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Editorial

Is Motor Unit Number Index (MUNIX) an index of Compound Muscle Action Potential amplitude rather than motor unit number?

See Article, pages 1734–1740

In neurodegenerative disorders affecting the peripheral nervous system, such as amyotrophic lateral sclerosis (ALS), the amplitude of the compound motor action potential (CMAP) is a poor measure of motor unit loss. The progression of degeneration is usually slow enough to allow for extensive collateral (terminal) sprouting of the surviving motor axons, leading to large motor unit potentials, which ultimately attenuate the drop in CMAP amplitude. This discrepancy between CMAP amplitude and motor unit number fueled the development of an increasing number of motor unit number estimation (MUNE) methods that could be used in assessment of disease progression as well as outcome measures in clinical trials (Daube, 2006; Dengler et al., 2005).

Motor unit number index (MUNIX) was proposed by Nandedkar and colleagues as a method to track the motor unit loss in ALS (Nandedkar et al., 2004). Due to its ease of recording (Nandedkar et al., 2010) and good reproducibility (Nandedkar et al., 2011), MUNIX has been rapidly incorporated into the software of commercial EMG machines and has become increasingly popular (de Carvalho et al., 2018). As such it tends to be forgotten that MUNIX is only a surrogate biomarker of MUNE as it does not estimate the number of motor units *per se*.

The MUNIX number (rounded to the nearest integer) is computed from the surface recorded CMAP and surface EMG interference pattern by means of a mathematical model (Nandedkar et al., 2010). Although MUNIX calculation depends on the CMAP, in some ALS patients MUNIX was found to be decreased even when the CMAP was normal, as expected from true MUNE measures (Nandedkar et al., 2004). There is accumulating evidence for utility of MUNIX, including comparison with MUNE techniques, in ALS, peripheral neuropathies, and other neurological disorders (Fatehi et al., 2018).

In the current issue of *Clinical Neurophysiology*, Bostock and colleagues (Bostock et al., 2019) question the extent to which MUNIX provides additional value beyond simple CMAP amplitude measurements. Based on a theoretical analysis of the MUNIX mathematical model, the authors conclude that when motor unit potentials overlap extensively, such as in normal muscles, information about motor unit size and number is lost. Importantly, MUNIX changes depend almost entirely on CMAP amplitude changes and appear to be insensitive to changes in the surface EMG interference pattern amplitude. These findings suggest that MUNIX is less accurate in healthy controls, which should be accounted for when establishing normal values in clinical trial design.

In ALS, MUNE techniques have been predominantly utilized as biomarkers of disease progression rather than diagnostic measures (Vucic and Rutkove, 2018). Intra- and inter-rater reproducibility would be important for a MUNE biomarker to be utilized in a clinical trial setting. MUNIX technique was shown to be a reliable neurophysiological biomarker of disease progression in ALS (Boekestein et al., 2012; Fathi et al., 2016; Neuwirth et al., 2015). Bostock and colleagues (Bostock et al., 2019) do confirm previous reports that MUNIX is highly reproducible in both ALS patients and healthy controls (Nandedkar et al., 2010, 2011), although this reproducibility is interpreted as a reflection of CMAP amplitude reproducibility.

Although detailed histological studies of human motor axon counting are available (Gesslbauer et al., 2017), there is no accepted gold standard for neurophysiological motor unit number counting. Notwithstanding that the MUNIX technique provides an index, rather than a motor unit count, it should be stressed that the true MUNE techniques exhibit also limitations pertaining to estimation of single motor unit amplitude and thereby reproducibility (Vucic and Rutkove, 2018). Recently, another quick MUNE technique, called MScanFit, was reported to exhibit greater utility in distinguishing ALS form healthy controls when compared to MUNIX and the multiple point stimulation MUNE (Jacobsen et al., 2017; Jacobsen et al., 2018a, 2018b). The MScanFit is dependent on generating a stimulus-response curve (referred to as CMAP scan), which is fitted off-line by a model to produce a MUNE value. The prognostic utility of this novel technique, however, needs to be further assessed in longitudinal multicenter studies and from multiple target muscles. Furthermore, since the clinical MScanFit could also be applied in experimental disease models (Dimintiyanova et al., 2019), it has the potential to emerge as a translational surrogate outcome biomarker of motor unit loss.

Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

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