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Letter to the Editor

A dilemma in stroke application: Standard or modified motor unit number index?

The recent advent of motor unit number index (MUNIX) technique has provided a convenient and clinically applicable approach to estimating motor unit population changes in a muscle (Nandedkar et al., 2004, 2010). It uses compound muscle action potential (CMAP) and surface electromyogram (EMG) at different voluntary contraction levels to produce an index associated with motor unit number changes in the muscle. Compared with laborious motor unit number estimation (MUNE) techniques, the MUNIX protocol is easy and quick to implement and can minimize discomforts caused by electrical stimuli. It takes less than five minutes to perform MUNIX examination of a muscle. Because of this, there have been multiple MUNIX applications in amyotrophic lateral sclerosis (ALS) for assessing or tracking disease progress (Furtula et al., 2013; Nandedkar et al., 2010; Neuwirth et al., 2010) and in aging (Drey et al., 2013, 2014; Kaya et al., 2013). MUNIX has also been applied in several cross-sectional studies of neurological disorders (Li et al., 2011, 2012a, 2014, 2015; Marciniak et al., 2015; Sandberg et al., 2011) and might be potentially useful in assessing neuromuscular changes of those patients undergoing a rehabilitation program. While multiple studies have confirmed the reproducibility and sensitivity of the MUNIX estimate for revealing motor unit loss (Ahn et al., 2010; Boekestein et al., 2012; Kaya et al., 2014; Li et al., 2012b; Nandedkar et al., 2011; Neuwirth et al., 2011), one important finding from a simulation analysis is that reduction in motor unit action potential (MUAP) amplitude can have a substantial impact on MUNIX calculation, leading to underestimation of the motor unit number (Li et al., 2012b). To overcome this effect, a modified method was proposed, which uses a variable that is associated with a muscle's CMAP area rather than an arbitrary constant value (i.e. 20 mV·ms) to define the MUNIX (Li et al., 2016).

For either standard MUNIX (sMUNIX) or modified MUNIX (mMUNIX), as a simplified method derived from a mathematic model, it is characterized with very convenient implementation. The current short report focuses on the MUNIX methodology discussion and alerts users both advantages and limitations of the two different MUNIX methods. To make a complex topic easy to understand, we applied both sMUNIX and mMUNIX measures to examine paretic muscles of strokes subjects. The results were compared and discussed. Such an approach can help an in-depth understanding of the MUNIX method and guide its appropriate application and interpretation in different diseases or situations.

Fourteen chronic stroke subjects (6 Female, and 8 Male), who survived from a unilateral cerebral lesion, participated in the study (Table 1). All subjects submitted the written consent approved by the local institutional review committee prior to any experiment procedures. The first dorsal interosseous (FDI) muscle was examined, using the Sierra Wave EMG system (Cadwell Lab Inc, Kennewick, WA, USA). A disk electrode (Ag–AgCl, 1.0 cm diameter) was placed over the motor point of the FDI muscle to record evoked muscle responses. A standard bar electrode was positioned on top of the ulnar nerve with the cathode oriented closer to the recording electrodes and 2 cm proximal to the wrist crease. Single stimulus was delivered through cathode with pulse width of 200 μs. The CMAP was acquired using supramaximal electrical stimulation. After the CMAP recording, surface EMG interference patterns (SIPs) were collected from the FDI muscle when subjects abducted their index finger and generated isometric contraction against the resistance provided by the operator. They were encouraged to use visual feedback of muscle activity (EMG) to gradually increase the force beginning with minimal effort till reaching the maximal force (each level lasting for at least 2 s). At least three trials were obtained for each muscle. Sufficient rest time was given between trials to prevent potential fatigue. Subjects were scheduled for a one-time visit having both paretic and contralateral hands examined (in a randomized order). The CMAP and SIP signals were sampled at 12.8 kHz and 32 kHz respectively, with band-pass filter setting 1 Hz–2 kHz for CMAP and 10 Hz–10 kHz for SIPs.

All data were processed offline in Matlab (MathWorks Inc, Natick, MA, USA). The SIP trials were down-sampled to 2 kHz and filtered to 10–500 Hz. A SIP trial was divided to 4–5 individual segments, each representing a different level of voluntary contraction. Then the area (S_{area}) and power (S_p) of the individual SIP segment, normalized over 1 s epoch, were calculated. A minimum of 12 pairs of SIP area and power values were obtained from one muscle. Validation of the SIP signals followed the same criteria as proposed in (Nandedkar et al., 2010). The CMAP parameters including peak-to-baseline amplitude, area (M_{area}) and power (M_p) were also calculated for the same muscle. The above SIP and CMAP parameters were used to calculate the "ideal case motor unit count (ICMUC)", defined as $ICMUC = \frac{M_p S_{area}}{M_{area} S_p}$ (Nandedkar et al., 2004, 2010). The relation between the ICMUC and the SIP area was then determined via a nonlinear regression analysis: ICMUC = $\beta*(S_{area})^{\tau}$, where β and τ are constant coefficients determined by the SIP-ICMUC curve. The sMUNIX is defined as the ICMUC value when the SIP area equals a constant value (20 mV·ms): $sMUNIX = \beta * (20)^{\tau}$. By contrast, the mMUNIX is defined as the ICMUC value when the SIP area equals a given percentile of an individual subject's CMAP area: mMUNIX = $\beta*(coeff*M_{\text{area}})^{\tau}$, where $0 < coeff < 1$. In the previous simulation work, *coeff* was set to be 0.4, so the mMUNIX and sMUNIX resulted in very similar values under default model parameters (Li et al., 2016). To compare the difference of mMUNIX and sMUNIX for examining paretic muscle of the stroke subjects, we set the contralateral muscle's mMUNIX value of a given subject the same as the muscle's sMUNIX value. This was implemented by setting

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Table 1
Stroke subject information.

ID	Gender	Age (years)	Duration (years)	Chedoke	Fugl-Meyer	Paretic side	Grip force (kg)	
							Paretic	Contralateral
1	M	68	8.9	3	21	Left	2.9	29.1
2	F	56	12.8	2	6	Left	2.6	20.8
3	M	68	30.0	2	7	Left	4.8	36.5
4	M	64	14.9	2	17	Right	11.9	52.9
5	F	51	6.0	5	38	Right	14.1	29.1
6	M	44	4.4	5	58	Right	24	67.9
7	F	58	18.0	3	29	Left	6.9	19.7
8	M	55	22.0	2	19	Left	3.4	45.7
9	M	81	16.4	2	21	Right	9.6	35.7
10	M	72	15.9	5	47	Right	8.6	26.3
11	F	61	14.2	3	34	Left	8.1	31.3
12	M	48	1.0	6	48	Right	23.1	50.7
13	F	57	1.1	2	12	Right	6.9	19.7
14	F	40	4.4	2	11	Left	9.3	29.6

the *coeff* as the ratio of 20 mV·ms to the contralateral muscle's CMAP area. The determined *coeff* was then used for calculating mMUNIX of the paretic muscle. The sMUNIX and mMUNIX were calculated respectively for each stroke subject. The standard motor unit size index (sMUSIX) and modified motor unit size index (mMUSIX) were also computed by dividing the CMAP amplitude by the sMUNIX or the mMUNIX respectively. Paired T test was used for statistical analysis. All data were expressed as mean ± standard error format.

Substantially lower CMAP amplitude was observed in the paretic muscle than in the contralateral muscle (Fig. 1a, paretic: 9.91 ± 0.68 mV, contralateral: 13.16 ± 0.56 mV, $p < 0.01$). A significant reduction of sMUNIX was observed in the paretic muscle compared with the contralateral muscle (Fig. 1b left panel, paretic: 157 ± 14, contralateral: 209 ± 12, $p < 0.02$). In contrast, the mMUNIX measures of the paretic muscles were similar to those of the contralateral muscles (Fig. 1b right panel, paretic: 194 ± 12, contralateral: 209 ± 12, $p = 0.3$). We did not find a significant difference in sMUSIX between the two sides (Fig. 1c left panel, paretic: 65.74 ± 3.26 μV, contralateral: 65.14 ± 3.43 μV, $p > 0.5$). However, the mMUSIX of the paretic muscle was significantly smaller than the contralateral muscle (Fig. 1c right panel, paretic: 52.17 ± 3.53 μV, contralateral: 65.14 ± 3.43 μV, $p < 0.02$).

With the sMUNIX or mMUNIX remaining the same for the contralateral side, we found that the sMUNIX yielded significantly lower values than the mMUNIX for the paretic muscle (Fig. 1b, paretic sMUNIX: 157 ± 14, paretic mMUNIX: 194 ± 12, $p < 0.01$). As the CMAP amplitude remained the same, this resulted in larger sMUSIX than the mMUSIX (Fig. 1c, paretic sMUSIX: 65.74 ± 3.26 μV, paretic mMUNIX: 52.17 ± 3.53 μV, $p < 0.01$).

As shown in Fig. 2, a significant correlation between CMAP amplitude and sMUNIX was observed for the paretic muscle, whereas no correlation was found between CMAP amplitude and mMUNIX. A significant correlation between CMAP amplitude and sMUNIX or mMUNIX was also observed for the contralateral muscle. In contrast, there was a significant correlation between CMAP amplitude and mMUSIX for the paretic muscle, whereas no correlation was observed between CMAP amplitude and sMUSIX (for the paretic muscle), or between CMAP amplitude and MUSIX (either sMUSIX or mMUSIX) for the contralateral muscle.

Application of sMUNIX and mMUNIX to the same group of stroke subjects clearly led to conflicting results and interpretations. Different from the findings using the sMUNIX measurement (which showed reduced value in paretic side), the mMUNIX estimation did not show a significant reduction in the paretic muscle compared with the contralateral side. There was substantially lower mMUSIX observed in the paretic muscle than in the contralateral muscle, whereas no significant difference in sMUSIX was observed between the two sides. For paretic muscle the mMUNIX showed significantly higher values than the sMUNIX, which are associated with their different definitions. The sMUNIX and mMUNIX were calculated for the same muscle with all parameters remaining the same except for the selection of SIP area for defining sMUNIX or mMUNIX. We found the SIP area for calculating mMUNIX was smaller than 20 mV·ms, resulting in higher mMUNIX estimations than the sMUNIX (in the paretic hand). As a result, the mMUSIX was significantly smaller than sMUSIX.

One should choose the appropriate MUNIX method depending upon the underlying disease process. The sMUNIX is most suitable for motor neuron diseases that demonstrate secondary evidence of muscle fiber reinnervation, such as ALS. As a comparison, the mMUNIX measurement is most suitable for applications when MUAP amplitude reduction (due to loss of muscle fiber size) is dominant. Given the complex nature of neuromuscular changes after stroke, it remains uncertain which approach (sMUNIX or mMUNIX) is more appropriate for stroke examination. For example, different studies have provided conflicting evidence as to whether post stroke involves loss of spinal motor neurons/motor units (Terao et al., 1997; McComas et al., 1973; Hara et al., 2004; Arasaki et al., 2006). Some investigators have reported the presence of electrophysiological abnormalities as evidence of spinal motor neuron degeneration (Chang, 1998; Lukacs, 2005; Lukacs et al., 2008), while others have not made such findings (Kouzi et al., 2014). Observance of different degrees of muscle volume loss has also been documented post stroke (Triandafilou and Kamper, 2012; Klein et al., 2010).

Therefore, it remains a dilemma to apply the MUNIX technique in stroke patients. We advocate application of a range of techniques (together with sMUNIX or mMUNIX measurement), to the same stroke patients (rather than solely relying on one technique) to obtain more definite information. These techniques (such as MUAP quantitative analysis, muscle fiber density analysis, electrical impedance myography, etc.) can address different aspects of the examined muscle and thus offer a significant amount of complementary information about muscle structure and function. A comprehensive examination from a range of combined techniques will help understand alterations in different neural and muscular factors that may contribute to muscle weakness and to other key intrinsic property changes in spastic-paretic muscles. Although the current MUNIX outcome is limited by not reaching a definite conclusion due to complex nature of neuromuscular changes after stroke, the analysis results can help provide an in-depth understanding of the two different MUNIX methods. This is important for further improvement of the MUNIX method as well as for