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Increased neuromuscular transmission instability and motor unit remodelling with diabetic neuropathy as assessed using novel near fibre motor unit potential parameters

Matti D. Allen [a,*], Daniel W. Stashuk [b], Kurt Kimpinski [c], Timothy J. Doherty [a,c,d], Maddison L. Hourigan [e], Charles L. Rice [a,e]

[a] School of Kinesiology, Faculty of Health Sciences, University of Western Ontario, London, Ontario, Canada
[b] Systems Design Engineering, University of Waterloo, Canada
[c] Department of Clinical Neurological Sciences, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada
[d] Department of Physical Medicine and Rehabilitation, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada
[e] Department of Anatomy and Cell Biology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada

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HIGHLIGHTS

- Novel near fibre (NF) motor unit potential (MUP) parameters are used to detect neuromuscular transmission instability and motor unit remodelling in patients with neuropathy.
- In both DPN patients and controls, more complex motor units had greater instability.
- NF MUP analysis can be performed concurrent with motor unit number estimates (MUNEs) to provide a detailed assessment of neuromuscular status in patients with neuropathy.

ABSTRACT

Objective: To assess the degree of neuromuscular transmission variability and motor unit (MU) remodelling in patients with diabetic polyneuropathy (DPN) using decomposition-based quantitative electromyography (DQEMG) and near fibre (NF) motor unit potential (MUP) parameters.
Methods: The tibialis anterior (TA) muscle was tested in 12 patients with DPN (65 ± 15 years) and 12 controls (63 ± 15 years). DQEMG was used to analyze electromyographic (EMG) signals collected during voluntary contractions. MUP and NF MUP parameters were analyzed. NF MUPs were obtained by high-pass filtering MUP template waveforms, which isolates contributions of fibres that are close to the needle detection surface. NF MUP parameters provided assessment of motor unit size (NF area), fibre density (NF fibre count) and contribution dispersion (NF dispersion) and neuromuscular transmission instability (NF jiggle).
Results: DPN patients had larger (+45% NF area), more complex (+30% NF fibre count), and less stable (+30% NF jiggle) NF MUPs ($p < 0.05$). No significant relationships were found between NF MUP stability and denervation, or strength; however NF MUP complexity was positively related to TA denervation in the DPN group ($r = 0.63$; $p < 0.05$). NF MUP complexity and instability were positively related in DPN patients ($r = 0.46$; $p < 0.05$).
Conclusions: DPN is associated with neuromuscular transmission instability and MU remodelling that can be assessed using DQEMG.
Significance: DQEMG-derived NF MUP parameters may be useful in identifying patients in early stages of neuromuscular dysfunction related to DPN.

1. Introduction

Diabetic polyneuropathy (DPN) is a progressive neuropathic disorder characterized by distal axonal loss (Ramji et al., 2007)

* Corresponding author. Address: School of Kinesiology, Faculty of Health Sciences, The University of Western Ontario, London, Ont. N6G 1H1, Canada. Tel.: +1 519 661 1628; fax: +1 519 661 2008.
E-mail address: mallen9@uwo.ca (M.D. Allen).

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and impaired regeneration (Kennedy et al., 2005). Early signs and symptoms may be predominantly sensory in nature (Boulton et al., 1986), however there is known involvement of the motor system, including loss of motor axons or motor units (Hansen and Ballantyne, 1977; Bril et al., 1996; Allen et al., 2013b; Ramji et al., 2007) which has been associated with muscle weakness (Allen et al., 2013a). Electrophysiologically, the demyelinating component of this neuropathy can be evaluated through nerve conduction studies (NCS), however NCS provide limited information regarding axonal properties and no information with regard to collateral reinnervation (axonal regeneration).

Standard concentric needle electromyography (NEMG) can provide more detailed information regarding the denervation–reinnervation process underlying DPN (Daube and Rubin, 2009). This is accomplished via the detection of spontaneous activity, polyphasic motor unit potentials (MUPs), and also the quantification of MUP amplitude, duration, and number of turns, as well as MU recruitment pattern (see Daube and Rubin, 2009 for review). Furthermore, the integrity of neuromuscular transmission can be examined in greater detail through the assessment of the degree of variability in the shape of consecutively detected MUPs (Stalberg and Sonoo, 1994). Two key properties related to MUP shape variability are termed jitter and jiggle (Stalberg and Sonoo, 1994). Jitter refers to the variability of the time intervals between pairs of individual muscle fibre potentials from a single MUP, and jiggle refers to the variability in overall MUP shape from one MUP discharge to the next. Increases in both jitter and jiggle have been reported under conditions of neuromuscular transmission disturbance and can reflect early axonal denervation (Sanders and Howard, 1986; Bril et al., 1996; Benatar et al., 2006). Additionally, increases in MUP instability (and thus jitter and jiggle) can be caused by variability in muscle fibre action potential velocity, a finding present in various myopathies (Gruener et al., 1979; Sanders and Stalberg, 1996; Blijham et al., 2011). Specific to DPN, a previous study using single fibre electromyography (SFEMG) found increased jitter in the tibialis anterior (TA) of patients with DPN, however jiggle was not reported (Bril et al., 1996). Additionally, increased fibre density in patients with DPN compared to controls was observed, which is indicative of reinnervation presumably to compensate for prior denervation (motor unit remodelling) (Bril et al., 1996). It is not known how jitter and jiggle may relate to functional parameters such as strength or fatigue, however they may share a negative association as the disturbances that lead to increased neuromuscular instability may also be a factor related to a decrease in strength.

Novel parameters of near fibre (NF) MUPs have been developed. A NF MUP is calculated by high-pass filtering a MUP template waveform, and therefore is primarily comprised of contributions from fibres that are close to the needle detection surface (Stashuk, 1999b). NF MUP parameters include: NF count (which, as described in Stashuk (1999b), is a measure of fibre density), NF jiggle (which can be used to assess the neuromuscular transmission variability of the near fibres), NF dispersion (which measures the temporal dispersion of the near fibre contributions) and maximum NF interval (which is the maximum time interval between consecutive near fibre contributions to a NF MUP). NF MUP parameters theoretically can provide similar types of information as traditional MUP analysis (i.e., metrics of motor unit size (MUP amplitude, duration or area), fibre contribution dispersion (MUP # of phases or turns), and neuromuscular transmission instability (MUP jiggle). However, because NF MUP parameters are dependent on the configuration and activity of the subset of motor unit fibres that are close (within ~350 μm) to the needle detection surface (Stalberg and Gath, 1979; Nandedkar et al., 1988; Dumitru et al., 1997; Stashuk, 1999a,b) they can potentially provide more robust and detailed information concerning neuromuscular transmission variability and motor unit remodelling in comparison to conventional MUP parameters. This is particularly relevant when the MUPs and NF MUPs analyzed were extracted from a moderately complex interference pattern using electromyographic (EMG) signal decomposition methods (see Section 2). At present, no study has reported these NF MUP parameter values for patients with neuropathy, although it is expected that the general characteristics associated with neuropathic MUPs (increased size, complexity, and instability) will also be evident in neuropathic NF MUPs.

All of the aforementioned MUP and NF MUP parameters are obtained using a concentric needle-electrode and decomposition-based quantitative electromyography (DQEMG) software (Stashuk, 1999a). DQEMG also provides data pertaining to motor unit firing rates and firing rate variability, as well as relative motor unit size, via surface motor unit potentials (SMUPs) (Boe et al., 2005; Allen et al., 2013b). In addition, if a maximal compound muscle action potential (CMAP) waveform is appropriately recorded, DQEMG can be used to calculate a motor unit number estimate (MUNE), which can provide further insight regarding the denervation of a muscle (Boe et al., 2005; Allen et al., 2013b).

The present study was designed to assess the effects of DPN on standard MUP and novel NF MUP parameters including NF jiggle, NF dispersion and maximum NF interval, compared to age and sex-matched controls. We compared results from the novel NF MUP parameters to standard MUP parameters including number of turns, area and traditional jiggle. Additionally we related measures of neuromuscular transmission variability and motor unit remodelling to dorsiflexion strength. Finally, we examined how changes in individual motor unit size, due to the DPN-associated denervation–reinnervation process, are related to NF MUP stability during sustained, low-level isometric contractions in patients with DPN. We hypothesized the following: (i) DPN patients would possess motor units with greater mean NF fibre count, NF jiggle, NF dispersion, and maximal NF interval; (ii) NF fibre count, NF jiggle and NF dispersion would be negatively related to dorsiflexion strength; (iii) positive relationships would exist between standard parameters of MUP size and NF fibre count, NF jiggle and NF dispersion.

2. Methods

2.1. Participants

Twelve patients (7 men, 5 women; ages 32–78 years) with DPN were recruited. They met the criteria for diagnosis of type 2 non-insulin dependent diabetes mellitus (DM) with clinical and electrophysiological characteristics of confirmed DPN (Dyck et al., 2011). Additionally, they had a thorough consultation and electrophysiological examination by an experienced neurologist with specialized training in neuromuscular disease to exclude other causes of nerve injury (i.e., other polyneuropathies, compressive mononeuropathies or radiculopathies). Patients with any neurological, metabolic or vascular diseases other than related to DM or DPN were excluded. Twelve healthy, age and sex-matched controls (7 men, 5 women; ages 29–77 years) were recruited from the community. Control participants were screened by physicians (neurologists) to ensure they met inclusion criteria. The study was approved by the local university research ethics board. Informed oral and written consent was obtained from all participants prior to testing.

2.2. Tibialis anterior DQEMG data acquisition

For the present investigation, the TA was selected due to its known involvement in DPN (Allen et al., 2013a,b) and its