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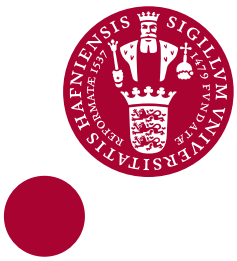

Development of Limb Muscle Dysfunction in Chronic Obstructive Pulmonary Disease Smoking, Inflammation, or Simply Disuse?

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Development of Limb Muscle Dysfunction in Chronic Obstructive Pulmonary Disease: Smoking, Inflammation, or Simply Disuse?

Limb muscle dysfunction in patients with chronic obstructive pulmonary disease (COPD) represents a significant clinical problem and is characterized by both intra- and extramuscular abnormalities (1, 2). The predominant extramuscular change is muscle wasting, which predicts a poor prognosis (2). The intramuscular pathology mainly affects the quadriceps muscle. Strong evidence indicates that patients with COPD demonstrate a shift in muscle fiber composition from type I (oxidative, slow-twitch fibers) to type II (glycolytic, fast-twitch fibers) when compared with healthy control subjects (3). Likewise, the muscle fiber cross-sectional area is smaller in individuals with COPD (4). Muscle metabolism mirrors the structural changes, and most studies have reported a low oxidative enzyme capacity in the quadriceps muscle of patients with COPD (5). In contrast, although the respiratory muscles adapt to achieve a more oxidative, fatigue-resistant profile in COPD, force generation is subnormal and increased ventilatory work redistributes the blood volume from locomotor to respiratory muscles (1). The functional consequences of COPD-associated limb muscle pathophysiology include impaired muscle strength and endurance, which leads to low exercise performance and aggravation of dyspnea during daily physical activities. These physiological and clinical effects are hallmarks of COPD symptomatology.

In this issue of the *Journal*, Chan and colleagues (pp. 217–230) report their findings from an animal model of cigarette smoke (CS)-induced COPD (6). They examined the impact of CS exposure on skeletal muscle regeneration after muscle injury (MI) in male BALB/c mice by comparing CS-exposed (+MI) with unexposed (+MI) mice. Two control groups of CS-exposed (−MI) and unexposed (−MI) mice were also included. After 8 weeks of CS exposure, the mice showed limb muscle abnormalities similar to those observed in patients with COPD. This included muscle atrophy and markedly reduced oxidative fiber type composition of the hindlimb compared with unexposed mice. At this time point, hindlimb MI was induced by injection of barium chloride, which normally induces a robust activation of muscle satellite cells. Muscle outcomes were evaluated over the next 3 weeks. Loss of muscle mass and oxidative fibers was sustained throughout the experiment in CS-exposed mice (+MI and −MI). During the first week after MI, muscle contractile force was also lower in CS-exposed mice (+MI) than in unexposed mice (+MI), but gradually recovered at 3 weeks follow-up (6). The notion that muscle force might be restored independently of muscle fiber composition or mass is indeed a novel concept and provides new insight into the regenerative potential of the most commonly used countermeasure to muscle dysfunction in COPD, namely, exercise training. Numerous studies have explored the effects of exercise training on muscle dysfunction in patients with COPD (4, 7–9). In an attempt to optimize the muscular response, investigators have explored the effects of resistance training, and although the intramuscular structure may adapt differently to resistance training and endurance training, the positive effects of these regimens on breathlessness and exercise capacity are similar (8). Likewise, resistance training provides no additional effects on muscle strength in individuals with COPD (10). The results from Chan and colleagues indicate that the regenerative potential is higher for muscle strength than for oxidative fiber-type proportions or atrophy in patients with COPD. This could explain why the intramuscular abnormalities are only partially reversible after 8–12 weeks of pulmonary rehabilitation (4, 8). Moreover, CS exposure seemed to reduce the activation of satellite cells in response to MI (6), which brings into question the rationale for using resistance training (which relies on activation of satellite cells to regenerate damaged myofibers) as a countermeasure to muscle dysfunction in COPD.

The etiology of limb muscle dysfunction in patients with COPD has been debated, and one of the prevailing hypotheses is that a local inflammatory process drives the breakdown of the muscle. The driver of this process is low-grade inflammation in the respiratory system, primarily caused by tobacco smoking, that spills over into the blood and consequently into skeletal muscle. However, investigators have not been able to confirm a highly proinflammatory environment in the quadriceps muscle of patients with COPD (9, 11). In CS-exposed mice, Chan and colleagues found a universal proinflammatory response in the pulmonary, circulatory, and muscular systems after 8 weeks of CS exposure that may constitute the mechanistic basis for the observed muscle adaptations (6). Studies in humans suggest that smoking impairs the muscle protein synthesis process and increases the expression of genes associated with impaired muscle maintenance, indicating that smoking *per se* likely increases the risk of sarcopenia and that muscle dysfunction may take place before the development of COPD (12). Another explanation for COPD-induced muscle dysfunction could simply be reduced physical activity. Because physical activity was not recorded by Chan and colleagues, we can only speculate about whether smoking induced physical inactivity relative to controls. In patients with COPD, the intramuscular characteristics deteriorate along with disease severity, and thus the proportion of type I fibers in the quadriceps muscle is inversely correlated with forced expiratory volume in 1 second (3). Hence, a decline in lung function might reduce physical activity and thereby contribute to the limb muscle deconditioning seen in COPD.

Finally, local muscle hypoxia might explain the maladaptation of limb muscles in COPD. Local muscle oxygen availability is

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determined by an integrated transport system comprised of ventilation, lung diffusion, muscle circulation, and muscle diffusion (13), all of which are impaired in COPD. Accordingly, muscle cells may adapt anaerobically to maintain their function in a local hypoxic environment. This seems plausible considering the characteristics of muscle dysfunction in COPD, including a glycolytic fiber type dominance, higher anaerobic metabolism, and lower oxidative enzyme activity as described above.

Direct evidence of local muscle hypoxia as a driver of muscle dysfunction in patients with COPD is limited. However, altitude studies in healthy subjects have shown that long-term exposure to hypoxia results in loss of muscle mass and a reduction in muscle fiber cross-sectional area. Likewise, muscle oxidative capacity is reduced together with muscle contractile function during hypoxia (14, 15). Thus, the muscle abnormalities observed in patients with COPD and in CS-exposed mice (6) are likely to develop in healthy individuals when they are exposed to chronic hypoxia. ■

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