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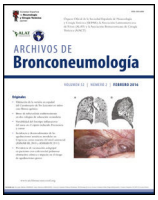

Editorial

Muscle Dysfunction in Chronic Obstructive Pulmonary Disease: Latest Developments☆

Disfunción muscular en la enfermedad pulmonar obstructiva crónica: novedades

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Chronic obstructive pulmonary disease (COPD) is a heterogeneous clinical entity associated with respiratory involvement, comorbidities, and numerous systemic manifestations.[1] One of the most important systemic manifestations is muscle dysfunction, affecting both the respiratory and peripheral muscles, although the causes vary among the different expressions.[1–3] To date, it is believed that the main factor for limb muscle dysfunction is deconditioning, resulting from the reduced level of physical activity often seen in COPD patients.[3,4] In contrast, the increase in lung volumes and subsequent changes in the geometry of the chest and the respiratory muscles are themselves the underlying cause of respiratory muscle dysfunction.[3,5] Naturally, other factors also affect muscle dysfunction, acting systemically on all muscle groups. These factors include smoking, nutritional changes, hypoxia, acidosis, systemic inflammation and oxidative stress, possible hormonal disorders, exacerbations, certain comorbidities, aging, and some drugs (e.g., steroids).[3–5] It is agreed that the biological mechanisms participating in muscle dysfunction include local inflammation and oxidative stress, apoptosis, muscle damage, and an increase in proteolysis with simultaneous reduction of protein synthesis and worsening muscle bioenergetics (a factor closely associated with changes in proportions of fiber types, mitochondrial activity, or blood flow availability in the muscle itself).[3–5] Evidence has also emerged in recent years on the role of epigenetic mechanisms,[6] imbalances between apoptosis, muscle damage, and autophagy,[7] and defects in mainly satellite cell-dependent muscle repair-regeneration mechanisms.[8] It is interesting to note that the regenerative capacity of female patients with COPD appears to be somewhat higher than that of male patients. Also of interest is the apparent role of internal muscle fat in altering the above-mentioned muscle bioenergetics.

Greater advances have been made recently in the understanding of muscle proteolysis routes in COPD, with evidence that ubiquitination plays a significant role in proteasome-mediated protein destruction.[3,9] This mechanism, moreover, seems to be partially related with the reduction in patients' physical activity. The first massive sequencing analyses using "omics" techniques in the study of loss of muscle mass and function have also appeared. In this respect, differing transcriptome and proteomic profiles have been described in patients with these changes.[10–12] It has also been interesting to learn that, despite some differing elements, such as the level of autophagy, many of the mechanisms associated with the loss of muscle mass and function are similar in COPD and other diseases,[3,7] reinforcing the idea that the biological response mechanisms to different toxins are limited. This raises the possibility that muscle dysfunction associated with different entities may be treated in the future with common biological therapies.

With regard to symptoms, the prevalence of loss of muscle mass and function in COPD patients (approximately 15%) and the clinical consequences of these changes are now better characterized.[13] Specifically, it has been determined that both loss of limb strength and progress to a less aerobic phenotype are negative factors for functional prognosis and life expectancy.[14] In an excellent meta-analysis of 21 studies, Evans et al. confirmed that not only strength but also resistance of the peripheral muscles are reduced in COPD patients, the latter probably being more important.[15] Resistance appears to be associated with both the above-mentioned changes in fiber types and molecular mechanisms (including a reduction in phosphorylated AMP kinase α [phospho-AMPK α] or lower iron availability).

There have been other interesting advances in diagnostics, particularly imaging techniques. These include high-resolution computed tomography, ultrasound, and magnetic resonance imaging that can be used to provide a more accurate evaluation of changes in muscle mass and function in specific territories of the body.[4,5,16,17] With regard to treatment, more importance has gradually been given in recent years to maintaining physical activity and combining training with nutritional supplements.[4] In patients with advanced muscle dysfunction, electrical and magnetic stimulation techniques have also shown promising results.[4,5,16] Finally, researchers are investigating new drugs with anabolic properties, such as growth hormone secretagogues, and the so-called calcium sensitizers (in reality, troponin C calcium-binding site sensitizers)

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that facilitate muscle contraction.[4,16] Phosphodiesterase 4 (PDE-4) inhibitors, such as roflumilast, have very recently been shown to reduce muscle proteolysis in patients with COPD and cachexia.[9]

Finally, we must emphasize that peripheral and respiratory muscle dysfunction is a clinically significant problem, highlighted in the official statements and guidelines published by SEPAR and other international societies in recent years.[4,5,16] These statements include causative factors, physiopathological mechanisms, and updates of diagnostic and therapeutic procedures.

In summary, advances have been made in recent years, particularly in the understanding of the mechanisms that cause muscle dysfunction in COPD, its clinical impact, and diagnostic methods. Advances in the field of therapeutics have been more modest, although new promising lines are opening up.

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