Inspiratory Muscle Training in Patients with Post-COVID19 Condition: Considerations on Efficacy, Safety, and Patient Perception

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Most patients, 2 years after surviving hospitalization with COVID-19 have improved physical and mental health and are able to return to their original work; however, the majority of them still suffer from a lower health status (1). Fatigue and muscle weakness are most frequent, while dyspnea with a modified Medical Research Council scale >1 is identified in 14% of patients (1). Last year, Regmi et al. identified, in patients with post-COVID-19 condition, diaphragm dysfunction and a correlation with exertional dyspnea (2). In his editorial accompanying this paper, Polkey suggested conducting a trial to study the effect of inspiratory muscle training (IMT) on dyspnea in these patients (3). His call was answered by Spiesshoefer and colleagues here (4). This well conducted study in 18 post COVID-19 patients with exertional dyspnea and respiratory muscle weakness, showed that 6 weeks of IMT at moderate intensity improves the dyspnea domain of the Chronic Respiratory Disease Questionnaire, inspiratory muscle strength (sniff nasal pressure), and endurance (time to task failure), in comparison with a sham training group.

The authors did an excellent job identifying the specific effects of IMT on the diaphragm. Carefully conducted volitional and non-volitional assessment of diaphragm function (twitch and sniff transdiaphragmatic pressures, diaphragm thickness and thickening fraction) were performed. The data showed a trend toward improvement in diaphragm function in the treatment arm. However, to the authors disappointment, no statistically significant differences in changes of diaphragm function between the groups were observed. Obviously, inspiratory maneuvers against an external load and high inspiratory flow up to total lung capacity provided additional stress on all the inspiratory muscles involved in overcoming the external resistance. Indeed, the present data suggest that improvement of extra-diaphragmatic muscle function was probably also contributing to the improvements in overall inspiratory muscle function, as was observed after IMT in patients with COPD (5), diaphragm

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paresis (6), or patients during difficult weaning (7). This is consistent with the increase in thickness of the parasternal intercostal muscle in the intervention group of the present study, although only present at total lung capacity, which suggests higher muscle recruitment during deep inspiration, rather than an actual change in muscle structure related to training.

Importantly, inspiratory muscle training was also accompanied by improvements in exertional dyspnea. The relationship between respiratory muscle function/activation and dyspnea is well established (8). The authors observed an increased maximal activation of the diaphragm after IMT and related this to the observed decrease in dyspnea. Indeed, increased cortical activation after muscle training is a known neural adaptation. However, the decrease in dyspnea seems more related to *less* activation of the diaphragm during activities of daily life, as previously shown after IMT in COPD patients (9). This is probably also the substrate for the increased muscle endurance following IMT observed in the treatment group. Stronger muscles perform any given task at a lower percentage of their maximum capacity compared to weaker muscles and are therefore able to sustain a given activity for longer periods (10).

Can we safely provide exercise training in patients suffering from post-COVID-19 condition? Over the last years, numerous studies have reported disabling signs and symptoms following physical and/or cognitive exertion in post-COVID19 patients, a condition known as post-exertional malaise (11). Appelman et al. indeed showed that high-intensity (maximal) cycling exercise in post-COVID-19 condition patients suffering from post-exertional malaise was accompanied by limb muscle abnormalities, which included alteration in mitochondrial activity, signs of muscle damage, and inflammatory response (12). These findings might support the NICE advice to discourage graded exercise as part of the treatment of these

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patients (13). However, it is now well accepted that the inflammatory response, in the context of exercise induced muscle damage, is crucial for functional recovery and muscle regeneration (14). Moreover, there is evidence that a first bout of exercise training, generating initial muscle damage, will lead to muscle adaptations characterized by less susceptibility to further exercise induced muscle damage, attenuated delayed-onset muscle soreness, and faster recovery (known as “the Repeated-Bout effect”); a process that seems to be at least partially mediated by the inflammatory response itself (15). Therefore, morphological abnormalities observed immediately after exercise are not necessarily in contrast with long-lasting muscle adaptations and long-term increase in muscle strength; they may represent instead different temporal muscle responses to the same (acute vs protracted) stimulus.

Meaningful changes in muscle strength and gradual restoration of muscle function in weakened muscles require a certain amount and intensity of load, below which no change in strength or reversal of dysfunction is observed (i.e. a load of 10% of maximal capacity, which was used for the control training group in the Spiesshoefer paper (4)). We can speculate that a similar phenomenon occurs during mechanical ventilation. Here, an excessive ventilatory support, providing too little load for the muscle, can lead to or perpetuate muscle atrophy and weakness (16). On the other hand, still experimental, findings suggest that insufficient ventilator assistance, resulting in too much load for the muscle, could also be injurious and contribute to muscle dysfunction (17). Probably, in training respiratory muscles, as well as in supporting them with mechanical ventilation, the secret lies in balance (the Aristotelian mesótes – μεσότης) – the level of load that will generate just the “right” amount of inspiratory effort for each patient, neither too little nor too much.

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In this regard, a maximal incremental ramp exercise test, as applied by Appelman et al. (12), is probably extremely different – both in terms of injurious and training effects and in terms of – from a strength training at moderate intensity (IMT resistance set at 40-50% of individual sniff nasal inspiratory pressure as applied in the present study (4). In fact, in the present study no adverse events were reported, which likely contributed to the excellent compliance with the scheduled training sessions (85-90%). The study has shown that well-controlled, individually tailored respiratory muscle training is effective in reducing dyspnea in this patient population. These findings further support the idea that advising against rehabilitation due to reported exercise intolerance and dyspnea in post-COVID-19 condition is likely not the best option. Symptoms will not resolve spontaneously, and respiratory muscle strength will not consistently improve on its own (as evidenced by observations in the patients of this study over the 2 years preceding the enrollment and in the sham training group). On the contrary, physical inactivity will only perpetuate (if not worsen) physical deconditioning. Indeed, patients with post-COVID-19 condition have been found to exhibit reduced stroke volume and left ventricular diameter, along with an increased resting heart rate – signs that are plausibly indicative of reduced levels of physical fitness (18). Cautious, individualized, and symptom-titrated exercise (considering specifically post-exertional malaise) is, at this point, probably the most advisable approach to prevent further muscle deconditioning and promote functional capacity in patients with post-COVID-19 condition (19).

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