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SHORT COMMUNICATION

Motor unit number index (MUNIX) in myopathic disorders: Clinical correlations and potential pitfalls

Manoel Wilkley Gomes de Sousa, Marcio Luiz Escorcio-Bezerra*, Wladimir Bocca Vieira Rezende Pinto, Paulo Victor Sgobbi Souza, Nadia Iandoli de Oliveira Braga, Acary Souza Bulle Oliveira, Gilberto Mastrocola Manzano

Department of Neurology, Universidade Federal de São-Paulo, São-Paulo, Brazil

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Summary Our aim was to study motor unit number index (MUNIX) in myopathic disorders. We studied 11 patients with myopathy, and healthy controls. We obtained MUNIX, compound muscle action potential (CMAP), motor unit size index (MUSIX) and alpha (α, power exponent from MUNIX equation) measurements from three different muscles. MUNIX and CMAP were significantly lower in one muscle. This MUNIX decrease may not be related to motor neuron loss, but rather to muscle fiber atrophy. MUSIX and α did not change and may be useful in determining whether the MUNIX decrease is indeed due to motor unit loss.

Introduction

Motor unit number index (MUNIX) is a neurophysiologic technique that provides an index related to the number of functional motor neurons. This technique has proven to be a feasible, reproducible and reliable outcome measure [2,5,14,15]. The method was able to effectively track motor unit (MU) loss in amyotrophic lateral sclerosis (ALS) patients [13] and has also been effective in detecting presymptomatic motor neuron degeneration in these patients [3].

We do not know however how MUNIX would perform in other neuromuscular disorders, especially those affecting primarily the muscle fibers. Simulation studies suggest that in these clinical situations MUNIX could potentially overestimate the motor neuron loss [4,6].

* Corresponding author: Department of Neurology, Escola Paulista de Medicina, Universidade Federal São-Paulo, Rua Pedro de Toledo, 650, 04039-002 São-Paulo, Brazil.
E-mail address: marciobzrra@gmail.com (M.L. Escorcio-Bezerra).

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The objective of this work was to evaluate whether MUNIX would remain unchanged and reflect a purely myopathic disorder or if it would show a decrease due to other factors not related to the MU number. We also aimed to evaluate how MUNIX changes correlated to clinical parameters in these conditions (muscle strength).

Methods

Subjects

We included 11 healthy individuals and 11 patients diagnosed either with acid maltase deficiency (Pompe disease) or limb-girdle muscular dystrophy (LGMD) proven genetically or through muscular biopsy. All individuals were from the Neuromuscular Diseases Center, Universidade Federal de São Paulo (UNIFESP, Brazil). The UNIFESP Research Ethics Board approved this study and we obtained written informed consent from all participants.

Healthy subjects were recruited after interview. Those with past history of medical conditions affecting the peripheral or central nervous system were excluded.

Study procedures

MUNIX was performed in healthy and affected subjects, by the same examiner, sequentially in three muscles on the right side of the individuals: abductor pollicis brevis (APB), biceps brachii (BB) and tibialis anterior (TA). This sequence was then repeated twice in order to collect three MUNIX samples per muscle. We averaged the value of the three MUNIX samples collected from each muscle and did the same for the compound muscle action potential (CMAP), so that all values expressed in the results represent the mean of three measures.

Using MUNIX and CMAP values from each muscle, we calculated the motor unit size index (MUSIX) as follows: MUSIX = CMAP amplitude/MUNIX. This parameter is related to the average amplitude of the surface-recorded motor unit potential (SMUP) [13]. We also registered from each patient the alpha (α), which is a parameter obtained from the power regression analysis necessary for the MUNIX.

Muscle strength was graded according to the Medical Research Council (MRC) scale. Muscles with strength below 3 were excluded from the study as it would not be possible to adequately exert the progressive force levels necessary for the MUNIX calculation.

Electromyography (EMG) with a disposable monopolar needle electrode was performed after MUNIX was obtained. We analyzed the morphology and recruitment pattern of the motor unit action potentials (MUAP) and determined whether it was normal or had neurogenic or myopathic findings.

MUNIX procedures

All individuals were examined in a supine position and studies were performed with a commercially available electromyography instrument (Neurosoft, Neuro-MEP-Micro), by the same Clinical Neurophysiology Board-certified neurologist. Skin temperature was kept above 32° in the region evaluated. We used disposable surface electrodes (10×30 mm) in all tests. MUNIX and compound muscle action potentials (CMAP) were recorded using standard techniques.

The stimulus site for each nerve was as follows:

- biceps brachii (BB) muscle: stimulus was applied at the axilla, between the axillary artery, the median nerve medially and the coracobrachialis muscle laterally [17];
- abductor pollicis brevis (APB) muscle: stimulus was delivered at the wrist (between tendons to the flexor carpi radialis and palmaris longus);
- tibialis anterior (TA) muscle: stimulus was applied at the lateral popliteal fossa.

Special attention was paid to obtaining the CMAP with the highest amplitude in every test. Active electrodes (E1) were placed over the respective muscle belly, at the motor point. Reference electrode (E2) placement was as follows:

- BB muscle: E2 was placed over the olecranon;
- APB muscle: E2 was placed over the first metacarpophalangeal joint;
- TA muscle: E2 was placed at the knee (medial patellar region);

The detailed procedures we used for MUNIX were further described in previous works [2,3].

Statistical analysis

Results were expressed as the mean $\pm$ SD for the whole group and as median and range when the subgroups where divided by strength. The Shapiro–Wilk test was used to assess normal distribution. Comparisons of the CMAP and MUNIX values between patients and healthy controls were performed using Mann–Whitney U-test. Differences were considered significant at $P < 0.01$.

Results

Eleven patients with myopathy (6 females) were included, with mean age of 46 ± 11 years old. Two patients had late onset Pompe disease and nine had LGMD: 5 LGMD type 2B; 3 LGMD type 2A; and 1 LGMD type 2L. Eight patients had pelvic girdle symptoms onset (one of them with Pompe disease), two had scapular girdle (all LGMD) and one had axial/respiratory weakness (Pompe disease) as first symptoms. The mean disease duration was 17 ± 9 years. Eleven healthy individuals (6 females) were also included with mean age of 41 ± 14 years old. MUNIX of controls showed a normal distribution (Shapiro–Wilk, $P > 0.1$).

The BB was the most clinically affected muscle according to the MRC strength grading. In one of the patients, the TA muscle strength was preserved (Pompe disease). In eight patients, the APB strength was preserved (one with Pompe disease and seven LGMD). Tables 1 and 2 show strength grading and neurophysiological data in controls and patients.

In all patients needle EMG showed motor unit action potentials (MUAP) with myopathic characteristics

Table 1 MUNIX, CMAP and MUSIX according to muscle strength.

Muscle	*N*	Strength (MRC)	MUNIX	CMAP (mV)	MUSIX
BB	6	4	153 (89—182)	7 (4—10)	44 (40—56)
	4	3	162 (112—173)	7 (5—8)	46 (43—48)
APB	8	5	226 (173—321)	11 (9—13)	46 (42—56)
	3	4	201 (167—230)	10 (8—11)	50 (43—54)
TA	1	5	193	7	38
	6	4	137 (119—180)	6 (5—8)	43 (42—48)
	2	3	151 (146—156)	6.7 (6.7—6.7)	44 (43—46)

MUNIX, CMAP and MUSIX median and range in muscles divided according to muscle strength. TA: tibialis anterior; APB: abductor pollicis brevis; BB: biceps brachii; mV: millivolts; *N*: number of individuals.

(potentials with small amplitude and durations, polyphasic and early recruitment) in at least one proximal muscle. In the BB and TA muscles from two individuals, there were also changes compatible with reinnervation/MU reorganization (MUAP with high amplitude) mixed with the myopathic potentials (both patients with LGMD). These two individuals had the longest disease duration.

The mean MUNIX and CMAP values of the BB muscle were significantly lower in the patient group compared to healthy individuals (Fig. 1). In the TA and APB muscles there was not a significant difference in the MUNIX or CMAP results between the patient and control groups.

The MUSIX and α values were not significantly different between the two groups of individuals in any of the three muscles. Two patients had muscle strength 0 in the TA (both LGMD) and one had strength 2 in the BB muscle (also LGMD). Therefore, these muscles were excluded from the analysis.

Discussion

Our study evaluated MUNIX performance in two disorders primarily affecting the muscle fibers. Compared to healthy controls and despite the muscle weakness, there was no significant MUNIX decrease in the APB and TA muscles in the patient group. The BB muscle however, showed a significant MUNIX and CMAP decrease in the patient group. Such CMAP reduction is known to possibly occur in muscle disorders, is attributable to muscle fiber atrophy/degeneration [4] and could potentially have affected MUNIX values.

The MUNIX decrease we observed in the BB muscle was not associated with a significant MUSIX increase, differing from what was described in disorders that lead to denervation, such as ALS [2,5,13]. MUSIX values are supposed to reflect the SMUP size, so that the MUNIX decrease observed in the BB was probably not accompanied by reinnervation/MU loss. In fact, in a myopathy a MUSIX decrease would theoretically be expected. The reason it did not occur in our patients may be related to the fact that in some of the cases of chronic myopathy, low and high amplitude MU are intertwined, so that MUSIX may have reflected the mean of the MU with variable sizes.

Another potentially useful parameter is the α. It has been demonstrated to be abnormal in ALS patients [2,13] probably mainly because of the MU loss. A decreased recruitment may be part of the reason for the changes in the α in these situations, because it hinders the acquisition of SMUPs with gradually progressive areas (strength levels), affecting the power regression curve that generates the α and MUNIX. In our myopathic patients α did not change (in relation to controls) differing from the ALS patients. Miralles also found that when MUNIX decreases solely due to MUAP amplitudes (e.g. myopathies) the α does not change, while if there is a true MU loss the α diverges from normality and contributes to a MUNIX decrease [12].

Previous works evaluated MUNIX results in disorders involving the upper motor neuron [7,9], and also found a decrease in MUNIX. Considering that these are disorders not expected to affect the lower motor neurons directly, the authors hypothesized that muscle fiber atrophy related to lack of use caused the muscle fiber potential to decrease and ultimately led to underestimation of MUNIX [7]. A modified form of the MUNIX that could potentially overcome MUNIX underestimation in conditions such as myopathies has been developed. It uses a variable that compensates changes supposedly not attributable to denervation. This modified technique is less sensitive to detect motor neuron loss, and as such is less attractive as biomarker. However, it could still be potentially useful in certain clinical settings [8].

The small sample of patients and the fact that two different muscle disorders were evaluated should be mentioned as limitations of our study. We should also mention that a significant MUNIX decrease was present only in the most clinically affected muscle, indicating that it may occur only after a certain extent of muscle involvement.

An early study demonstrated a decrease in the incremental motor unit number estimation (MUNE) in patients with Duchene and myotonic dystrophies [10,11]. These authors considered at the time that a primary neurogenic process was responsible for the findings. This claim was later contested, based on post mortem, histopathologic and clinical studies [16]. These results indicate that MUNE values obtained in myopathic patients could not necessarily accurately reflect the population of functioning MU [1]. MUNIX may potentially present this same kind of pitfall, as indeed we observed a significant decline in its values in clinically affected muscles from myopathic patients. Mathematical modeling studies are in line with these findings, since they predicted that muscle fiber loss or atrophy could artifactually decrease MUNIX [12]. In our study, MUSIX and α did not change significantly and could be used to help determine whether MUNIX decrease is indeed accompanied by motor neuron loss, which is also in line with the

Table 2 Data from controls and patients.

Control	Gender	Age	MUNIX			CMAP (mV)			ALPHA			MUSIX		
			BB	APB	TA	BB	APB	TA	BB	APB	TA	BB	APB	TA
1	M	36	366.7	293	168	14.37	15.67	7.7	− 1.004	− 0.97	− 0.988	39	53	46
2	F	44	252.5	167	155.3	10.1	8.4	8.1	− 0.981	− 0.96	− 0.997	40	50	52
3	F	67	191.7	168	85.3	8.37	8.57	4.37	− 0.986	− 0.96	− 0.971	44	51	51
4	M	28	376.7	261.7	135	15.8	13.17	6.17	− 0.989	− 0.95	− 1.013	42	50	46
5	F	31	232.3	186.7	129.3	9.13	9.63	6.73	− 1.023	− 0.95	− 0.961	39	52	52
6	F	28	132	195	186.5	7.6	8.9	7.1	− 0.972	− 1	− 1.035	58	46	38
7	M	32	245.3	291	143	9.9	14.23	6.8	− 0.997	− 0.98	− 0.986	40	49	48
8	M	30	308	226.3	141	12.2	10.93	6.43	− 0.995	− 0.99	− 1	40	48	46
9	F	58	235	205.7	134	9.3	9.2	6.5	− 0.98	− 0.97	− 0.99	40	45	49
10	F	34	263.3	223.6	168.3	8.2	8.3	6.8	− 0.99	− 1	− 1.03	31	37	40
11	M	61	240.8	208.3	142.9	8.48	9.9	5.6	− 1.03	− 0.98	− 0.99	35	48	39

Patient	Diagnosis	Gender	SSO	Age	Strength − MRC			MUNIX			CMAP (mV)			ALPHA			MUSIX		
					BB	APB	TA	BB	APB	TA	BB	APB	TA	BB	APB	TA	BB	APB	TA
1	POMPE	M	PG	22	III	IV	V	173.3	229.7	192.7	7.53	9.93	7.37	− 1.018	− 1.006	− 1.09	43	43	38
2	POMPE	M	A/D	45	IV	V	IV	142	258.7	177.3	5.73	13.43	7.37	− 0.999	− 0.95	− 1.01	40	52	42
3	LGMD 2B	M	PG	38	IV	V	IV	166	205.3	118.7	7.53	9.37	4.93	− 0.99	− 0.97	− 1.007	45	46	42
4	LGMD 2A	F	PG	40	IV	V	III	182.3	321.7	146	10.13	13.43	6.67	− 0.964	− 1.027	− 1.02	56	42	46
5	LGMD 2L	F	SG	59	IV	IV	IV	144.3	166.7	122.7	6.13	8.26	5.93	− 0.95	-0.96	-0.99	42	50	48
6	LGMD 2A	F	PG	36	III	V	IV	161.3	219.0	179.7	7.33	10.17	7.97	− 0.954	− 0.9706	-1.003	45	46	44
7	LGMD 2B	F	PG	54	II	IV	0	-	201.3	-	-	10.96	-	-	− 0.921	-	-	54	-
8	LGMD 2B	M	PG	55	IV	V	0	89	217	-	3.6	11.25	-	− 1.01	− 0.935	-	41	52	-
9	LGMD 2B	F	PG	55	IV	V	III	161.6	233.5	156.1	7.4	10.77	6.71	− 0.97	− 0.98	− 0.95	46	46	43
10	LGMD 2A	F	PG	51	III	V	IV	163	235.8	149.4	7.86	10.62	6.86	− 0.972	− 0.98	− 1.02	48	45	46
11	LGMD 2B	M	SG	50	III	V	IV	112	172.8	123.7	5.12	9.61	5.26	− 0.98	− 0.99	− 0.94	46	56	43

APB: abductor pollicis brevis; BB: biceps brachii; TA: tibialis anterior; LGMD: limb-girdle muscular dystrophy; mV: millivolts; PG: pelvic girdle; SG: shoulder girdle; A/D: axial/diaphragmatic; SSO: site of symptom onset.

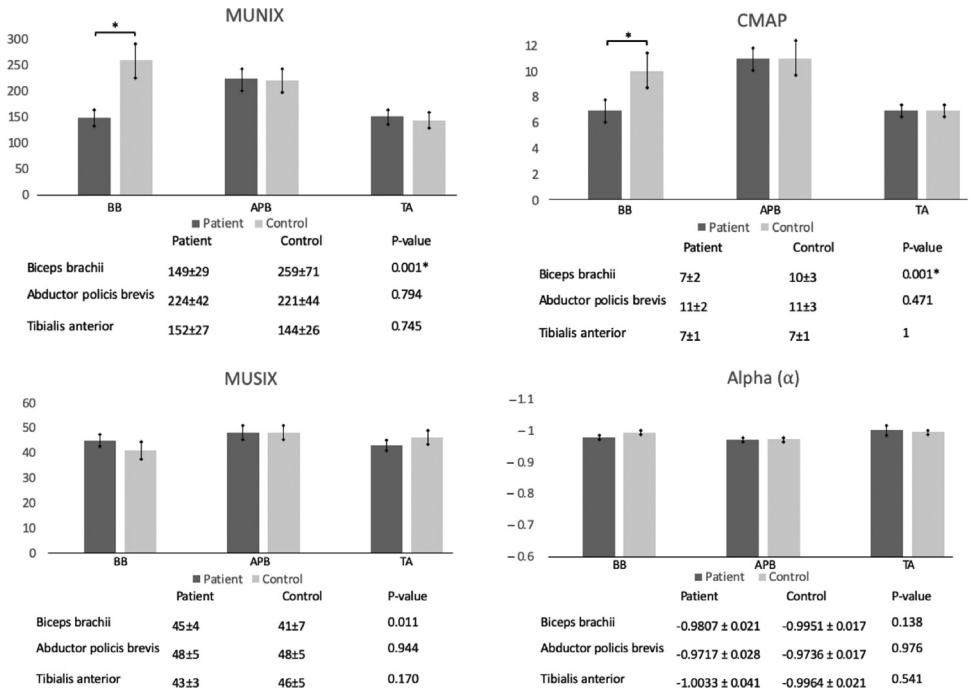

Figure 1 MUNIX, CMAP, MUSIX and alpha (α) values in patients with myopathy and healthy individuals. MUNIX and CMAP values where significantly decreased in the BB muscle in comparison with the control group. MUSIX and α did not change significantly. CMAP: compound motor action potential; BB: biceps brachii; APB: abductor pollicis brevis; TA: tibialis anterior.

aforementioned mathematical models [12]. Thus, despite being a marker of disease progression with proven value in primarily denervating disorders, it is recommendable to consider the underlying clinical setting beforehand, as it could potentially influence analysis/interpretation of MUNIX results.

Disclosure of interest

The authors declare that they have no competing interest.

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