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Increased motor unit potential shape variability across consecutive motor unit discharges in the tibialis anterior and vastus medialis muscles of healthy older subjects

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HIGHLIGHTS

- Motor unit potential (MUP) shape variability was quantified across consecutive motor unit (MU) discharges in healthy older men compared to young control subjects.
- Near fiber (NF) jiggle was significantly higher in the older age group, and was significantly correlated with multiple MUP parameters indicative of MU loss.
- NF jiggle may be a valuable quantitative measure used in conjunction with other MUP parameters indicative of MU remodeling and the stability of neuromuscular transmission.

ABSTRACT

Objective: To study the potential utility of using near fiber (NF) jiggle as an assessment of neuromuscular transmission stability in healthy older subjects using decomposition-based quantitative electromyography (DQEMG).
Methods: The tibialis anterior (TA) and vastus medialis (VM) muscles were tested in 9 older men (77 ± 5 years) and 9 young male control subjects (23 ± 0.3 years). Simultaneous surface and needle-detected electromyographic (EMG) signals were collected during voluntary contractions, and then analyzed using DQEMG. Motor unit potential (MUP) and NF MUP parameters were analyzed.
Results: NF jiggle was significantly increased for both the TA and VM in the old age group relative to the younger controls ($P < 0.05$). NF jiggle was significantly higher in the TA compared to VM ($P < 0.05$). For TA, NF jiggle was negatively correlated with MUNE, and positively correlated with S-MUP amplitude, NF count, MUP duration, MUP peak-to-peak voltage, and MUP area ($P < 0.05$). For VM, NF jiggle was positively correlated with NF count and MUP area ($P < 0.05$), and no significant correlations were found between NF jiggle and S-MUP amplitude, MUP duration, or MUP peak-to-peak voltage (MUNE was not calculated for VM, so no correlation could be made).
Conclusions: Healthy aging is associated with neuromuscular transmission instability (increased NF jiggle) and MU remodeling, which can be measured using DQEMG.
Significance: NF jiggle derived from DQEMG can be a useful method of identifying neuromuscular dysfunction at various stages of MU remodeling and aging.

1. Introduction

Sarcopenia describes the decline in skeletal muscle mass, strength, and contractile quality associated with the normal aging

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process (Doherty, 2003). Skeletal muscle atrophy and weakness associated with sarcopenia ultimately leads to profound functional impairment, disability, and when severe, loss of independence (Baumgartner et al., 1998; Roubenoff, 2001; Janssen et al., 2002).

There are a number of factors that contribute to the development or progression of sarcopenia. Numerous studies suggest that the most significant cause of skeletal muscle strength decline, as well as associated disability and functional impairment, is the loss of skeletal muscle mass (Doherty, 2003). Evidence including reduction in type I and II muscle fibers, type II muscle fiber atrophy, muscle fiber grouping, and coexpression of myosin heavy chain isoforms in the same muscle fiber suggest the occurrence of a chronic progressive denervation and reinnervation process (Essen-Gustavsson and Borges, 1986; Oertel, 1986; Andersen et al., 1999; Doherty, 2003; Kovacic et al., 2009). It has been shown that axons damaged due to natural aging undergo a "dying back" process whereby the distal axon regresses towards the cell body (Misgeld, 2011; Manini et al., 2013). This axonal damage seen in senescence is thought to be caused by inflammation and oxidative damage to myelinated peripheral nerves (Kovacic et al., 2009; Opalach et al., 2010; Misgeld, 2011; Manini et al., 2013) that preferentially effects type II muscle fibers (Krutki et al., 2013). Thus it has been postulated that one of the more significant causes of sarcopenia is the loss of alpha motor neuron innervation to muscle with age (Brown, 1972; Essen-Gustavsson and Borges, 1986; Doherty and Brown, 1993, 1997; Roos et al., 1997; Doherty, 2003). Anatomical data are consistent with this hypothesis from studies showing decreased anterior horn cells in the spinal cord and decreased ventral roots with age (Kawamura et al., 1977a,b; Tomlinson and Irving, 1977; Mittal and Logmani, 1987; Doherty and Brown, 1993; Doherty et al., 1993; Doherty, 2003; McNeil et al., 2005a).

The change in alpha motor neuron innervation can be studied *in vivo* electrophysiologically using quantitative electromyographic (EMG) techniques, which allow for the examination of MU number and size. As a result of collateral reinnervation, the process by which surviving motor units (MUs) supply new nerve sprouts to denervated muscle fibers, the recorded surface and needle detected MU potentials (MUPs) of surviving MUs often have higher amplitudes and longer durations. As a result of fewer contributing MUs, the firing rates are often increased for a given level of contractile force (Larsson and Ansved, 1995; Gordon et al., 2004). Krutki et al. (2013) reported in mice an age-related decrease in MUP amplitude for MUs comprised of type II muscle fibers with a corresponding decrease in force production, but a twofold increase in mean MUP amplitude for MUs comprised of type I muscle fibers; suggesting that aging targets type II MUs first, with a relative preservation of type I fibers due to the collateral reinnervation process. Using electrophysiological techniques, age-related declines in MU number estimates (MUNEs) have been found in many upper and lower limb muscles (Brown, 1972; Campbell et al., 1973; Sica et al., 1974; Vandervoort and McComas, 1986; Brown et al., 1988; Doherty and Brown, 1993; Doherty et al., 1993; Galea, 1996; Murga Oporto et al., 2003; McNeil et al., 2005b). McNeil et al. (2005b) found that collateral reinnervation compensated for MU loss and maintained skeletal muscle strength until a critical threshold of MU loss was reached in the very old (McNeil et al., 2005b).

Decomposition-based quantitative electromyography (DQEMG) is capable of extracting clinically useful information regarding the MU pool from simultaneously acquired surface and needle-detected signals (Stashuk, 1999a). DQEMG has been shown to be a valid and reliable tool for obtaining information regarding MU number, size, and complexity within healthy subjects, as well as from patients with neuromuscular disease and peripheral neuropathy (Boe et al., 2004; McNeil et al., 2005a,b; Boe et al., 2006, 2009, 2010; Calder et al., 2008; Berger et al., 2011; Ives and Doherty, 2012, 2014; Allen et al., 2013). Using these techniques, we can evaluate the extent of collateral reinnervation following MU loss and the stability of neuromuscular transmission.

Whereas the exact mechanism is not entirely understood, evidence suggests that age-related post-synaptic damage and muscle fiber atrophy lead to neuromuscular junction remodeling and impaired neuromuscular transmission (Deschenes, 2011; Jang and Van Remmen, 2011; Li et al., 2011; Manini et al., 2013). DQEMG can be used to assess the stability of neuromuscular transmission by measuring the shape variability of MUPs created by a single MU. Two key aspects of MUP shape variability measured electrophysiologically are jitter and jiggle (Stalberg and Sonoo, 1994). Jitter refers to the variability in the time intervals between pairs of individual muscle fiber contributions to MUPs detected across consecutive discharges of a single MU, and is increased in cases of disturbed neuromuscular transmission. In more severe cases, intermittent failures in neuromuscular transmission may occur, which is referred to as impulse blocking (Stalberg and Sonoo, 1994). Jitter has been extensively studied and will not be the focus of this study. Jiggle describes the amount of variability in the overall shape of MUPs detected across consecutive discharges of a single MU (Stalberg and Sonoo, 1994). Increased jiggle is thought to be the result of increased jitter and impulse blocking of the contributing single fiber action potentials (Stalberg and Sonoo, 1994). In contrast to jitter, the quantification of jiggle has been minimally studied. Prior studies were limited by the EMG algorithms available at the time, but two studies still found higher jiggle values in the small number of MUPs studied in patients with ALS (Stalberg and Sonoo, 1994; Campos et al., 2000). Another study conducted by Benatar et al. (2006) found significantly increased jiggle in patients with myasthenia gravis; a disorder of neuromuscular transmission. Most recently, increased jiggle was found in subjects with diabetic neuropathy (Allen et al., 2015).

Despite advancements in quantitative EMG, the validity of using jiggle as a clinically useful MUP parameter has yet to be studied. The objective of our study was to assess whether jiggle could be a valuable MUP parameter indicative of the stability of neuromuscular transmission. The jiggle of MUPs detected in tibialis anterior (TA) and vastus medialis (VM) muscles of healthy older men compared to young controls was quantified. More specifically, near fiber (NF) jiggle (Allen et al., 2015), as opposed to traditional jiggle (Stalberg and Sonoo, 1994) was measured. NF jiggle is primarily related to the consistency of the activity and contributions of muscle fibers close to the selective detection surface of a concentric needle electrode (within ~350 μm) (Stashuk, 1999b). NF jiggle in a proximal (VM) versus a distal (TA) lower limb muscle was also compared. In addition, NF jiggle was compared to other MUP parameters, including indicators of MUP size and complexity, and to MUNEs. Finally, traditional jiggle was measured for comparison to NF jiggle.

The following was hypothesized: (i) NF jiggle would be significantly increased in old men compared to younger controls; (ii) based on findings from previous studies that showed greater age-related neurogenic changes in distal muscles, there would be greater changes in NF jiggle in the TA muscle compared to the VM muscle (Campbell et al., 1973; Galea, 1996); (iii) NF jiggle would be negatively correlated with MUNE; (iv) NF jiggle would be positively correlated with increased values of MUP parameters indicative of collateral reinnervation including surface MUP (S-MUP) amplitude, as well as MUP duration, area, and peak-to-peak voltage; (v) NF jiggle would be positively correlated with NF count, a measurement similar to fiber density that reflects the number of muscle fibers close to the selective detection surface of a concentric needle contributing to a recorded MUP, and therefore related to reinnervation (Stashuk, 1999b); and (vi) traditional jiggle would be lower than NF jiggle and exhibit non-significant age-related changes.