Elucidating the neurophysiology of local vibration: changes in neuromodulatory drive rather than presynaptic inhibition?

Jakob Škarabot[1], Ricardo N.O. Mesquita[2] & Paul Ansdell[3]

1 School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, United Kingdom

2 Centre for Exercise and Sport Science Research (CESSR), School of Medical and Health Sciences, Edith Cowan University, Joondalup, Australia

3 Department of Sport, Exercise and Rehabilitation, Faculty of Health & Life Sciences, Northumbria University, Newcastle upon Tyne, United Kingdom

Local vibration (LV) involves targeted application of vibration to the muscle-tendon unit, imposing repetitive length changes that act as a powerful stimulus for activation of muscle spindles, inducing excitatory drive from Ia-afferents onto the alpha-motoneurons. Typically utilised in rehabilitation setting or in an adjunct role to training, chronic LV has the potential to augment neuromuscular output in healthy individuals, or attenuate neuromuscular deconditioning in clinical populations. Despite its promising application, the physiological responses to LV are unclear, with speculation and assumptions as to the neurophysiological mechanisms commonplace in the literature.

Although vibration-induced Ia input is excitatory to the alpha motoneuron pool, it may also paradoxically inhibit motoneuronal output when LV is applied for a prolonged period of time (i.e. 20-60 minutes). Prolonged exposure to LV decreases force production and acutely reduces excitability of the spinal reflex loop, as evidenced by depression of the Hoffman (H) reflex. Many mechanisms have been proposed for such a depression, including changes in motoneuron excitability, Ia afferent firing threshold, homosynaptic post-activation depression (HD), and presynaptic inhibition through primary afferent depolarisation (PAD) interneurons, with the latter having been assumed as the most likely mediator. However, methodological differences

between studies and a lack of concomitant investigation of the proposed mechanisms prevented more definitive conclusions.

A recent study published in *The Journal of Physiology* by Souron *et al.* (2019) addresses the aforementioned issues, and provides novel mechanistic insight into the effect of prolonged LV on the central nervous system. Through a series of three experiments, Souron and colleagues examined the effect of prolonged Achilles tendon LV (30 mins, 100 Hz) on presynaptic Ia afferent inhibition, neurotransmitter release at the level of the Ia-alpha motoneuron synapse, and intrinsic motoneuron excitability, respectively. In the first experiment, changes in presynaptic inhibition following LV were investigated by two paradigms aimed at activating PAD interneurons by conditioning soleus H-reflexes with fibular nerve stimulation, and heteronymous facilitation via assessment of the monosynaptic facilitatory effect of the femoral nerve on the soleus H-reflex amplitude. When preceded by fibular nerve stimulation, the test reflex amplitude increased following LV, suggesting reduced responsiveness of PAD interneurons. The monosynaptic facilitatory effect of femoral nerve stimulation tended to increase the amplitude of the test reflex, again suggesting reduced responsiveness of PAD interneurons converging onto femoral Ia afferents. Taken together, these data provided evidence against increased presynaptic Ia inhibition, contradictory to previous hypotheses about the mechanisms of H-reflex depression following LV. In the second experiment, HD was investigated by pairing two submaximal stimuli evoking two H-reflexes in the soleus. Conditioned H-reflex following LV was unchanged, suggesting that the prolonged vibration stimulus does not affect HD. In the last experiment, responses to electrical stimulation of the corticospinal tract at thoracic spinal level were assessed before and after LV to discern changes in motoneuron excitability. Thoracic stimulation, unlike the H-reflex, is devoid of the classical presynaptic influence, and considered a more direct and appropriate method to assess the responsiveness of motoneurons to synaptic input. The bout of prolonged LV resulted in

decreased amplitude of thoracic evoked potentials (TMEPs) and thus decreased motoneuron excitability, suggesting intrinsic changes to the motoneuron pool. Overall, Souron and colleagues provide new insight into the effect of a prolonged LV stimulus on spinal circuitry that warrant further discussion into the mechanism underlying the modulation of the intrinsic motoneuron excitability and its clinical relevance.

Are changes in neuromodulatory drive responsible?

The authors proposed that decreased motoneuron excitability could be related to a reduced strength of persistent inward currents (PIC) in the spinal motoneurons. Motoneuron firing is not solely determined by differences in the organisation of ionotropic synaptic input. Rather, the activation of voltage-dependent channels on the motoneuron dendrites allows the generation of strong PICs, amplifying and prolonging the effects of synaptic input. The amplifying nature of PICs is enhanced by descending monoaminergic drive – specifically by the neuromodulators serotonin and noradrenaline released by axons from the medulla and pontine nuclei (Heckmann *et al.*, 2005). Given that afferent stimuli have been shown to affect the sensitivity of serotonergic neurons in raphe nucleus, the authors suggested that LV could lead to changes in serotonin release, impairing PIC activity, and thus decreasing spinal motoneuron excitability. This is indeed a possible explanation for the attenuation of TMEP amplitude during a light contraction. Decreased strength of PIC activity would be translated in a decreased flow of positively charged ions into the motoneurons. Consequently, the motoneurons involved in directly activating the muscle during the contraction will likely have a more accentuated afterhyperpolarization, with increased probability of insufficient change in the membrane potential to reach threshold and generate an action potential upon the electrical stimulus. Similarly, the number of neighbouring, *subliminal fringe* motoneurons near threshold should decrease (Figure 1). This would possibly

lead to decreased total number of motoneurons being activated upon stimulation, decreasing the TMEP size.

It should be noted that the aforementioned proposed explanation is somewhat speculative and that changes in the strength of PIC activity have not been previously associated with changes in the size of evoked responses of motoneurons. Whilst authors cautioned the readers from inferring changes in PIC activity from TMEP amplitude, techniques exist that could quantify any potential LV-induced changes in PIC activity. The paired motor unit technique involves recording single motor unit action potentials through decomposition of electromyographic signals. During the ascending phase of a ramp contraction, the firing frequency of a relatively low-threshold (control) motor unit increases while a second, higher-threshold (test) unit is recruited. As the contraction effort is gradually reduced in the descending phase of a ramp contraction, the test unit continues to fire at levels of synaptic input that are lower than the level required to recruit the test unit. The difference between the instantaneous firing frequency of the control unit at test unit recruitment and the instantaneous firing frequency of the control unit at test unit derecruitment is an estimate of the strength of PIC activity (Gorassini *et al.*, 2002). In future research, this technique could be used to quantify the strength of PIC activity in response to interventions such as LV, enabling better insight into changes in intrinsic motoneuron excitability.

It worth noting that TMEPs, unlike H-reflexes, had to be evoked during a light contraction due to difficulty in evoking responses in a resting muscle, a common challenge with this type of stimulation. As acknowledged by the authors, eliciting responses during contractions represents a potential for contribution of post-synaptic mechanisms that could impede interpretation of the results (e.g. convergence of Ia afferents onto Ib, Renshaw cell activity). Concomitantly, recording H-reflex responses at the same background activity might be a way of reducing bias in interpretation of reduced motoneuron excitability. Alternatively, evoking responses lower on

the spinal column (e.g. at the lumbar level) also activates corticospinal axons at a subcortical level, similar to thoracic stimulation. A potential benefit of this form of stimulation is its ability to elicit responses of 10-15% of maximal compound action potential in resting lower limb muscles with ease (Škarabot *et al.*, 2019). Whilst responses to lumbar stimulation seem to increase with increased background muscle activity with no change in onset latency (Škarabot *et al.*, 2019), implying monosynaptic activation of motoneurons, the extent of direct activation of motoneurons with this type of stimulation remains to be directly investigated. Nevertheless, lumbar evoked potentials might provide an alternative paradigm to study spinal excitability in resting musculature following LV. It should be noted that given the proposed mechanism above, a change in TMEP size is less likely to be expected if measured at rest, as PICs will not be active in the absence of any excitatory input. However, this notion remains to be tested directly. The modulation of TMEP size would also likely depend on the characteristics of the recruited motoneuron pool, as low-threshold motoneurons are characterised by long-lasting PICs, while the strength of PIC activity in higher-threshold motoneurons is likely to be lower (Heckmann *et al.*, 2005).

A potential strategy to alleviate spasticity?

Changes in intrinsic motoneuron excitability following prolonged LV could have significant applications for pathological conditions accompanied by motoneuron hyper-excitability. For example, modulation of the strength of PIC activity due to abnormal neuromodulatory drive has been linked to muscle spasms and long-lasting hyperactive reflexes in individuals with chronic spinal cord injury and chronic hemiparetic stroke (Heckmann *et al.*, 2005). It remains to be seen whether a bout of prolonged LV could alleviate some of the PIC-induced symptoms in these pathological states. It is further of interest whether longer-term therapeutic approaches

of repeated bouts of prolonged LV can cause chronic changes in intrinsic motoneuron properties in the aforementioned patient populations. In a healthy sample, Souron *et al.* (2017) demonstrated increased voluntary activation following eight weeks of LV; an effect that could potentially compliment resistance exercise to augment maximum strength, or counteract immobilisation-related disuse and associated neuromuscular deterioration. The application of LV shows promise in a wide range of scenarios; highlighting the importance of fully comprehending the neurophysiological mechanisms underpinning the acute and chronic responses, an exciting area of research that Souron and colleagues have made great progress with.

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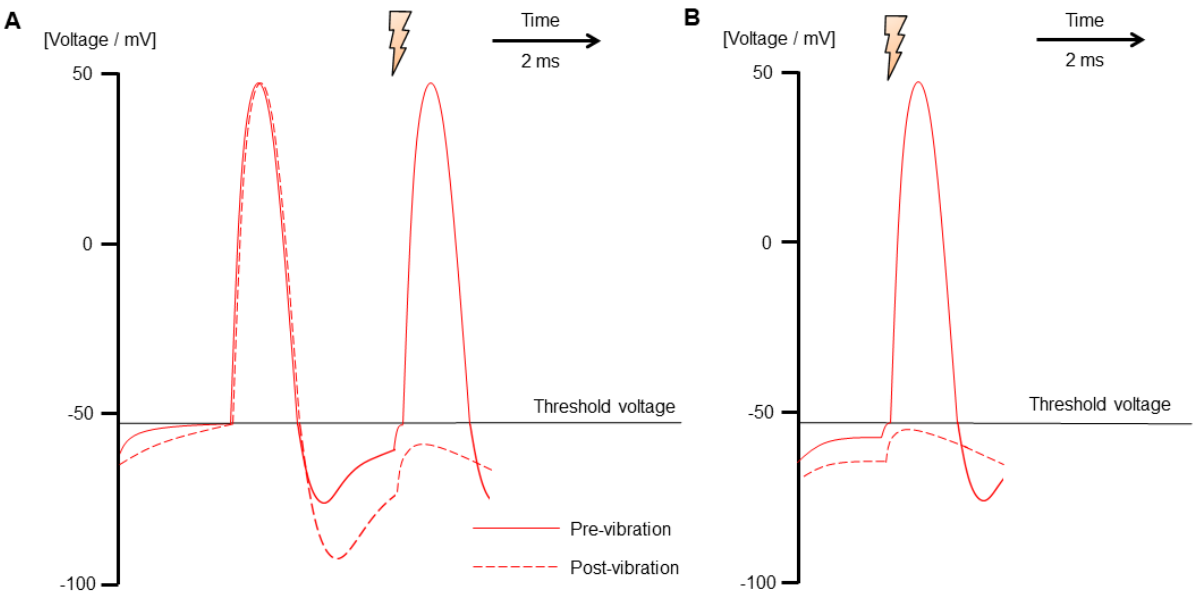
Figure 1. Graphical representation of a hypothetical underlying mechanism for reduction in motoneuron excitability following prolonged local vibration. Souron and colleagues suggested that the reduced size of thoracic motor evoked potentials during a light contraction following prolonged local vibration could stem from decreased strength of persistent inward current (PIC) activity of the spinal motoneurones. Given that decreased strength of PIC activity would be translated in a decreased flow of positively charged ions into the motoneurons, the number of depolarised motoneurons upon stimulation could be modulated. The motoneurons involved in directly activating the muscle during the contraction (**A**) will likely have a more accentuated afterhyperpolarization, and the number of neighbouring, *subliminal fringe* motoneurons near threshold (**B**) should decrease. Consequently, there might be increased probability of insufficient change in the membrane potential to reach threshold and generate an action potential upon the electrical stimulus, in both populations of motoneurons.



Competing interests

The authors declare no competing interests, financial or otherwise.

Author contributions

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