Correlations between MUNIX and adapted multiple point stimulation MUNE methods

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HIGHLIGHTS

- AMPS and MUNIX are equally sensitive to distinguish patients with and without motor neuron disease.
- Data of both methods are strongly correlated.
- The utility of AMPS and MUNIX as a reliable marker to document motor unit loss is similar.

ABSTRACT

Objective: The aim of this study was to evaluate how the motor unit number index (MUNIX) is related to the adapted multiple point stimulation (AMPS) technique.

Methods: MUNIX and AMPS technique were prospectively performed on thenar muscles in 20 consecutive patients referred to our neurophysiological laboratory with the clinical diagnosis of a possible motoneurone disorder (MND). The clinical and paraclinical assessment confirmed the diagnosis of MND in 13 out of 20 patients, amyotrophic lateral sclerosis (ALS) in 9 (with MND group). In the other 7 patients, there were neither evidence of MND, nor of any peripheral nervous system disease (without MND group).

Results: AMPS and MUNIX data were significantly ($p < 0.001$) lower in patients with MND than in patients without MND. There was a strong significant positive linear correlation between AMPS and MUNIX values ($n = 20$; $R = 0.83$; p < 0.01).

Conclusion: Both MUNIX and AMPS methods could serve as a reliable marker to document the motor unit loss.

Significance: The present paper constitutes one more clue of MUNIX reliability.

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1. Introduction

Motor unit number estimate (MUNE) usually represents the ratio of the maximal compound muscle action potential (CMAP) divided by the average surface-recorded motor unit potential (SMUP). MUNE techniques differ in how single motor units (MU) are obtained. McComas et al. (1971) introduced the first MUNE technique, referred as the incremental technique. Incremental stimulation was applied at one stimulation point on the nerve and the stimulus intensity was gradually increased from a subthreshold value until 11 increments in the muscle response were obtained. The average SMUP size was derived by dividing the amplitude of the response by the number of increments. To eliminate the inherent problem of alternation that affects the incremental MUNE technique, the multiple point stimulation (Brown and Milner-Brown, 1976) and then the adapted multiple point stimulation (AMPS) technique were introduced (Kadrie et al., 1976; Wang and Delwaide, 1995; Shefner et al., 2011). MUNIX is a more recently developed method providing a motor unit number index (Nandedkar et al., 2010).

In the current study, data derived, in the daily practice, by MUNIX and AMPS technique performed unilaterally on the thenar muscles, in patients with a possible clinical diagnosis of motoneurone disorder (MND), were compared. The goal of the study was on one hand to reveal the relation between both methods, and on the

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other hand to determine if these procedures were equally sensitive to distinguish patients with and without MND.

2. Material and methods

Prospectively from February 2016 to February 2017, MUNIX and AMPS technique were performed on thenar muscles in 20 consecutive patients, referred to our neurophysiological laboratory with the clinical diagnosis of a possible MND, after having obtained their informed consent.

The clinical and paraclinical assessment confirmed the diagnosis of MND in 13 out of 20 patients (with MND group). Definite amyotrophic lateral sclerosis (ALS) was diagnosed in 9 patients according to the Awaji criteria (de Carvalho et al., 2008). The diagnosis for the other 4 patients with MND was Hirayama disease in one, syringomyelia in another one and cervical spondylotic myelopathy in the other two. In the other 7 patients, there were neither evidence of MND, nor conduction velocity slowing, conduction block, sensory or motor axon loss, fibrillation, positive sharp wave and muscular denervation/reinnervation. For these patients (without MND group), the assessment conclusion was either absence of peripheral nervous disease (patients referred because of an ALS case in the family) or benign fasciculations.

MUNIX and AMPS were performed on the right side or, if amyotrophy was present, on the side with the lesser thenar atrophy to avoid technical limitation related to a very small CMAP amplitude. All data were collected by the same investigator using a Keypoint G3 EMG machine (Natus Medical Incorpored) without removal and replacement of surface recording electrodes for the second technique. AMPS and MUNIX recordings started with a CMAP size measurement. The CMAP amplitude was maximized by moving the position of active recording electrode. Then, AMPS was performed first for 50% of the patients and for the other 50%, MUNIX was first realized. The bandpass filter setting was set from 3 to 10,000 Hz for MUNIX and from 20 to 5,000 Hz for AMPS technique. The hand temperature was maintained over 30 °C.

2.1. The adapted multiple point stimulation

"AMPS was a two-step procedure. The first step consisted of estimating the MU size by collecting and averaging 10 well-identified SMUP after stimulation at distinct points along the course of the median nerve between the wrist and the elbow. At each stimulation site, only two or three SMUP were successively evoked by incremental stimulation. The second step consisted of eliciting CMAP by supramaximal stimulation of the median nerve at the wrist 7 cm from the stigmatic electrode. By dividing the CMAP size by the average SMUP size, a MUNE was obtained" (Wang et al., 2002). Four to 5 stimulation sites were required to get the average SMUP size. To minimize the effects of temporal dispersion, there was only one stimulation point at the elbow; the other stimulation sites were located at the distal part of the forearm. SMUP whose negative peak area was less than 25 µV·ms was not included in the count.

2.2. The motor unit number index

MUNIX was applied according to the description of Nandedkar et al. (2010). The recordings were done on a 300 ms window. Ten isometric contractions during abduction of digit 1 were registered as surface interference patterns (SIP) ranging from approximately 10–100% of contraction. To avoid interference with volume-conducted activity, conditions that should be fulfilled in order that the test be accepted were the following ones: SIP area >20 mV.ms; ideal case motor unit count (ICMUC) <100; SIP area/CMAP area >1; CMAP amplitude >0.5 mV (Nandedkar et al., 2010).

2.3. Data analysis

Quantitative data about age, CMAP amplitude, AMPS MUNE, MUNIX, average SMUP amplitude evaluated by AMPS and motor unit size index (MUSIX) were considered individually (Table 1). The significance of differences between groups was assessed by the nonparametric Mann-Whitney U Test. Correlations between AMPS and MUNIX results were tested by the nonparametric Spearman correlation coefficient.

3. Results

There were no significant differences in age between patients from both groups. The muscle strength assessed manually remained normal, grade 5 of the Medical Research Council (MRC) scale, in all patients without MND and slightly decreased, grade 4 of the MRC scale, in 5 out of 13 patients with MND. Related to distinct bandpass filter settings between both procedures, CMAP amplitudes were slightly higher during MUNIX evaluations, compared to AMPS (Table 1). CMAP amplitude was below the lower limit of normal in 2 out 20 patients. CMAP amplitude was significantly ($p < 0.01$) lower in patients with MND than in patients without MND (Table 1). AMPS and MUNIX data were significantly ($p < 0.001$) lower in patients with MND than in patients without MND (Table 1, Fig. 1). AMPS value was below the lower normal limit for age (Wang and Delwaide, 1995) in one 58 y.o. non-MND patient, while MUNIX was reduced in another 86 y.o. non-MND patient. Average SMUP amplitude evaluated by AMPS and MUSIX were significantly ($p < 0.01$ and $p < 0.05$ respectively) higher in patients with MND than in patients without MND (Table 1).

There was a strong and significant positive linear correlation between AMPS and MUNIX values ($n = 20$; $R = 0.83$) (Fig. 2). This correlation was statistically significant ($p < 0.01$).

4. Discussion

AMPS technique and MUNIX are both non-invasive, painless and rapidly executed procedures. MUNIX can be performed in less than 5 min (Nandedkar et al., 2010) and a couple of minutes more for the CMAP and SIP signal importation and analysis in an excel table. The mean duration for AMPS evaluation is 13 ± 4 min ($n = 100$) (Wang et al., 2009). AMPS has good reproducibility based on the test-retest coefficient of variation (COV) in healthy subjects (COV = 10.4%) (Wang and Delwaide, 1995), and is even higher in amyotrophic lateral sclerosis (ALS) patients where the number of MU is reduced (COV = 4%) (Wang and Delwaide, 1998). A good within raters COV (between 5.8 and 9%) and between raters COV (between 13.5 and 16.4%) is also found when MUNIX is applied to *abductor pollicis brevis* muscle of healthy subjects (Neuwirth et al., 2016). MUNIX and AMPS were widely used in clinical studies, particularly to document the motor unit loss which characterized ALS (Wang and Delwaide, 1998; Wang et al., 2002, 2009; Nandedkar et al., 2010; Boekestein et al., 2012; Furtula et al., 2013). Shefner et al. (2011), using a MUNE technique similar to AMPS, concluded " Multipoint incremental MUNE has a number of attributes that make it attractive as an outcome measure in ALS and other diseases characterized by motor unit loss."

There are also differences between both methods. AMPS is not applicable in proximal muscles, while a MUNIX value may be obtained both in proximal and distal muscles. AMPS method does not require any specific recording system or software. MUNIX requires specific software available only on some EMG machines. MUNIX requires patient cooperation and voluntary activation, while with AMPS, subjects have only to be relax. But the main difference is the completely distinct technique principle. AMPS is

Table 1
Comparisons between patients with (G1, n = 13) and without (G2, n = 7) MND.

Age (years)		AMPS CMAP amplitude (mV)		AMPS MUNE (MU)		SMUP amplitude (µV)		MUNIX CMAP amplitude (mV)		MUNIX		MUSIX	
G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2
46	86	2.7°	5.3	36°	76	75°	70	2.7°	5.7	12°	57°	224°	99°
59	46	5.9	9.7	32°	313	184°	31	6.0	10.7	63°	157	95°	68
67	39	3.4°	10.1	16°	266	213°	38	3.5°	10.5	59°	246	60	42
73	59	4.3	9.2	17°	206	253°	45	5.6	9.4	49°	209	114°	45
70	58	4.3	6.8	25°	87°	172°	78°	4.3	6.9	50°	124	86°	55
29	65	5.6	7.4	12°	147	467°	50	5.9	8.2	37°	150	159°	55
64	59	4.5	9.7	80°	135	56	72	4.5	10.3	86°	222	53	46
64		6.3		61°		103°		6.4		94°		68	
51		8.0		35°		229°		8.8		55°		160°	
63		4.4		137		32		4.4		87°		51	
66		5.5		60°		92°		5.6		92°		61	
48		8.5		23°		370°		9.5		48°		198°	
39		5.0		33°		152°		5.4		40°		134°	
NS*		p < 0.01*		p < 0.001*		p < 0.01*		p < 0.01*		p < 0.001*		p < 0.05*	

AMPS: adapted multiple point stimulation, CMAP: compound muscle action potential, MUNE: motor unit number estimate, MU: motor unit, SMUP: surface-recorded motor unit potential, MUNIX: motor unit number index, MUSIX: motor unit size index, MND: motoneurone disorder, ° values beyond normal limits, * comparison between G1 and G2 by nonparametric Mann-Whitney U testing.
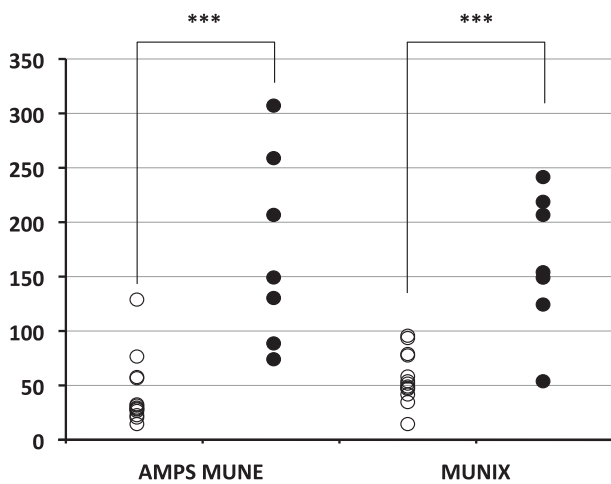
Fig. 1. Comparisons, by nonparametric Mann-Whitney U Test, between patients with a motoneurone disorder (n = 13, black circle) and patients without a motoneurone disorder (n = 7, black disc) evaluated by AMPS and MUNIX on thenar muscles. p < 0.001 (***).
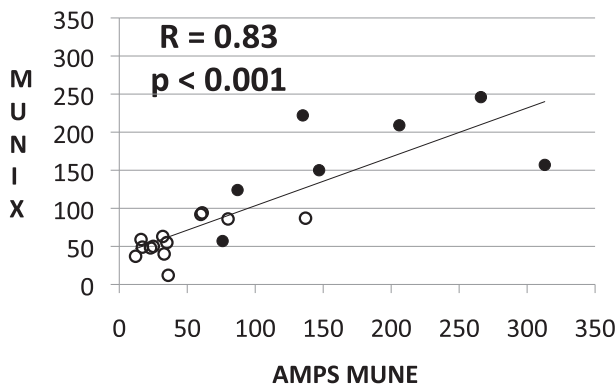
Fig. 2. Correlation between the adapted multiple point stimulation (AMPS) motor unit number estimate (MUNE) technique and the motor unit number index (MUNIX) in 20 patients with (n = 13, black circle) and without (n = 7, black disc) a motoneurone disorder. R: Spearman correlation coefficient.

based on the sequential activation of single motor axons to estimate the average SMUP size, while MUNIX is based on a mathematical model which uses area and power of the CMAP and SIP

obtained by voluntary contraction against manual resistance at increasing isometric force levels. Sometimes, when the SMUP show a bimodal amplitude distribution, MUNIX may be less reliable (Nandedkar et al., 2010). It is because of these differences that it is necessary to compare the methods between them. To date, there hasn't been any comparison between both techniques. There were comparisons between MPS and MUNIX method (Paramanathan et al., 2016; Jacobsen et al., 2017). However, MPS is clearly distinct from AMPS. MPS may sometimes not be applicable when it is impossible to evoke 10 distinct SMUP at 10 different stimulation sites along the accessible course of the nerve, particularly in patients presenting a severe motor unit loss. In these situations, the physician has to switch to the AMPS or another alternative procedure. Thus, the present data are not only confirmative but also original and useful for the MUNE community.

In the present study, patients with MND (n = 13) were at an early or compensate stage of their disease. Consequently, the muscle strength was only slightly decreased (grade 4 of the MRC scale) in 5 patients and CMAP amplitude was decreased only in 2. AMPS and MUNIX techniques were equally sensitive to one another to distinguish patients with MND and without MND (Table 1, Fig. 1). In the with MND group, by comparison to the without MND group, MUNIX values and AMPS MUNE were significantly reduced (Fig. 1). MUNIX was clustered at higher values compared to AMPS, particularly when AMPS was <60 MU (Table 1). Nevertheless, it should be remembered that MUNIX derived an index related to the MU number, but not the actual number. In 11 out 13 patients with MND, CMAP amplitude remained within normal limits while AMPS value was reduced in 12 and MUNIX was reduced in 13. This suggested that the MU loss was compensated by the MU size increase due to collateral reinnervation, which was confirmed by SMUP amplitude or MUSIX increase in most patients with MND (Table 1).

The other way to study the relation between 2 distinct techniques consisted in searching a significative correlation between results derived by them. Literature data are contrasted. There was no linear correlation between MPS and MUNIX techniques in control subjects, but a linear correlation was found in patients with inflammatory demyelinating polyneuropathies (Paramanathan et al., 2016) or with ALS (Jacobsen et al., 2017). Boekestein et al. (2012) found a significant positive correlation between high den-

sity MUNE and MUNIX values in ALS patients but not in healthy controls. Furtula et al. (2013) did not find any correlation between MUNIX and incremental stimulation MUNE in ALS patients and control subjects.

In the current study there was a strong significant linear positive correlation between AMPS and MUNIX values ($R = 0.83$, $p < 0.01$) in patients referred to our neurophysiological laboratory to confirm or not a MND diagnosis (Fig. 2).

Conflict of interest

Karim Benmouna, Christophe Milants and François C Wang have no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for profit sectors.

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