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Recommendations of SEPAR

Guidelines for the Evaluation and Treatment of Muscle Dysfunction in Patients With Chronic Obstructive Pulmonary Disease☆

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ABSTRACT

In patients with chronic obstructive pulmonary disease (COPD), skeletal muscle dysfunction is a major comorbidity that negatively impacts their exercise capacity and quality of life. In the current guidelines, the most recent literature on the various aspects of COPD muscle dysfunction has been included. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) scale has been used to make evidence-based recommendations on the different features. Compared to a control population, one third of COPD patients exhibited a 25% decline in quadriceps muscle strength, even at early stages of their disease. Although both respiratory and limb muscles are altered, the latter are usually more severely affected. Numerous factors and biological mechanisms are involved in the etiology of COPD muscle dysfunction. Several tests are proposed in order to diagnose and evaluate the degree of muscle dysfunction of both respiratory and limb muscles (peripheral), as well as to identify the patients' exercise capacity (six-minute walking test and cycloergometry). Currently available therapeutic strategies including the different training modalities and pharmacological and nutritional support are also described.

Normativa SEPAR sobre disfunción muscular de los pacientes con enfermedad pulmonar obstructiva crónica

Palabras clave:
Enfermedad pulmonar obstructiva crónica
Disfunción muscular
Guía española

RESUMEN

La disfunción muscular de pacientes con enfermedad pulmonar obstructiva crónica (EPOC) constituye una de las comorbilidades más importantes, con repercusiones negativas en su capacidad de ejercicio y calidad de vida. En la presente normativa se ha resumido la literatura publicada más recientemente sobre los diferentes aspectos del tema y se ha utilizado también la escala *Grading of Recommendations Assessment,*

Abbreviations: ATP, adenosine triphosphate; ATS, American Thoracic Society; BIA, bioimpedance analysis; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; EMG, electromyography; ERS, European Respiratory Society; FFM, fat-free mass; FRC, functional residual capacity; FVC, forced vital capacity; GH, growth hormone; HICP, high-intensity constant-power; IMT, inspiratory muscle training; LLM, lower limb muscles; MD, muscle dysfunction; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MM, muscle mass; MR, maximal repetition; MRI, magnetic resonance imaging; MSV, maximum sustainable ventilation; MVIC, maximal voluntary isometric contraction; MVV, maximal voluntary ventilation; NIV, non-invasive mechanical ventilation; Pdi, transdiaphragmatic pressure; Pdi*twitch*, transdiaphragmatic twitch pressure; PR, pulmonary rehabilitation; PTP, pressure/time product; Q-MVC, maximal voluntary isometric contraction of the quadriceps; QTw, quadriceps twitch force; RV, residual volume; *Sniff*Pdi, transdiaphragmatic pressure during maximal sniffs; SniffPesmax, esophageal pressure during maximal sniffs; SNIP, sniff nasal inspiratory pressure (maximal); TENS, transcutaneous electrical nerve stimulation; TLC, total lung capacity; Tlim, time limit; ULM, upper limb muscles; VO2max, maximum oxygen consumption; W*R*, work rate; W*R*max, maximum work rate.

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Development, and Evaluation (GRADE) de recomendaciones sobre el grado de evidencia de las diferentes propuestas de la normativa. Respecto a una población control, se estima que en un tercio de los pacientes EPOC la fuerza del cuádriceps es un 25% inferior incluso en estadios precoces de su enfermedad. Aunque tanto los músculos respiratorios como los de las extremidades están alterados, estos últimos suelen verse mayormente afectados. Diversos factores y mecanismos biológicos están involucrados en la disfunción muscular de los pacientes. Se proponen diversas pruebas para evaluar y diagnosticar el grado de afectación de los músculos respiratorios y de las extremidades (periféricos), así como identificar la capacidad de esfuerzo de los pacientes (prueba de marcha de 6 min y cicloergometría). Se describen también las posibles estrategias terapéuticas vigentes que incluyen las diversas modalidades de entrenamiento y de soporte farmacológico y nutricional.

Introduction

These guidelines discuss the latest findings on muscle dysfunction in patients with chronic obstructive pulmonary disease (COPD), and examine the general problem, etiology, diagnosis, evaluation, and treatment. To that end, the expert authors have summarized the most recent publications on the various aspects of the topic, and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) scale has been used to make recommendations on the grade of evidence for the various proposals discussed in this document.[1] Due to space constraints, an extended version expanding on these guidelines has been made available online.

Epidemiology, Pathophysiology and Implications for Patients

Muscles in any part of the body have 2 main functional properties: strength, the maximum expression of their ability to contract; and endurance, the ability to maintain less than maximum strength over time.[2] Strength depends mainly on muscle mass, while endurance is determined by the aerobic capacity of the muscle.[3] Strength and endurance in different muscle groups can be measured in routine clinical practice.

Muscle dysfunction is defined as the inability of a muscle to perform its task,[2] as a result of loss of strength or endurance, or both. Dysfunction of the respiratory muscles or the muscles of the limbs (also known as peripheral muscles) is common in respiratory diseases. Patients with limb muscle dysfunction lose their independence, which adversely affects their quality of life.[4,5] COPD is probably the respiratory disease in which muscle dysfunction has been studied in most depth, and it has been established that up to one third of COPD patients, even in the early stages of the disease, have a loss of muscle function in their limbs (25% less strength than control subjects).[4] Respiratory muscle dysfunction is seen in advanced COPD patients, whose diaphragmatic strength is between 20% and 30% of that of control subjects.[6–8]

Observational studies consistently show that COPD patients have muscle dysfunction, irrespective of the severity of their pulmonary obstruction. Evidence GRADE 1A.

Muscle Dysfunction Pathophysiology

Research over the last 20 years has revealed that several factors and mechanisms are involved in the multifactorial etiology of muscle dysfunction in COPD patients.

Limb Muscle Dysfunction (Quadriceps)

As indicated in Fig. 1A, cigarette smoke, genetic and epigenetic alterations, metabolic disorders (including vitamin D and testosterone deficiencies), drugs (corticosteroids), comorbidities, exacerbations, systemic inflammation, malnutrition, physical inactivity, and aging are some of the factors involved in limb muscle dysfunction in COPD patients.[2,3] The biological events implicated in limb muscle dysfunction most notably include a series of structural changes,[9–11] oxidative stress,[9,11,12] chronic hypoxia, hypercapnia and acidosis, and structural and mitochondrial changes[13,14] (Fig. 1B). Other mechanisms, such as proteolysis, apoptosis, autophagy, and epigenetics, are also involved in the physiopathology of limb muscle dysfunction in these patients.[9,15–19]

Observational studies consistently point to biological mechanisms and factors involved in the development of muscle dysfunction in COPD patients. Evidence GRADE 1A.

Respiratory Muscle Dysfunction

The major factors involved in the respiratory muscle dysfunction of COPD are shown in Fig. 2A. The most important of these are mechanical factors, but there are also factors that induce positive adaptation, which gives the respiratory muscles of these patients certain endurance[3,20] (Fig. 2A). Adaptive biological phenomena have also been found in the diaphragm, counteracting the potential deleterious effects; these phenomena include shortening of the sarcomere length, increased myoglobin content and higher proportions of fatigue-resistant fibers and capillary contacts, increased mitochondrial density, and improved aerobic muscle potential[3,21–25] (Fig. 2B). In COPD, the final muscle phenotype will be a result of the balance between the adaptive factors and mechanisms, and those involved in muscle function, as well as between stable disease and exacerbations (Fig. 2B). In advanced COPD however, biological mechanisms[8,9,15–19,26] identical to those described in limb muscle dysfunction affect the diaphragm, prevailing over the adaptive mechanisms (Fig. 2B).

Observational studies consistently point to biological mechanisms and factors involved in the development of muscle dysfunction in COPD patients. Evidence GRADE 1A.

Evaluation of Respiratory Muscles: Voluntary and Involuntary Maneuvers (Table 1)

Evaluating Respiratory Muscle Strength: Volitional Tests of Respiratory Muscle Strength

Non-Invasive Testing

Spirometry. Forced spirometry,[27] although non-specific, can detect a decline in forced vital capacity (FVC) that can be indicative of a non-obstructive ventilatory defect.[28] A FVC decrease of greater than 25% between spirometries performed in the sitting and supine positions, or FVC less than 75% of the predicted values in the supine position, with normal values in the sitting position, indicate diaphragmatic weakness.[29]

Measuring Pressure at the Mouth. Maximum pressures generated at the mouth, whether inspiratory (MIP) or expiratory (MEP), are