"SIT" down and relax: the interpolated twitch technique is still a valid measure of central fatigue during sustained contraction tasks

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The interpolated twitch technique is a practical method used to determine whether impairments in voluntary drive are a limiting factor in the reduction of muscle contractile force during and following fatiguing efforts. This method has been validated and is extensively employed in neuromuscular research, although its accuracy has been questioned (Taylor, 2009). The principal component of the technique is that if an electrically evoked maximal twitch (SIT) elicits extra force when superimposed upon a maximal voluntary isometric contraction (MVC), this may represent the extent to which voluntary drive is impaired. Thus, a fatigue-induced increase in the SIT amplitude can be attributed to central fatigue (i.e., decreased volitional drive from the motor cortex to the skeletal muscle; (Gandevia *et al.*, 2013)), which may be responsible in part for the fatigue-induced force loss. Fatigue-related increase in SIT force likely results from either activation of additional motor units or from an increase in the instantaneous firing frequency of motor units to the muscle. Surprisingly, Place et al. (2008) observed that a relative fatigue-related increase in the SIT amplitude also occurs during in-vitro experiments. Specifically, in mouse single fibres, superimposed stimuli (350ms in duration) were applied every 2-3s on repeated near-maximal fatiguing contractions that lasted ~1-2min. A relative increase in the SIT was explained by a shift in the force elicited by 70 Hz constant frequency stimulation to the steep part of the force-Ca^{2+} relationship during fatigue. In other words, a small increase in myoplasmic free [Ca^{2+}] ([Ca^{2+}]$_i$) with a superimposed stimulus results in a relatively larger increase in force than compared to the plateau portion of the force-Ca^{2+} relationship.

Recently, Gandevia et al. (2013), the manuscript under focus for this Journal Club discussion, evoked SITs during an involuntary sustained contraction at 30 Hz stimulation frequency lasting 1min in the human adductor pollicis muscle. This stimulation frequency represented stable maximal in vivo motor unit firing rates in this particular muscle. Interestingly and in opposition to the single fibre model, the human adductor pollicis SIT amplitude progressively decreased until task failure. It could be suggested that the decrease in the SIT amplitude throughout the fatigue task in the human adductor pollicis was caused by decreased membrane excitability, as indicated by impairments in the corresponding M-wave properties for the SIT, in particular the large decrease in M-wave amplitude. Because motor unit discharge rates typically decrease during a high-intensity fatigue task, it is possible that maintaining a high stimulation frequency (i.e., 30 Hz) throughout a sustained isometric effort exceeds the physiological capacity to propagate action potentials along the sarcolemma. Importantly, the main finding that SIT force does not increase with time during an involuntary tetanic contraction of a human muscle (Gandevia *et al.*, 2013) was opposite to the finding from fatigued single mouse muscle fibres (Place *et al.*, 2008) in which the SIT amplitude increased progressively until task failure.

Gandevia et al. (2013) argued that the force-Ca^{2+} relationship is unimportant to the assessment of central fatigue during sustained contractions performed in humans because impaired action potential propagation seems to occur upstream of the site of sarcoplasmic reticulum Ca^{2+} release. Thus, even large changes in the force-Ca^{2+} relationship would be masked by sarcolemmal or t-tubular membrane depolarization failure. The implication here is that when assessing central fatigue using the interpolated twitch technique during sustained voluntary contractions, fatigue-induced increases in SIT amplitude can largely be explained by central fatigue mechanisms when action propagation failure is evident.

In contrast to a sustained contraction task, Place and colleagues (2008) used intermittent isometric contractions to induce fatigue of single muscle fibres. Tasks involving intermittent contractions do not necessarily exhibit fatigue-induced reductions in M-wave amplitude (Duchateau & Hainaut, 1985), because intermittent contractions may provide sufficient recovery of membrane excitability between subsequent contractions. Accordingly, increased SIT amplitudes were observed during fatigue induced by intermittent contractions in the study by Place et al., (2008). Furthermore, membrane excitability problems may not be the sole explanation for the decreased SIT during sustained contractions. In mammalian single fibres, it was shown during 12s of sustained 100 Hz stimulation that force rapidly decreased to 10% of initial force (Duty & Allen, 1994). The fast progression of force loss was due to decreased Ca^{2+} release but also by large decreases in myofibrillar Ca^{2+} sensitivity as the force-$[Ca^{2+}]_i$ relationship during fatigue was shifted to the right of the unfatigued force-$[Ca^{2+}]_i$ curve. This observation could be explained by a rapid accumulation of metabolites such as inorganic phosphate that greatly reduces myofibrillar Ca^{2+} sensitivity during a sustained contraction without rest intervals. Nonetheless, these data support the observation by Gandevia et al. (2013) that intramuscular mechanisms are more likely to decrease rather than increase SIT during a sustained fatiguing contraction.

Gandevia et al. (2013) have presented strong evidence that the development of SIT force during a sustained fatiguing contraction is not of peripheral origin but is primarily a result of central fatigue. That is, the increase in SIT force reflects the failure to recruit some motor units or to discharge them fast enough. In instances in which sarcolemmal action potential propagation failure has not occurred, it cannot yet be ruled out that intramuscular factors do not affect the SIT amplitude given that the interpolated twitch technique depends intrinsically on the properties of skeletal muscle to generate force. Therefore, it should be kept in perspective that both peripheral and central factors can contribute to the SIT force depending on the fatigue task performed. Ultimately, we believe that the interpolated twitch technique remains a useful and practical tool to provide a qualitative assessment of central fatigue.

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