Interpolated twitches decline progressively during a tetanic contraction of human *adductor pollicis*

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The size of an interpolated muscle twitch produced by nerve stimulation during a voluntary muscle contraction can indicate the extra force that the central nervous systems fails to harness from a muscle with volition (Merton, 1954). During human exercise this interpolated twitch commonly increases in size and this reduced voluntary activation of the muscle is termed 'central' fatigue (*e.g.* Gandevia *et al.* 1996; Gandevia, 2001). Recent work on isolated mouse muscle fibres suggests an alternative 'peripheral' explanation for the increase in the size of the interpolated twitch which is based on altered sensitivity to intracellular calcium within the muscle fibre (Place *et al.* 2008). To test whether this problem would develop in whole human muscle, we studied 6 healthy subjects with supramaximal tetanic stimulation of the ulnar nerve while measuring the force of thumb adduction. We delivered maximal tetanic stimulation to the ulnar nerve (≥ 60 s at physiological motoneuronal frequencies, 30 Hz and 15 Hz). During the tetanus (at 30 Hz) in which the force declined by 42%, the absolute size of interpolated stimuli delivered regularly during the tetanus diminished progressively to less than 1% of the original size. With stimulation at 30 Hz there was also a marked reduction in size and area of the interpolated compound muscle action potential (M wave). With the 15-Hz tetanus, there was also a progressive decline in the interpolated twitch force (to ~10%) but this decline occurred before the area of the interpolated M wave diminished. The reduction in size of superimposed twitches occurred whether or not the M wave indicated marked impairment at sarcolemmal/t-tubular levels. In conclusion, we suggest that the central fatigue measured with twitch interpolation in human fatiguing exercise is likely to reflect low volitional drive to high-threshold motor units, which are discharging at low frequencies or have stopped firing altogether.

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