DOES CENTRAL FATIGUE LIMIT MUSCLE FORCE GENERATION CAPACITY DURING FATIGUE?

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There is general agreement on peripheral factors of muscle fatigue that develop within the muscle and impair muscle fiber contractile mechanisms and muscle performance. Central factors of muscle fatigue that arise within the central nervous system have also been suggested to influence muscle force during fatigue. However, no direct empirical evidence of their influence on muscle force capacity has yet been reported. We used a force model to investigate whether peripheral factors are sufficient to explain the loss of muscle force generation capacity during fatiguing submaximal voluntary contractions that is commonly attributed to central factors. Our simulations showed that the force behavior during fatigue could be explained solely by peripheral factors. These data raise concerns about the influence of central factors on muscle force generation capacity during fatigue.

KEY WORDS: motor units; interpolated twitch; voluntary drive

INTRODUCTION: Both peripheral and central factors of muscle fatigue have been suggested to affect muscle performance during fatiguing contractions. Peripheral factors relate to impairments in muscle fiber contractile mechanisms that develop within the muscle, such as metabolite accumulation during prolonged exercise (Bergström, Hermansen, Hultman & Saltin, 1967). Their influence on muscle fatigue can be quantified as a decrease in the amplitude of the muscle force twitch, i.e. the force generated by supramaximal electrical stimulation delivered to a resting muscle or to a nerve supplying the muscle (Burke, 1982). Central factors of muscle fatigue are suggested to arise within the central nervous system and diminish the level of voluntary drive to the motoneuron pool of a muscle (Gandevia, 2001; among others), leading to the development of Central Fatigue. Central Fatigue is typically estimated by measuring the interpolated twitch, i.e. the additional force elicited by supramaximal electrical stimulation delivered to a nerve or muscle during a voluntary contraction (Merton, 1954). A decrease in the amplitude of the interpolated twitch is assumed to represent a decrease in the level of voluntary drive to the muscle and the development of Central Fatigue (Gandevia, 2001). However, while peripheral factors have been empirically verified in the literature, no direct empirical evidence that central factors are causally related to decreases in muscle performance during fatigue has yet been reported. In this work, we used a simulation model to investigate whether peripheral factors of muscle fatigue are sufficient to reproduce the decrease in the level of voluntary drive that is reported during repeated fatiguing contractions and that is commonly attributed to Central Fatigue. The results of this study provide important insights for understanding the control of motor units during muscle fatigue.

METHODS: The model simulates the firing behavior of motor units and the force generated by the first dorsal interosseous (FDI) muscle during voluntary and electrically elicited contractions (Contessa, Puleo & De Luca, 2016). It is based on the model previously developed by Contessa and De Luca (2013). The model is based on physiological observations and empirical data, and was validated by comparing the motor unit firing behavior simulated during fatiguing repeated contractions with those observed empirically (Contessa and De Luca 2013).

Model Description: The model includes two sources of excitation to the motoneuron pool of the muscle: the voluntary input excitation (Figure 1, A1) and elicited input excitation (Figure 1, A2). The voluntary input excitation ($E_{vol}$) represents the combined excitation from the central and peripheral nervous systems to the motoneuron pool of the muscle during voluntary contractions. It ranges from $E_{vol} = 0$, when no motor unit is active and no force is produced,
to $E_{vol} = 1$, the maximal level of voluntary input excitation required to produce maximal voluntary contraction (MVC) force. The motoneuron pool of the FDI muscle is modeled to include 120 motor units (Feinstein, Lindegård, Nyman & Wohlfart, 1955). Motor units are activated when $E_{vol}$ is greater than or equal to their recruitment threshold value, which ranges between 0-67% MVC, as described in De Luca and Hostage (2010). The firing rate of each active motor unit increases as a negative exponential with increasing voluntary excitation, as empirically observed in De Luca and Contessa (2012) and as described in Contessa and De Luca (2013). The motor unit firing rate is translated into a time-varying impulse trains, to which noise is added by modeling the inter-pulse interval as a random variable with a Gaussian distribution and a coefficient of variation of 20% (Fuglevand et al., 1993) (Figure 1, B1). Each motor unit firing represents a motor unit action potential that is generated at the neuron body as a result of voluntary excitation and travels to the muscle to generate a motor unit force twitch.

The elicited input excitation ($E_{stim}$) represents the excitation delivered by electrical stimulation to the nerve supplying the muscle. It ranges from $E_{stim} = 0$, when no motor unit is activated, to $E_{stim} = 1$, the maximal level of elicited input excitation that activates all motor units in the motoneuron pool of the muscle. When a motoneuron is activated by $E_{stim}$, two motor unit action potentials are generated at the stimulation site. They travel toward the muscle and toward the neuron body (Figure 1, B2), respectively, and interact with the action potentials generated by $E_{vol}$, if the motoneuron is concurrently active as a result of $E_{vol}$. The interaction between voluntary and elicited motor unit action potentials is modeled according to the work of Crago and Makowski (2014), and has been previously described in Contessa et al. (2016). The motor unit firing trains that result from the interaction of $E_{vol}$ and $E_{stim}$ (Figure 1C) are convolved with the motor unit force twitches (Figure 1D), calculated based on the work of Raikova and Aladjov (2002) so that later-recruited motor units have progressively higher-amplitude and shorter-duration force twitches than earlier-recruited motor units (Henneman & Olson, 1965). The resultant motor unit forces are summed to produce the output force generated by the muscle (Figure 1E). The simulated output force is calibrated in percentage of the MVC force. A force feedback loop is implemented to simulate muscle force sustained at fixed target force levels (Figure 1F).

![Figure 1. Schematic illustration of the simulation model. See text for details.](image)

**Simulated Protocol:** We simulated a fatigue protocol of voluntary contractions sustained for 30 sec at 20% MVC and repeated to the endurance limit, i.e. until the force could no longer be maintained within 5% of the target level. At the end of each contraction repetition, 3-s MVC contractions with superimposed maximal electrical stimuli were simulated to calculate the amplitude of the interpolated twitch. Electrical stimuli were also simulated in between contractions to calculate the amplitude of the muscle force twitch at rest, referred to as resting twitch ($T_{rest}$). This protocol was chosen to replicate previous empirical studies of sub-maximal fatiguing contractions that reported a decrease in voluntary drive and the development of Central Fatigue (Eichelberger & Bilodeau, 2007; Lloyd, Gandevia, & Hales, 1991).
Peripheral factors of muscle fatigue were included by modeling a time-varying decrease in the amplitude of each active motor unit force twitch, as reported in Adam and De Luca (2005) and Contessa and De Luca (2013). We ensured that no central factors of muscle fatigue were included in the model by constraining the voluntary drive to the muscle (E\text{vol}) to remain maximal during the brief MVCs. This approach allowed us to investigate the influence of peripheral factors of muscle fatigue alone on the estimated level of voluntary drive.

Quantification of Voluntary Drive: We quantified the level of voluntary drive with two parameters that are commonly used in studies of Central Fatigue: the voluntary activation index (VA) and the central activation ratio (CAR) (Eichelberger & Bilodeau, 2007; Lloyd et al., 1991). They are defined as:

- **VA (%)** = \((1 - T_{\text{interp}} / T_{\text{rest}}) \times 100\)
- **CAR (%)** = \(\left[ \frac{F_{\text{vol}}}{(T_{\text{interp}} + F_{\text{vol}})} \right] \times 100\)

where \(F_{\text{vol}}\) is the muscle force produced during a voluntary effort over which \(T_{\text{interp}}\) is delivered.

RESULTS AND DISCUSSION: The simulated muscle force (Figure 2A, blue line) remained at the 20% MVC target force level until the endurance time, which occurred after 21 min. As the motor unit force twitches decreased over time, the level of voluntary excitation required to sustain the 20% MVC target force level increased progressively in subsequent contraction repetitions (Figure 2A, red line). The simulated muscle force during the brief MVC contractions decreased over time (Figure 2A, blue line). The decrease was exclusively due to the decrease in the amplitude of the motor unit force twitches because the voluntary excitation was constrained to remain at maximal levels (100%) during the brief MVC contractions (Figure 2A, red line). Note that the simulated muscle force during the brief MVC was greater than 100% MVC in the first contraction of the series because motor unit force twitch amplitude was modeled to increase in the first 60 s of the protocol to replicate the potentiation phase that is reported to occur at the beginning of a sustained contraction (Contessa and De Luca 2013).

The amplitude of \(T_{\text{interp}}\) (Figure 2B, black line), the voluntary activation index (Figure 2B, blue line) and the central activation ratio (Figure 2B, red line) decreased significantly (P < 0.05, 2-tailed 2-sample t-test) during the simulated protocol from 9.5 ± 1.0 % MVC to 3.1 ± 0.3 % MVC, from 77.0 ± 2.3 % to 63.7 ± 3.0 %, and from 92.5 ± 0.7 to 86.6 ± 1.0 %, respectively. A similar decrease in these parameters was previously observed in empirical studies of fatiguing sub-maximal contractions (Eichelberger and Bilodeau, 2007; Lloyd et al.,1991), and was attributed to the development of Central Fatigue. However, the results of our study indicate that the decrease in voluntary drive can be attributed exclusively to peripheral factors of muscle fatigue, i.e. to the decreasing amplitude of the motor unit force twitch, because central factors of muscle fatigue were not included in the model.

CONCLUSION: Our findings indicate that, during simulated repeated sub-maximal fatiguing contractions, peripheral factors of muscle fatigue alone can reproduce a decrease in voluntary drive that is commonly attributed to Central Fatigue. This observation raises
important concerns about the interpolated twitch as a measure of voluntary drive, and about
the influence of central factors on muscle performance during fatiguing contractions.
Consequently, reports of a decrease in voluntary drive and their implications concerning the
presence of central fatigue should be interpreted carefully.

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