Published in final edited form as:
IEEE Trans Inf Technol Biomed. 2012 November ; 16(6): . doi:10.1109/TITB.2012.2193410.

An Examination of the Motor Unit Number Index (MUNIX) in Muscles Paralyzed by Spinal Cord Injury

Xiaoyan Li,
Sensory Motor Performance Program (SMPP) of the Rehabilitation Institute of Chicago, Chicago, 60611, USA

Faezeh Jahanmiri-Nezhad,
Department of Bioengineering of the University of Illinois at Chicago and the SMPP of the Rehabilitation Institute of Chicago, Chicago, 60611, USA

William Zev Rymer, and
SMPP of the Rehabilitation Institute of Chicago, and Departments of Physical Medicine and Rehabilitation, Physiology, and Biomedical Engineering of Northwestern University, Chicago, 60611, USA

Ping Zhou [Senior Member, IEEE]
SMPP of the Rehabilitation Institute of Chicago, and Department of Physical Medicine and Rehabilitation of Northwestern University, Chicago, 60611, USA, and the Institute of Biomedical Engineering of the University of Science and Technology of China, Hefei, China, phone: 01-312-238-1365;

Ping Zhou: p-zhou@northwestern.edu

Abstract

The objective of this study was to assess whether there is evidence of motor unit loss in muscles paralyzed by spinal cord injury (SCI), using a measurement called motor unit number index (MUNIX). The MUNIX technique was applied in SCI (n=12) and neurologically intact (n=12) subjects. The maximum M waves and voluntary surface electromyography (EMG) signals at different muscle contraction levels were recorded from the first dorsal interosseous (FDI) muscle in each subject. The MUNIX values were estimated using a mathematical model describing the relation between the surface EMG signal and the ideal motor unit number count derived from the M wave and surface EMG measurements. We recorded a significant decrease in both maximum M wave amplitude and in estimated MUNIX values in paralyzed FDI muscles, as compared with neurologically intact muscles. Across all subjects, the maximum M wave amplitude was 8.3 ± 4.4 mV for the paralyzed muscles and 14.4 ± 2.0 mV for the neurologically intact muscles ($p<0.0001$). These measurements, when combined with voluntary EMG recordings, resulted in a mean MUNIX value of 112 ± 71 for the paralyzed muscles, much lower than the mean MUNIX value of 228 ± 49 for the neurologically intact muscles ($p<0.00001$). A motor unit size index was also calculated, using the maximum M wave recording and the MUNIX values. We found that paralyzed muscles showed a mean motor unit size index value of 80.7 ± 17.7 μV, significantly higher than the mean value of 64.9 ± 10.1 μV obtained from neurologically intact muscles ($p<0.001$). The MUNIX method used in this study offers several practical benefits compared with the traditional motor unit number estimation technique because it is noninvasive, induces minimal discomfort due to electrical nerve stimulation, and can be performed quickly. The findings from this study help understand the complicated determinants of SCI induced muscle weakness and provide further evidence of motoneuron degeneration after a spinal injury.

Correspondence for this study should be addressed to P. Zhou.

Index Terms

EMG; motor unit index; M-wave; SCI

I. Introduction

Spinal cord injury (SCI) leads to neurological deficits that diminish health-related quality of life [1–2]. Damage to the spinal cord may cause varying degrees of paralysis, depending on the location and severity of the injury. Weakness for voluntary movement after SCI is almost universally present, and it can be highly debilitating. Paralyzed and spastic muscles may also experience progressive changes in their intrinsic mechanical properties, giving rise to muscle contractures and to alterations in muscle structure (such as a loss of muscle fibers, an increase of interstitial connective tissue, and changes in the viscoelastic muscle properties). The neurological origins of these phenomena remain unclear. They could be the result of different mechanisms, including disuse, autonomic changes, a loss of central motoneuron trophic influences, trans-synaptic motoneuron degeneration, and/or their combinations. Regardless of the origins of SCI induced muscle weakness and other clinical signs, it is very important to determine how a spinal injury affects motor unit survival and function. This information could guide development of effective treatment and management of SCI patients.

Electrophysiological studies have played an important role in assessing the pathological alterations in motoneuron and motor unit functions following spinal injury. Using different electromyogram (EMG) techniques (e.g, single fiber EMG, concentric needle EMG, macro EMG, and surface EMG), the pathophysiology of paralyzed muscles can be assessed at muscle fiber, motor unit, and muscle levels. The abnormal EMG findings from paralyzed muscles of SCI subjects include fibrillation and positive sharp waves [3–6], spontaneous motor unit activities [7–9], increased motor unit action potential (MUAP) size and complexity [10–13], increased muscle fiber density [14–16], disorganization of motor unit control properties (i.e., recruitment and firing rate) [17]. These changes revealed by electrophysiological studies might be attributable to a different pathophysiology such as degeneration of spinal motoneurons and peripheral neuromuscular deterioration.

In addition to various EMG methods, the motor unit number estimation (MUNE) technique and its various modifications have been used to examine muscles paralyzed by spinal injury. Consistent with different histological studies using stereological or other techniques [18–19], the MUNE studies have shown varying degrees of reduction in motor unit number in paralyzed muscles [20–22].

The traditional MUNE methods involve estimates of single motor unit action potential size, using either incremental nerve stimulation or spike triggered averaging techniques, both potentially laborious and time-consuming. A recently developed technique uses the maximum M wave or the compound muscle action potential (CMAP) and surface EMG interference patterns, recorded during voluntary muscle contraction, to derive an index proportional to the number of motor units in a muscle [23]. This method, called motor unit number index (MUNIX), is easy and quick to perform. Upon introduction of the concept, it has been effectively used to quantitatively assess the pathophysiology of motoneuron loss in amyotrophic lateral sclerosis (ALS) patients [23]. Furthermore, in recent years, the method has attracted increasing attention and achieved encouraging outcomes in providing an objective measure of the disease progression of ALS and in other neurological illnesses [24–31].

The current study presents a novel application of the MUNIX technique in SCI. The objective of the study was to use the MUNIX measurement to examine whether the numbers of motor units in muscles partially paralyzed by SCI are lower than those estimated from matched control muscles. Assessment of motor unit loss in paralyzed muscles can help understand complicated determinants of SCI induced muscle paresis and provide evidence of spinal motoneuron degeneration after the injury. Estimation of motor unit number after SCI is also clinically important for monitoring the progress in the course of recovery after initial injury, as such to provide better and realistic prognosis earlier on to prepare for care needs. The MUNIX method used in this study needs minimal electrical stimulation, and the procedure can be performed quickly. The demonstrated effectiveness and efficiency of the method in the present SCI study indicate great promise for its applications in clinical practice.

II. Method

A. Subjects

Twelve incomplete SCI subjects with injury levels from C2–C7 and American Spinal Injury Association (ASIA) impairment levels of C and D (10 males, 2 females, 49 ± 10 years), and 12 neurologically intact subjects (6 males, 6 females, 46 ± 11 years) participated in this study. All the SCI subjects were recruited by using the Clinical Neuroscience Research Registry at the Rehabilitation Institute of Chicago (Chicago, IL, USA). The duration of the injury was 6.8 ± 4.0 years (range: 1–14 years). All procedures of the study were performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board at Northwestern University (Chicago, IL, USA). Prior to participation in the study, all subjects gave written informed consent.

B. Experimental Protocol

The experiments were performed on the first dorsal interosseous (FDI) muscle in each subject. The primary equipment used for this recording was a Sierra Wave EMG system (Cadwell Lab Inc, Kennewick, WA, USA). The experimental details were the same as used in our previous report [25] and are briefly described here. Subjects were seated comfortably in a chair with the examined forearm placed in a natural, resting position on a height-adjustable table. Two 10 mm silver/silver chloride disc surface recording electrodes were used to record electrical activity from the FDI muscles. Electrode placement was similar to that for standard ulnar motor conduction studies. The active surface electrode was positioned over the motor point of the FDI muscle with the reference surface electrode positioned over the second metacarpophalangeal joint. An adhesive ground electrode was placed on the back of the hand. All surface electrode positions were further reinforced with the use of strips of surgical tape to reduce movement during the recording.

To begin, the maximum M wave was recorded first. The ulnar nerve was stimulated about 2 cm proximal to the wrist crease. The duration of each single pulse stimulation was 200 μs. The stimulation intensity started around 15–20 mA. The intensity was further increased in increments of approximately 20% above that until the stimulation intensity eliciting the maximal response was reached. Then, the stimulation intensity was increased to 120% of the final intensity to confirm no further enlargement in the peak-to-peak amplitude of the maximum M wave.

After the maximum M wave recording, with the EMG recording electrode maintained at the same position, the voluntary surface EMG signals were recorded from the FDI muscle while the subject generated an isometric muscle contraction force at different levels, defined by the examiner offering resistance to the tested FDI muscle. The different force levels were recorded using a single trial with graded contraction consisting of necessary interference

EMG epochs representing minimal to maximal effort. Subjects were allowed substantial rest to avoid muscle fatigue during the recording. The surface EMG signals were sampled at 2 kHz, with a bandpass filter setting at 10 Hz – 500 Hz. All signals were recorded to a hard disk and analyzed offline.

C. Data Analysis

The maximum M wave and different levels of surface interference pattern (SIP) EMG were used to compute the MUNIX values for the examined FDI muscle using the method developed by Nandedkar et al. [23]. The MUNIX derivation was described in detail elsewhere [23] [26] and its procedures are outlined in Figure 1.

In brief, the area and power of the maximum M wave (the first negative phase) were first computed. Then, for each voluntary contraction level, the average area and power of the SIP for a one-second epoch were also calculated. The area and power of a signal were obtained by summating the absolute and square of the sample values of the waveform, respectively, and the sum was multiplied by the sampling interval for the measurement. The values calculated from the maximum M wave and different levels of SIPs were used to compute the "ideal case motor unit count (ICMUC)":

$$ICMUC=\frac{M_p S_a}{M_a S_p} \quad (1)$$

where M_p and M_a represent the maximum M wave power and area, while S_p and S_a represent SIP power and area. Thus, each level of SIP gave two results: SIP area and ICMUC. The ICMUC refers to the motor unit count under an ideal situation where the individual MUAPs are identical for all motor units and do not superimpose. In reality, the MUAP size varies and the MUAPs are routinely superimposed, which significantly influences the ICMUC value. Regression analysis was then used to define the relationship between SIP area and ICMUC by the following formula:

$$ICMUC=\beta\,(S_a)^{\alpha} \quad (2)$$

The parameters β and α obtained from the regression were used to define the MUNIX:

$$MUNIX=\beta\,(20)^{\alpha} \quad (3)$$

In MUNIX analysis, it is noted that very low amplitude voluntary surface EMG signals may give very high ICMUC values. To exclude this artifact, three criteria were imposed to accept an SIP epoch for MUNIX calculation as routinely used in MUNIX studies [26]: (1) SIP area> 20mVms; (2) ICMUC<100; and (3) SIP area/CMAP area>1. In addition, only those CMAPs whose amplitude is greater than 0.5 mV were accepted for the MUNIX analysis. The first negative phase of the CMAP was used to compute its amplitude, area, and power.

With MUNIX values available, the motor unit size index (MUSIX) of the muscle can be obtained by dividing MUNIX into the maximum M wave amplitude [26]:

$$MUSIX=\frac{M_v}{MUNIX} \quad (4)$$

where M_v represents the maximum M wave amplitude. MUSIX is measured in volts and an index that reflects the average amplitude of the individual surface MUAPs. Since the

acronyms “MUNIX” and “MUSIX” are very similar, in the rest of the paper we use underline, i.e. “MUSIX”, to avoid any confusion with “MUNIX”.

We measured the maximum M wave, the MUNIX and the MUSIX values in paralyzed FDI muscles of SCI subjects and compared with the match control muscles, and examined whether these measurements in the SCI subjects were significantly different from those obtained in the neurologically intact subjects. One-way ANOVA was performed to assess the differences between the paralyzed and healthy control muscles.

III. Results

Recordings of the maximum M waves and voluntary surface EMG signals at different levels of contraction were obtained from paralyzed FDI muscles and from neurologically intact muscles. We observed a significant decrease in maximum M wave amplitude in the paralyzed FDI muscles, as compared with the neurologically intact muscles (Figure 2). Across all subjects, the maximum M wave (the first negative phase) amplitude was 8.3±4.4 mV (range: 0.8–14.7 mV) for the paralyzed FDI muscles and 14.4 ± 2.0 mV (range: 11.7–16.7 mV) for the neurologically intact muscles ($p<0.0001$).

Maximum M wave recordings, in combination with voluntary surface EMG at different muscle contraction levels, were used to calculate the MUNIX measurements. Figure 3 demonstrates an example of the MUNIX calculation from neurologically intact and paralyzed FDI muscles, respectively, where the maximum M wave, the voluntary EMG, and the MUNIX all showed a decrease in the paralyzed muscle. Analysis of SIP measurements (the individual data points in Figure 3) shows an excellent fit with the mathematical model used to calculate the MUNIX. In this example, the maximum M wave amplitude was 4.0 mV for the paralyzed muscle and 16.5 mV for the healthy control muscle. It is noted that the maximum voluntary surface EMG generated by the paralyzed muscle was also much lower than that from the healthy control muscle, as indicated by the x-axis values of the individual data points used for the curve fitting. With the measured maximum M wave and different levels of voluntary surface EMG values, this paralyzed muscle showed a MUNIX value of 49, which was much lower than the MUNIX value of 267 for the healthy control muscle.

For all the subjects, exponential regression analysis showed a good fit for the relationship between SIP area and ICMUC. As indicated in Figure 4(a), across all SCI and intact subjects we observed a significant decrease in MUNIX values in the paralyzed FDI muscles when compared with the matched control muscles. Twelve SCI subjects showed a MUNIX value of 112 ± 71 for the paralyzed FDI muscles, which was significantly lower than the MUNIX value of 228 ± 49 for the healthy control muscles ($p<0.00001$).

MUSIX values of paralyzed and healthy control FDI muscles were obtained from maximum M wave and MUNIX calculation. Across all subjects we also observed a significant change in MUSIX values in the paralyzed FDI muscles when compared with the healthy control muscles (Figure 5). Twelve SCI subjects showed a mean MUSIX value of 80.7 ± 17.7 μV for the paralyzed FDI muscle and 64.9 ± 10.1 μV for the healthy control muscle ($p<0.001$). The MUSIX values also showed a wider range in both ends for paralyzed muscles (range: 46.6 – 104.4 μV) when compared with the healthy control muscles (range: 49.9 – 79.5 μV).

Figure 6 shows the correlation of the maximum M wave with the MUNIX and MUSIX values of the SCI and neurologically intact subjects, respectively. For both paralyzed and healthy control muscles, a strong correlation was observed between the maximum M wave and the MUNIX values ($p<0.02$), while the MUSIX showed no significant correlation with the maximum M wave amplitude ($p>0.2$). However, a trend was observed, particularly for the paralyzed muscles, that the MUSIX value tended to decrease with the increase of the M

wave amplitude. Similar to the maximum M wave, no significant correlation was observed between the MUSIX and the maximum voluntary surface EMG.

IV. Discussion

Since its introduction in 1971[32], the MUNE technique and its various modifications have been used to detect motoneuron loss and to measure disease progression in ALS and other related motoneuron diseases (see reviews [33–36]). A major feature of the present study is the primary reliance on the MUNIX measurement, which offers several practical benefits compared with the traditional MUNE technique because it is noninvasive, induces minimal discomfort due to electrical nerve stimulation, and can be performed quickly [23]. Following its introduction, the technique has been successfully used to detect motoneuron loss and measure disease progression in ALS and in other investigations [24–31].

This study presents the first application of the MUNIX technique in examination of muscles paralyzed by spinal injury. It should be noted that the MUNIX measurement is not an absolute count of the motor units in a muscle. Instead, it provides an index that is proportional to the motor unit numbers in the muscle. In this respect, the emphasis of the MUNIX methods should always be the comparison of the MUNIX changes in different muscles (e.g., in neurologically intact and disease state muscles), or the comparison of the MUNIX changes in the same muscles in a longitudinal study (such as tracking progress of a motoneuron disease). During such comparisons, the same definition for all parameters is required throughout the study.

The emphasis of the current study was to demonstrate findings from the paralyzed muscles when compared with neurologically intact muscles. The MUNIX measurement is based on CMAP recordings via stimulation of peripheral motor axons innervating the examined muscles. Our study findings that the maximum M wave amplitude was significantly lower in the paralyzed muscles as compared with the neurologically intact muscles are consistent to previous observations [37–41]. Decreased CMAP or maximum M wave provides further evidence of muscle fiber loss or atrophy after a spinal injury. The alteration in motor unit number in paralyzed muscles of SCI subjects was further assessed by applying the MUNIX technique and comparing with the healthy control muscles. The MUNIX values were estimated from the mathematical model describing the relation between the surface EMG signal and the ideal motor unit number count derived from M wave and surface EMG measurements. With the same definition for all parameters throughout the study, the absolute values of MUNIX are not important, in contrast to the changes seen from paralyzed and healthy control muscles.

We found a significant reduction of MUNIX values in the paralyzed muscles of SCI subjects compared with the neurologically intact muscles, thus providing evidence of motor unit loss in paralyzed muscles or motoneuron degeneration after the spinal injury. The findings are consistent with previous reports from traditional MUNE studies. Variable level of motor unit reduction has been reported using MUNE techniques, either due to direct injury to the anterior aspect of the spinal cord at the relevant segmental levels [21] or due to transsynaptic degeneration, distal to SCI segmental levels [20]. A more recent study [22] using adapted multiple point stimulation method found that the mean estimated motor unit number of the tibia anterior muscle was significantly lower in the sub acute SCI patients than in the control group. A continuous increase in motor unit number was observed in the sub acute SCI patients during the later follow up period. In the chronic SCI group, the estimated motor unit number was similar to that of the control group. The findings of the study [22] implied that transsynaptic degeneration was not prominent or at least reversible. Alternatively, the

observations may be related to the peripheral nerve excitability change after the acute spinal injury, which may confound the MUNE results [42–43].

In our current study, the MUNIX values were found to be significantly lower in paralyzed muscles than in neurologically intact muscles. This provides further evidence of motor unit loss or motoneuron degeneration after the injury. Such motor unit or motoneuron loss could be due to different mechanisms such as direct injury of relevant segmental levels, transsynaptic degeneration distal to injured segmental levels, or both. In addition to a significant drop in MUNIX values of paralyzed muscles, we also observed a significant difference in MUSIX values between paralyzed and neurologically intact muscles. The range of MUSIX values from the paralyzed muscles was also wider than that from the neurologically intact muscles. Compared with the neurologically intact muscles, the shift of the MUSIX towards small values observed in paralyzed muscles may be due to denervation or atrophy of the muscle fibers. On the other hand, the shift of the MUSIX towards large values may be potentially due to incidence of muscle fiber reinnervation in the paralyzed muscles. Evidence of muscle fiber reinnervation in muscles paralyzed by SCI has been reported using several EMG techniques. For example, using quantitative MUAP analysis based on concentric needle EMG and macro EMG recordings, enlarged MUAPs and increased MUAP complexity have been observed in paralyzed muscles compared with matched control muscles [10–12, 40]. Collateral reinnervation of muscle fibers was also suggested by single fiber EMG, where increased muscle fiber density and evidence for neuromuscular instability were reported in paralyzed muscles [14–16]. The findings of the current study, i.e., the significant increase of the MUSIX values in paralyzed muscles compared with neurologically intact muscles, provide further support of muscle fiber reinnervation occurring as a marker of altered muscle fiber composition. This can be viewed as secondary evidence of motoneuron degeneration after the spinal injury.

Finally, it should be noted that the MUNIX values are estimated from a mathematical model that relies on both maximum M wave and voluntary surface EMG signals at different muscle contraction levels. The examiner-defined voluntary contraction level is subjective. However, this does not bias the MUNIX measurement since the method relies on different levels of voluntary EMG for curve fitting, so an accurate force measurement with a load cell is not required for the MUNIX computation [23]. It is also acknowledged that the ability in activating motor unit pool could be impaired in some patients with neurologic disorders or motoneuron diseases [17, 44–45], thus constraining the voluntary EMG generation. In this study, three criteria were imposed to accept a segment of voluntary EMG as a valid SIP epoch for MUNIX calculation. These criteria can effectively reduce the artifacts in MUNIX estimation induced by the very low amplitude voluntary surface EMG signals.

V. Conclusion

In conclusion, the present cross-sectional study examined whether there is evidence of motor unit loss in muscles paralyzed by SCI using the MUNIX measurements. A significant decrease in both maximum M wave and MUNIX values was found in paralyzed FDI muscles, as compared with neurologically intact muscles. The paralyzed muscles also showed significantly higher MUSIX values than those obtained from neurologically intact muscles. These findings provide further electrophysiological evidence of motor unit loss or motoneuron degeneration following a spinal injury. Moreover, the MUNIX measurement requires minimum amount of electrical stimulation and is convenient to implement. Thus, the findings of the study also have potential clinical value for the diagnosis of SCI, the improvement of outcome measurements, and the evaluation of the effects of medication or therapies.

Acknowledgments

This work was supported in part by the U.S. National Institutes of Health under Grants 1R21NS075463, 2R24HD50821, and the Searle-Chicago Community Trust Foundation.

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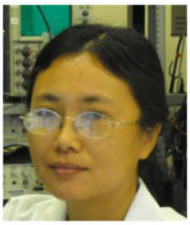
Biographies



Xiaoyan Li received her B.S. degree in Electrical Engineering from Anhui University, and M.S. degree in Biomedical Engineering from University of Science and Technology of China, both in Hefei, China. She obtained her second M.S. degree in Computer Sciences from Loyola University Chicago in 2002, and her Ph.D. degree in Bioengineering from the University of Illinois at Chicago (UIC) in 2008. Later she was a Postdoctoral Research Fellow in Institute for Neural Computation of the University of California at San Diego (UCSD), CA, and in Department of Physical Medicine and Rehabilitation of Northwestern University, Chicago, IL, respectively. Currently she is a Research Associate at the Sensory Motor Performance Program of the Rehabilitation Institute of Chicago, IL. Her research interests focus on motor control, neurological disorders and rehabilitation. Her current research is supported by the Brinson Stroke Foundation and the U.S. Department of Education, the National Institute on Disability and Rehabilitation Research.

Faezeh Jahanmiri-Nezhad received the B.S. degree in Biomedical Engineering from the AmirKabir University of Technology, Tehran, Iran, and the M.S. degree in Systems Design Engineering (in Biomedical Engineering) from the University of Waterloo, Ontario, Canada. From 2009 to 2010, she was a Research Engineer in the Sensory Motor Performance Program of the Rehabilitation Institute of Chicago, IL. She is currently a Ph.D. student in

Department of Bioengineering at University of Illinois at Chicago (UIC), IL, and a Research Assistant in the Sensory Motor Performance Program of the Rehabilitation Institute of Chicago.

William Zev Rymer received the M.B.B.S. degree from Melbourne University, Melbourne, Australia, in 1962, and the Ph.D. degree in neurophysiology from Monash University, Melbourne, in 1973. After residency training in internal medicine and neurology, he returned to graduate training. After postdoctoral training at the National Institutes of Health and Johns Hopkins University Medical School, Baltimore, MD, he became an Assistant Professor of neurosurgery and physiology at the State University of New York in 1976. He became an Assistant Professor in 1978 at Northwestern University Medical School, Chicago, IL, an Associate Professor in 1981, and a Professor in 1987. He now holds the John G. Searle Chair in Rehabilitation Research and is Vice President for Research at the Rehabilitation Institute of Chicago, IL, and President of the Rehabilitation Institute Research Corporation, Chicago, IL. He is also Director of the Sensory Motor Performance Program, Rehabilitation Institute of Chicago and the Medical Biomechanics Program at Northwestern University Medical School.

Ping Zhou (S’01–M’05–SM’07) received the B.S. degree in electrical engineering and the M.S. degree in biomedical engineering from the University of Science and Technology of China, Hefei, China, in 1995 and 1999, respectively, and the Ph.D. degree in biomedical engineering from Northwestern University, Evanston, IL, in 2004. His Ph.D. dissertation project was performed as part of the Sensory Motor Performance Program (SMPP), Rehabilitation Institute of Chicago, Chicago, USA.

From 2004 to 2006, he was a Research Associate in the Neural Engineering Center for Artificial Limbs (NECAL), Rehabilitation Institute of Chicago. After that he has been a Research Scientist in NECAL and later in SMPP at the Rehabilitation Institute of Chicago. He has been an Adjunct Assistant Professor since 2006 in the Department of Physical Medicine and Rehabilitation, Northwestern University, Chicago, USA, and a Professor since 2012 in the Institute of Biomedical Engineering, University of Science and Technology of China, Hefei, China. His current research interests include biomedical signal (in particular, EMG) processing, spinal motor neuron/motor unit pathophysiology in neurologic disorders, noninvasive electrodiagnosis of neuromuscular diseases, computational modeling of neuromuscular systems, myoelectric prosthesis control, and assistive devices.

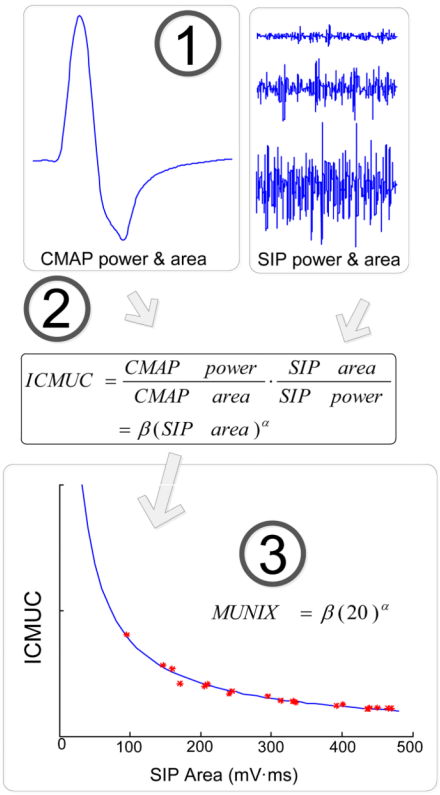


Fig. 1.
Diagram of three-step MUNIX calculation

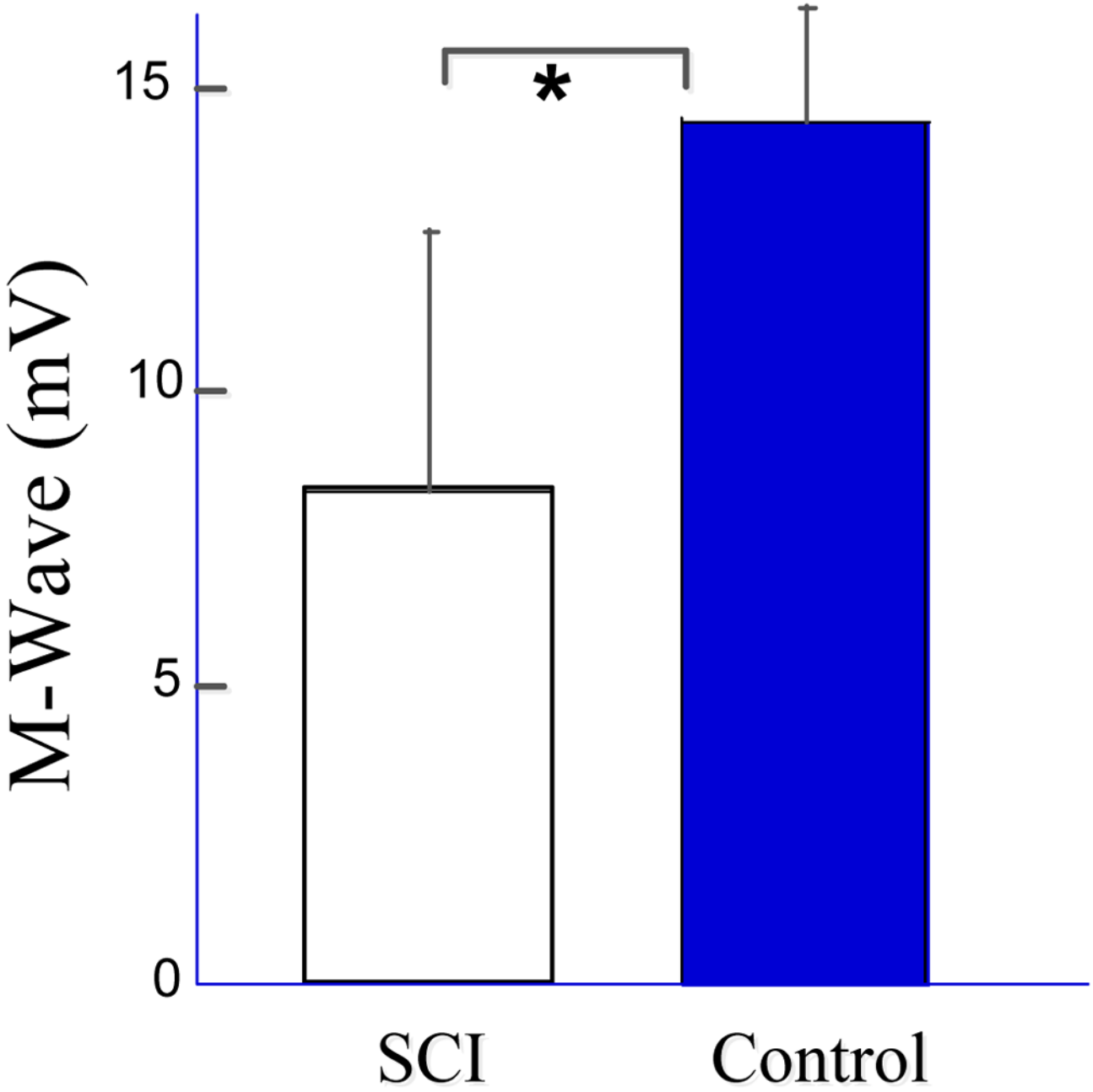


Fig. 2.
A comparison of the maximum M wave amplitude in paralyzed and neurologically intact FDI muscles. A significantly difference was observed (indicated by the star).

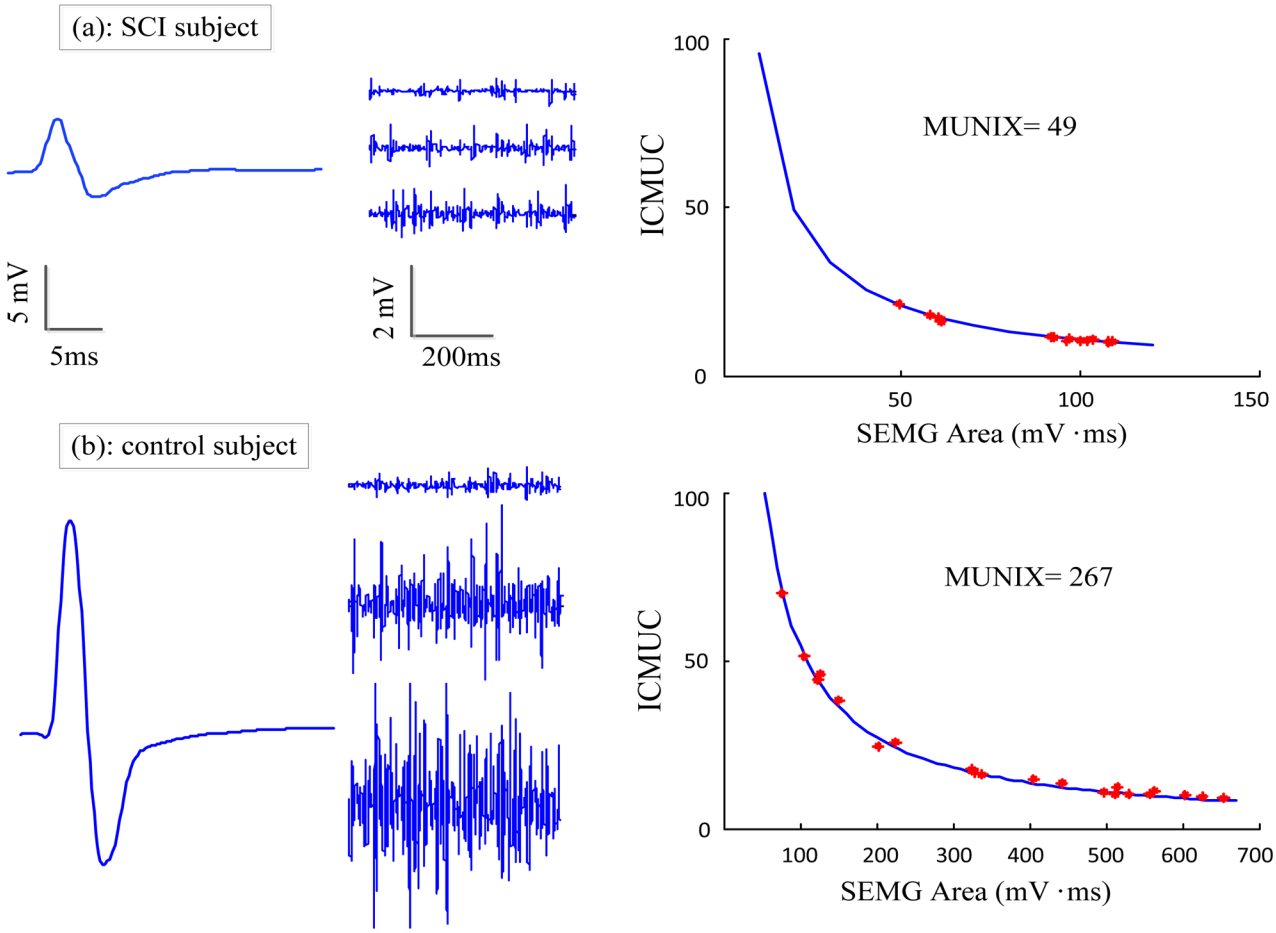


Fig. 3.

A demonstration of the MUNIX computation from paralyzed (a) and neurologically intact (b) FDI muscles. Each panel shows the maximum M wave, voluntary surface EMG at different muscle contraction levels, and the curve fitting between the voluntary surface EMG area and the ideal case motor unit counts (ICMUC) using the exponential regression model. A significant reduction in M wave amplitude, voluntary surface EMG and MUNIX measurement was observed in the paralyzed muscle compared with the neurologically intact muscle.

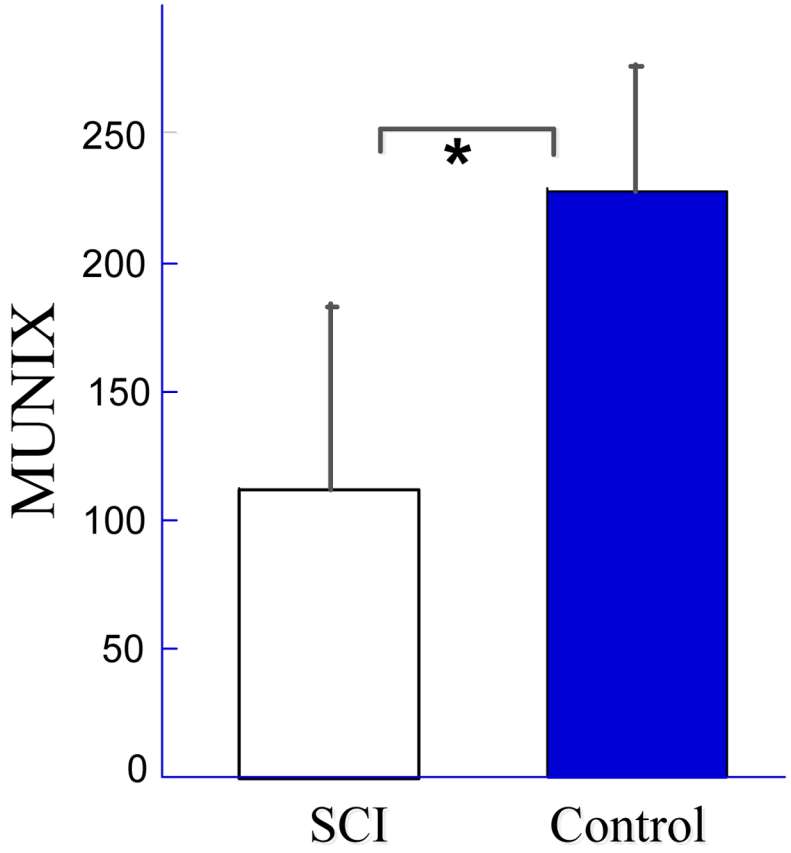


Fig. 4.
A comparison of the MUNIX values in paralyzed and neurologically intact muscles. A significant difference was observed in MUNIX values between the two groups (indicated by the star).

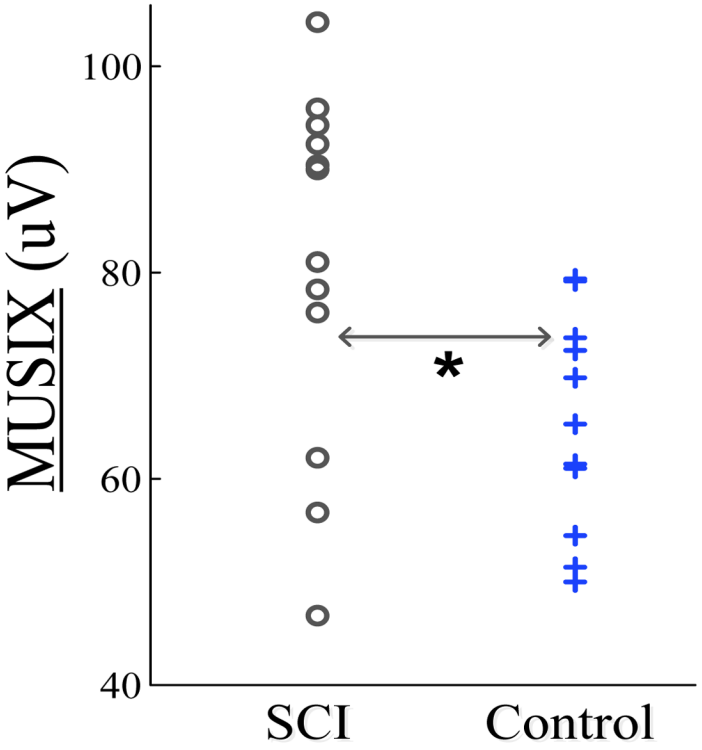


Fig. 5.
A comparison of the MUSIX values in paralyzed and neurologically intact muscles. A significant difference was observed in MUSIX values between the two groups (indicated by the star).

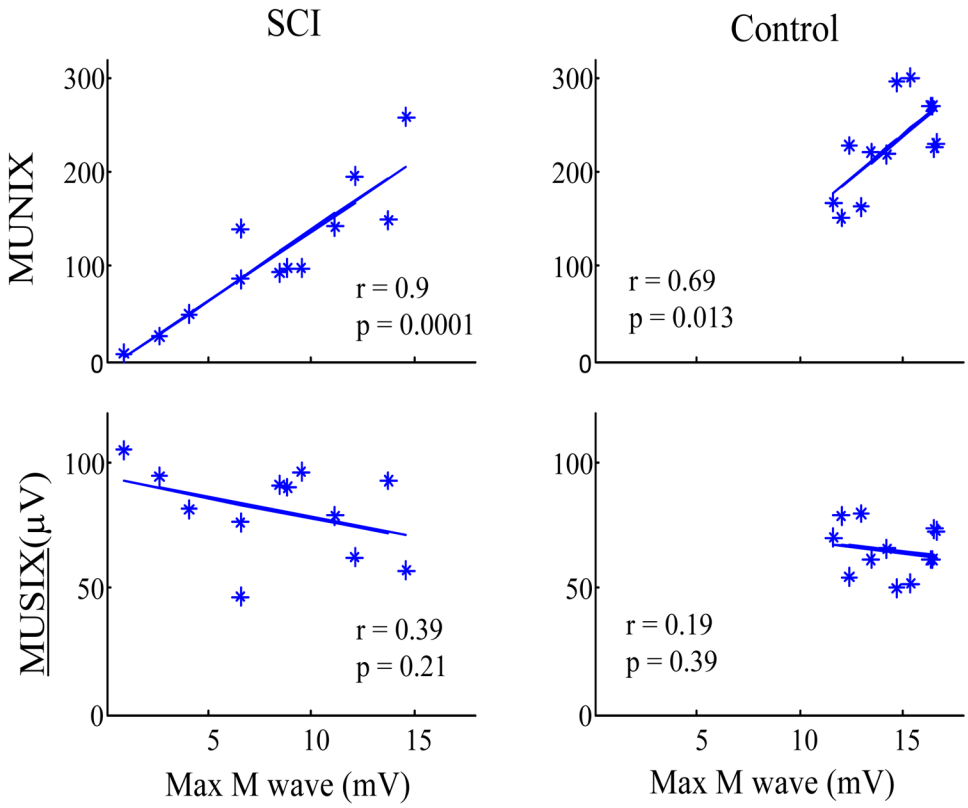


Fig. 6.
The correlation of the maximum M wave amplitude with the MUNIX and MUSIX values, respectively, for both paralyzed and neurologically intact FDI muscles.