



Editorial

Impact of Physical Activity and Exercise on Chronic Obstructive Pulmonary Disease Phenotypes: The Relevance of Muscle Adaptation



Impacto de la actividad física y el ejercicio en los fenotipos de enfermedad pulmonar obstructiva crónica: la importancia de la adaptación muscular

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Limb muscle dysfunction is one of the most relevant systemic manifestations in patients with chronic obstructive pulmonary disease (COPD). Interestingly, one third of COPD patients experience muscle dysfunction even at early stages of their disease.^{1,2} Muscle dysfunction may be associated with the loss of muscle mass, which may further worsen the function of the affected muscles. Importantly, muscle dysfunction and mass loss negatively impact the patients' prognosis regardless of the degree of the airway obstruction.^{1,2} Exercise capacity, which deteriorates the quality of life in the patients, is also negatively influenced by limb muscle dysfunction. Several clinical phenotypes have been established on the basis of the degree of the airflow limitation and the extent of the body weight and muscle mass loss with different prognosis characteristics.^{1,2}

In the multifactorial etiology of COPD limb muscle dysfunction, a great variety of clinical factors and cellular and molecular events have been shown to contribute.^{1,2} Moreover, structural alterations such as atrophy of the muscle fibers, especially of the fast-twitch, have also been consistently demonstrated in the vastus lateralis (VL) of those patients.^{3,4} Disruptions of the normal sarcomere structure along with significant reductions in myosin filaments and other muscle-specific enzymes were also shown in the VL of COPD patients.^{3,4} Inverse correlations were also detected between the number of sarcomere disruptions and myosin protein loss.⁴

Furthermore, increased levels of autophagy and apoptosis and epigenetic modifications have also been reported in the limb muscles of these patients.^{4–7} A rise in oxidative stress levels including the myonuclei has also been demonstrated in the VL of the COPD patients.^{3,4} Moreover, increased protein oxidation levels were negatively associated with clinical parameters such as oxygen consumption and quadriceps muscle strength,^{8,9} suggesting that the oxidative events taking place in several key muscle

proteins probably alter their function, thus inducing deleterious effects on muscle performance in the patients. Importantly, interactions among the different biological mechanisms also occur, which may enhance the damaging effects on the myofibers of the patients. Besides, nutritional abnormalities, which are also common in COPD, leading to characteristic phenotypes, may further aggravate muscle mass and performance, especially of the lower limbs.

So far the most effective therapeutic intervention to palliate the reported impairment in muscle mass loss and dysfunction associated with COPD is pulmonary rehabilitation, especially muscle and exercise training modalities. In addition, the combination of exercise training with nutritional support may further improve muscle status and performance as well as exercise tolerance.^{1,2} In order to achieve the desired effects on the skeletal muscles and exercise intolerance, general exercise training on a cycloergometer must be of relatively high intensity (70% of the maximal tolerated load) and prolonged duration (usually between 8 and 10 weeks). Shorter periods of time of lower intensity of the training may induce deleterious effects, especially on the myofibers of the quadriceps. In this regard, several studies conducted on patients and even in animals clearly showed a significant rise in several oxidative stress markers in the skeletal muscles along with a decline in muscle performance in response to chronic exercise programs of short duration (approximately three weeks).^{10,11} However, significant clinical and biological effects were seen in COPD patients that followed a 10-week endurance exercise training program of high intensity.^{12,13} Specifically, in those studies^{12,13} clinical outcomes improved along with a decline in systemic lactate levels, while oxidative stress markers were reduced or showed no changes in both muscle (VL) and blood compartments in patients with very severe COPD following a 10-week training program. These findings imply that oxidative stress is probably a relevant mediator of skeletal muscle performance during exercise and could be used as a surrogate to monitor the response to endurance exercise training programs at least in severe COPD.

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Other alternatives of muscle training may also be applied to those COPD patients with a very severe airflow limitation and/or very limited exercise capacity. In many patients, general exercise training cannot be applied as their exercise tolerance is compromised leading to a significant rise in dyspnea perception and stress. As such, magnetic or electric muscle stimulation modalities are very promising tools to treat muscle dysfunction in this specific COPD patient phenotype. The advantage of passive magnetic or electrical stimulation is that muscle training is applied without the respiratory stress induced by high-intensity exercise. In line with this, improvements in muscle structure, especially of the slow-twitch fibers, and no increases in oxidative stress markers were observed in the VL of patients with very severe COPD and limited exercise capacity following a 10-week training program using magnetic stimulation of the quadriceps muscle.^{14,15} These findings suggest that magnetic stimulation is suitable for this specific COPD phenotype of patients with severe airflow limitation and severely impaired exercise capacity.

In conclusion, impaired muscle mass and function determine specific phenotypes in patients with COPD regardless of the degree of the airway obstruction. Skeletal muscle dysfunction, especially of the lower limbs negatively influences the prognosis of these patients independently of the airflow limitation. Nutritional status and other factors such as the level of physical activity of the patients may aggravate muscle dysfunction in COPD. Endurance exercise training programs of high intensity and long duration induce beneficial effects on the skeletal muscles through several key biological mechanisms. Alternatively, magnetic or electrical muscle stimulation modalities were also shown to induce beneficial effects on muscles and other clinical outcomes in COPD. Skeletal muscle mass and function define specific clinical phenotypes of COPD patients irrespective of the status of the lung disease. These systemic manifestations deserve special attention at the time of defining the best therapeutic strategies in patients with COPD. Finally, skeletal muscle status and function may also determine the response to different exercise and muscle training modalities.

Funding

CIBERES, FIS 14/00713, FIS 18/00075, SEPAR 2016, FUCAP 2016.

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