>
<td>7.46±1.76</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Bilobed High-low (n=24)</td>
<td></td>
<td>6.98±1.61</td>
<td>7.77±2.03</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Unilobed (n=19)</td>
<td></td>
<td>8.02±1.08</td>
<td>8.52±1.98</td>
<td>0.16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALS patients</th>
<th>Amplitude of CMAP-dE2 (mV)</th>
<th>Amplitude of CMAP-pE2 (mV)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall analysis</td>
<td>4.97 ± 2.30</td>
<td>4.53 ± 2.51</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Grouping by EMG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMG (-)</td>
<td>7.41 ± 1.29</td>
<td>7.67 ± 1.50</td>
<td>0.285</td>
</tr>
<tr>
<td>EMG (+)</td>
<td>4.05 ± 1.89</td>
<td>3.34 ± 1.64</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Grouping by muscular atrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADM atrophy (+)</td>
<td>6.57 ± 1.55</td>
<td>6.63 ± 1.79</td>
<td>0.724</td>
</tr>
<tr>
<td>ADM atrophy (-)</td>
<td>3.51 ± 1.86</td>
<td>2.62 ± 1.20</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

ADM atrophy (+), with ADM muscular atrophy; ADM atrophy (-), without ADM muscular atrophy; EMG (+), with spontaneous activity; EMG (-), without spontaneous activity.
Table 4. The stratification criteria of CMAP amplitude.

<table>
<thead>
<tr>
<th>CMAP</th>
<th>High normal</th>
<th>Low normal</th>
<th>Mild decrease</th>
<th>Moderate decrease</th>
<th>Severe decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMAP-dE2</td>
<td>≥ 5.87</td>
<td>[4.05, 5.87]</td>
<td>[2.03, 4.05]</td>
<td>[1.21, 2.03]</td>
<td>&lt;1.21</td>
</tr>
<tr>
<td>CMAP-pE2</td>
<td>≥ 5.83</td>
<td>[3.96, 5.83]</td>
<td>[1.98, 3.96]</td>
<td>[1.19, 1.98]</td>
<td>&lt;1.19</td>
</tr>
</tbody>
</table>

Table 5. Subgroup comparison of CMAP stratification levels.

<table>
<thead>
<tr>
<th>CMAP stratification</th>
<th>High normal (n)</th>
<th>Low normal (n)</th>
<th>Mild decrease (n)</th>
<th>Moderate decrease (n)</th>
<th>Severe decrease (n)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall analysis</td>
<td>CMAP-dE2</td>
<td>52</td>
<td>33</td>
<td>26</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>CMAP-pE2</td>
<td>37</td>
<td>33</td>
<td>36</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

Grouping by EMG

<table>
<thead>
<tr>
<th>CMAP stratification</th>
<th>High normal (n)</th>
<th>Low normal (n)</th>
<th>Mild decrease (n)</th>
<th>Moderate decrease (n)</th>
<th>Severe decrease (n)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMG (-)</td>
<td>CMAP-dE2</td>
<td>33</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0.317</td>
</tr>
<tr>
<td></td>
<td>CMAP-pE2</td>
<td>31</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>EMG (+)</td>
<td>CMAP-dE2</td>
<td>19</td>
<td>31</td>
<td>26</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>CMAP-pE2</td>
<td>6</td>
<td>29</td>
<td>36</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Grouping by muscular atrophy

<table>
<thead>
<tr>
<th>CMAP stratification</th>
<th>High normal (n)</th>
<th>Low normal (n)</th>
<th>Mild decrease (n)</th>
<th>Moderate decrease (n)</th>
<th>Severe decrease (n)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADM atrophy (+)</td>
<td>CMAP-dE2</td>
<td>43</td>
<td>15</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CMAP-pE2</td>
<td>37</td>
<td>23</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ADM atrophy (-)</td>
<td>CMAP-dE2</td>
<td>9</td>
<td>18</td>
<td>23</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>CMAP-pE2</td>
<td>0</td>
<td>10</td>
<td>35</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

ADM atrophy (+), with ADM muscular atrophy; ADM atrophy (-), without ADM muscular atrophy; EMG (+), with spontaneous activity; EMG (-), without spontaneous activity; p, tested by Wilcoxon test

Figures
Figure 1

Diagram of the new proximal E2 montage. We placed E1 at the muscle belly of the abductor digiti minimi (ADM) and E2 at the proximal tendon (at the centre of the dorsal wrist) following the study of Nandedkar et al. (4).
Figure 2

Comparison of waveform patterns of CMAP-pE2 and CMAP-dE2 in controls and ALS patients. A-F: In controls, CMAP-dE2 presented as bilobed (A, B, D, E) and unilobed (C, F) patterns, but CMAP-pE2 was unified and unilobed. G-H: In ALS patients, CMAP-dE2 became unilobed with ulnar nerve injury. CMAP-pE2 consistently presented a unilobed pattern, regardless of the decline of CMAP amplitude.
The changes in the amplitude stratification levels of CMAP-pE2 and CMAP-pE2. A: Among the amplitudes of CMAP-dE2, there were 42 data points classified into more severely decreased groups. B: In the EMG (+) group, there were 39 data points classified into more severely decreased groups, and ten of them were in the normal group when using the traditional method. C: In the ADM atrophy (+) group, the level of CMAP-pE2 was significantly higher ($p<0.01$). There were 27 data points classified into more severely decreased groups.

Figure 3

A

\[ r = -0.31, p = 0.014 \]

B

\[ r = -0.47, p = 0.006 \]
The partial correlation analysis adjusting for the confounding effects of sex, age and onset site showed a significant inverse correlation between the amplitude of CMAP-pE2 and disease duration ($r=-0.31$, $p=0.014$) (A). The amplitude of CMAP-pE2 also declined significantly with ALSFRS-R ($r=0.47$, $p=0.006$) (B).