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PERSPECTIVE

Neuromuscular function in experimental disuse – a prime suspect?

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Linked articles: This Perspective article highlights an article by Sarto et al and Inns et al. To read these papers, visit https://doi.org/10.1113/JP283381 and https://doi.org/10.1113/283425.

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Most people will, throughout their lifetime, experience periods of muscle unloading, disuse and inactivity, relating to disease, injury or hospitalization. Today, physical inactivity of either short or long duration is acknowledged as a factor contributing to the development of several diseases (Booth et al., 2017). However, bed-rest was an integral part of the medical treatment of many diseases as late as the 1970s (Burch & McDonald, 1971), and even today patients spend the majority of their time either sitting or lying down (Baldwin et al., 2017). One of the striking features of experimental disuse (bed-rest, dry immersion, limb immobilization or limb suspension) is the well-described incongruent decline in muscle function relative to muscle mass (Marusic et al., 2021), as illustrated in Fig. 1, which indicates a malfunction somewhere along the path from a signal being generated in the motor cortex to the resulting muscle contraction. This observation serves as a focal point, from which one can ponder what the involved mechanisms might be. In two new articles published in *The Journal of Physiology*, an alteration within the neuromuscular system in response to disuse is the prime suspect.

In these studies, young men were investigated before and after disuse induced by limb immobilization (Inns et al., 2022) or limb suspension (Sarto et al., 2022), with assessment of muscle function (strength and power) and muscle mass. Strength relative to mass (specific force) declined by >15% in both studies, confirming the disproportionally larger debilitating effect of disuse on function relative to mass. Intramuscular EMG during submaximal isometric contractions was used in both studies to assess neuromuscular alterations after disuse.

Inns et al. (2022) recruited 10 men (mean ± SD, 23.7 ± 3.4 years of age), who underwent 15 days of unilateral limb immobilization using a leg brace on one leg (experimental leg), and an air-boot on the other leg (control leg). Using this design, the authors made within-subject comparisons between the immobilized and the control leg. Motor unit potential (MUP) area and amplitude, which are measures that represent the sum of all muscle fibres belonging to a single motor unit, were reduced by immobilization, suggesting fibre atrophy and/or partial denervation. Furthermore, they also found that immobilization led to a reduction in motor unit (MU) firing rate and an increase in MUP complexity, while jiggle, a measure of neuromuscular junction instability, remained unaltered. No changes were seen in the control leg. Overall, these findings are strongly supportive of neuromuscular malfunction as a factor explaining why the loss of muscle function is more pronounced than the loss of muscle mass.

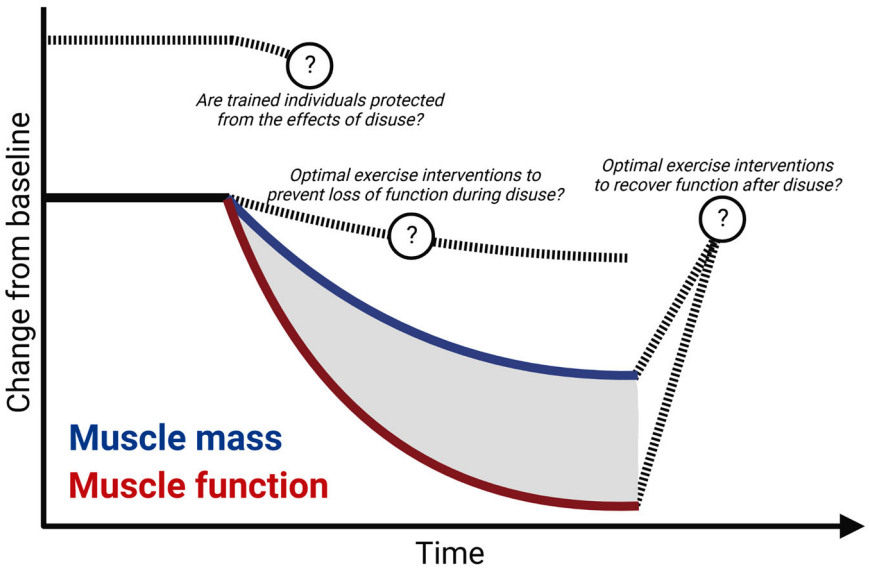

Figure 1. Conceptual model of the incongruent decline in muscle function (red line) relative to muscle mass (blue line) in response to disuse (grey area)
There are still open questions concerning whether trained individuals are protected from the detrimental effects of disuse, in addition to what type and amount of exercise is needed during and/or after disuse to maintain muscle function.

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In the study by Sarto et al. (2022), 11 men (mean ± SD, 22.1 ± 2.9 years of age) underwent 10 days of unilateral lower limb suspension, which was achieved using straps to keep the unloaded leg in a static flexed position and a shoe with an elevated sole on the control leg. After disuse, all participants underwent 21 days of unilateral resistance exercise performed three times per week. In agreement with Inns et al. (2022), MU firing rate (larger mean interdischarge interval) was reduced, MUP complexity increased and neuromuscular junction stability unaltered after unloading. Unloading also led to a reduction in activation capacity, but it did not lead to changes in MUP area. Next, the authors analysed blood samples and vastus lateralis muscle biopsies for markers of impaired synaptic transmission. C-Terminal agrin fragment, a biomarker of neuromuscular junction instability, and neurofilament light chain, a biomarker of axonal damage, were both increased in the circulation after unloading. The number of $NCAM^+$ muscle fibres, a marker of denervation, was also increased after disuse.

To corroborate these findings further, a targeted RNA sequencing analysis of the muscle biopsies was undertaken. This analysis showed that disuse led to an altered expression of genes known to be associated with neuromuscular innervation and muscle ion channels. Importantly, the disuse-induced changes were ameliorated by 21 days of resistance exercise, highlighting the impressive plasticity of the neuromuscular system in the young and healthy.

These studies collectively provide evidence for rapid deterioration of the neuromuscular system being a key mechanism that underlies the loss of muscle function during disuse. One caveat of the currently available intramuscular EMG methodologies is that they allow neuromuscular function to be assessed only at relatively low contraction intensities. Nevertheless, these intensities are relevant to most activities of daily life, which highlights the importance of reducing the amount of sedentariness during hospitalization.

Looking ahead, as pointed out in Fig. 1, further studies should decipher whether an individual's level of physical activity before disuse might confer protective effects on neuromuscular function, in addition to how much training is needed during and after disuse to maintain function (Soendenbroe et al., 2021). Finally, given that other mechanisms, such as changes in tendon properties, single-fibre mechanical properties, extracellular matrix and others, are likely to be involved simultaneously in the disproportional loss of muscle function, there is a need for further studies on the topic. In truth, one villain was caught, but others are still out there.

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Additional information

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History