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

Esther Barreiro, Víctor Bustamante, Pilar Cejudo, Juan B. Gáldiz, Joaquim Gea, José Miguel Rodríguez González-Moro

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.
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.5,5 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.4–6

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 changes13,14 (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 endurance1,20 (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 potential11,21–23 (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 mechanisms9,15–19,26 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
Invasive Testing

A good expression of the pleural pressure generated by activation of the inspiratory muscles can be obtained from the esophageal pressure determined by placing a pressure catheter in the mid-third of the esophagus during forced inhalation (SNIP).\(^{27,31,32}\) Inspiratory muscle dysfunction can be ruled out if S\(_{\text{NIP}}\) values are higher than \(-80\) cm H\(_2\)O in men or \(-70\) cm H\(_2\)O in women.\(^{27}\)

Diaphragmatic strength or transdiaphragmatic pressure (Pdi) can also be determined by measuring the difference between gastric and esophageal pressure, estimated by placing 2 catheters connected to pressure transducers (one in the esophagus and the other in the gastric cavity).\(^{27}\) S\(_{\text{NIP}}\)Pdi values lower than 75 cm H\(_2\)O in men or 53 cm H\(_2\)O in women suggest diaphragmatic dysfunction.\(^{24}\)

The various studies consistently show that volitional testing for evaluating respiratory muscle function is useful and provides reliable inter-individual measurements over time. Evidence: GRADE 1A.

Non-Volitional Tests of Respiratory Muscle Strength (Table 1)

External stimulation techniques, using phrenic nerve stimulators generating electric or magnetic fields (Pdwitch), have been...
considered the gold standard. Technological advances have led to complex and even non-volitional testing methods. Normal Pdi values are about 20%–30% of the sniff Pdi.\textsuperscript{27,34}

The different studies consistently show that non-volitional testing for evaluating respiratory muscle function is useful and provides reliable inter-individual measurements over time. Evidence: GRADE 1A.

**Evaluating Respiratory Muscle Endurance (Table 1)**

Pressure–time product (PTP) is calculated by integrating the respiratory pressure measured at the mouth, esophagus or Pdi over time (cm H\textsubscript{2}O/min).\textsuperscript{27} Maximal sustainable ventilation (MSV) is expressed as a fraction of maximal voluntary ventilation (MVV); normal values are between 60% and 80% of the MVV.\textsuperscript{27} MSV is a measure of respiratory muscle endurance and the function of other elements of the rib cage.\textsuperscript{35} Inspiratory or expiratory threshold loading tests are more specific. There are two types: incremental, measuring the sustained maximal pressure (SMIP and SMEP, depending on whether inspiratory or expiratory), and constant sub-maximal loading (percentage of SMIP or MEP for inspiratory, and SMEP or MEP for expiratory).\textsuperscript{36–39}

The different studies consistently show that endurance testing for evaluating respiratory muscle function is useful and provides reliable inter-individual measurements over time. Evidence: GRADE 1A.

**Evaluation of Limb Muscles: Volitional and Non-Volitional Testing**

**General Evaluation of Limb Muscles (Fig. 3)**

**Evaluating Muscle Mass (MM)**

Initial calculations are based on systems determining body compartments, such as the Matiegka method,\textsuperscript{40} which takes body weight (W) as the sum of 4 components: O, skeletal weight; D, skin and subcutaneous adipose tissue weight; M, skeletal muscle weight; and R, remaining weight. Skinfold anthropometry requires several measurements, including height, length and width of the limb, folds and calculated body surface area, but this technique generally overestimates the fat-free mass, compared to other methods.\textsuperscript{41} Technological advances have led to complex and even invasive systems, such as deuterium dilution,\textsuperscript{42} considered the gold standard. Although its use is limited to research centers, it has been used to validate a series of more commonly used measurements.

**Bioimpedance Analysis (BIA) or Bioelectric Impedance**

This method is based on the principle that the electrical conductivity of a fat-free mass (comparable to the MM) is greater than that of fat.\textsuperscript{42}

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**Table 1**

<table>
<thead>
<tr>
<th>Functional property</th>
<th>Muscle group</th>
<th>Test/Variable</th>
<th>Volitional</th>
<th>Pathological values</th>
<th>References</th>
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<tbody>
<tr>
<td>Strength</td>
<td>Non-specific</td>
<td>Forced spirometry</td>
<td>Yes</td>
<td>FEV\textsubscript{1} /FVC &gt; 80%</td>
<td>28,29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plethysmography</td>
<td>Yes</td>
<td>TLC &lt; 80% pred.</td>
<td>28,30</td>
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<tr>
<td>Inspiratory</td>
<td>MIP</td>
<td>Yes</td>
<td>&lt; 80 pred. or &lt; 65% pred. or suspected if &lt; 80 cm H\textsubscript{2}O</td>
<td>28,31</td>
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<td>Men: &lt;- 60 to 50 cm H\textsubscript{2}O; Women: &lt;- 40 to 35 cm H\textsubscript{2}O</td>
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<tr>
<td>Upper limbs</td>
<td>Handgrip</td>
<td>Yes</td>
<td>&lt; 80% pred.</td>
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<tr>
<td>Lower limbs (quadriceps)</td>
<td>Q-MVC</td>
<td>Yes</td>
<td>&lt; 80% pred.</td>
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<td>Quadriceps</td>
<td>Tlim at % QMCV</td>
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<td></td>
<td>Pair of forces (torque)</td>
<td>Yes</td>
<td>Not defined</td>
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**Table 2**

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<thead>
<tr>
<th>Grades</th>
<th>Overview</th>
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<tr>
<td>A</td>
<td>Excellent effort with excellent repeatability (&lt;5 cm H\textsubscript{2}O difference among maneuvers)</td>
</tr>
<tr>
<td>B</td>
<td>Good effort with good repeatability (5–10 cm H\textsubscript{2}O difference among maneuvers)</td>
</tr>
<tr>
<td>C</td>
<td>Fair effort with fair repeatability (10–20 cm H\textsubscript{2}O difference among maneuvers)</td>
</tr>
<tr>
<td>D</td>
<td>Only one good maneuver</td>
</tr>
<tr>
<td>E</td>
<td>Poor maneuvers or poor repeatability</td>
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Abbreviations. MIP, maximum inspiratory pressure at the mouth (static or Müller maneuver); MEP, maximum expiratory pressure at the mouth (static or Valsalva maneuver); SNIP, sniff nasal inspiratory pressure (dynamic sniff maneuver); Pesmax, maximum esophageal inspiratory pressure (generally obtained during sniff maneuver); Pdimax, diaphragmatic pressure on inspiration (generally obtained during sniff maneuver); Pdi, respiratory pressure measured at the mouth, esophagus or Pdi over time (cm H\textsubscript{2}O); TLC, total lung capacity; Q-MVC, maximal voluntary isometric contraction of the quadriceps; Qtw, contraction induced by twitch of the quadriceps muscle; MSV, maximum sustainable ventilation; MVV, maximal voluntary ventilation; SMIP, sustained maximal inspiratory pressure with incremental threshold loads; SMEP, sustained maximal expiratory pressure with incremental threshold loads; Tlim, time limit or endurance time for submaximal constant loads (generally percentage of SMIP or MEP for the inspiratory test or of SMEP or MEP for the expiratory test, and percentage of Q-MVC (generally 10%) for the quadriceps; SMEP, sustained maximal expiratory pressure with incremental threshold loads. 

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Alternatives

magnetic resonance imaging

Reference values are available.

is based on claudication after exercise

Reference values are available for different

63,73,74

and ultrasound,

44

58

Muscle biopsy is a morphological

It is highly standardized,

This would explain the high predictive value of this test

used for the overall and comprehensive evaluation of

44

(see below).

but the 6-minute walk is the most popular, and

particularly for measuring quadriceps

75,78,81

and mortality.

Exercise capacity and electromyography are useful and provide reliable

and comparable inter-individual measurements over time. Evidence:

GRADE 1A.

Limb Muscle Function Testing

Voluntary Maneuvers

Handgrip Dynamometry

This is a simple measurement, carried out with various types of
dynamometers. It is widely used and is recognized as a prognostic
factor in COPD.54 Reference values are available for different
populations.55,56

Maximal Isometric Contraction of the Quadriceps Femoris
(Q-MVC)

This procedure is normally performed with the patient in a
sitting position, with hips and knees bent at an angle of 90°.
Quadriceps extension is measured with the leg fixed at the ankle,
connected to a dynamometer.57 Reference values are available.58

Test of Endurance Time at 10% of the Q-MVC

This endurance test59 is based on claudication after exercise
involving cycles of contractions against a load equivalent to 10%
of the Q-MVC (cycles of 2 s quadriceps contraction and 3 s of relax-
ation). Other maneuvers, more specific for estimating endurance,
are used for measuring pairs of forces (torque) in Nm (Newton-

meters).

The different studies consistently show that tests for evaluating con-
traction function and muscle mass in COPD patients are very useful and
provide reliable and comparable inter-individual measurements over
time. Evidence: GRADE 1A.

Involuntary Maneuvers

Supramaximal Quadriceps Twitch Force (QTw)

This technique is based on the electrical or magnetic stimulation of
the femoral nerve in a single stimulus, or “twitch”, measuring the
force generated after quadriceps activation.61,62

The various studies consistently show that involuntary maneuver
tests for the evaluation of muscle function in COPD patients are useful
and provide reliable and comparable inter-individual measurements over
time. However, their use has not been extended to routine clinical
practice. Evidence: GRADE 1B.

Evaluation of Exercise Tolerance: The 6-Minute Walk Test

The 6-minute walk test is a simple exercise protocol measuring
the distance walked quickly by the patient on a hard, flat
surface over a period of 6 min.63 Several other tests are used
in the field (stair-climbing, Bruce, 12-minute walk, incremental
walk, etc.).63-65 but the 6-minute walk is the most popular, and
is the most simple exercise test used as a reference in COPD and
other diseases.66-72 It is highly standardized,63,73,74 is reasonably
reproducible,75 and is valuable for measuring the effects of different
interventions in many chronic diseases.76-81

The 6-minute walk is a high-intensity sustainable submaximal
exercise82 used for the overall and comprehensive evaluation of
various physical functions (cardiac, respiratory, peripheral oxygen
transport, muscle bioenergetics and neuromuscular integration)
that determine the patient’s aerobic capacity. Some studies82,83
suggest that exercise intensity during the test is an indication of
the patient’s maximal sustainable power output over time (critical
power).84 This would explain the high predictive value of this test
for mortality76,79,80 and its valuable role in the clinical decision-
making process.75,78,81

Most common tests of muscle mass and function assessment

Muscle mass evaluation

General: BMI; skinfold anthropometry
Bioimpedance/DXA; MM, MM index, localized MM
(DEXA)

Local: Thigh circumference, skinfold
Thigh circumference slice (CT, MRI)
Cross-sectional area of the quadriceps rectus femoris by ultrasound
Muscle biopsy

Muscle function evaluation

General: Exercise testing: ergometry, 6-minute walk test,
Activity measures: questionnaires, accelerometers

Local:
  – Strength measurements:
    Volitional: maximal voluntary contraction (MVC), handgrip, thigh extension
    Non-volitional: Supramaximal twitch of thumb abductor, quadriceps, etc.
  – Resistance measurements:
    Volitional: endurance time at 10% of MVC
    Non-volitional: EMG fatigue after repetitive neuromuscular stimulation

EMG

Fig. 3. List of the most commonly used tests in routine clinical practice for evaluating
muscle mass and dysfunction. Tests are classified as general or specific for evaluating
muscle mass and function.

Dual-Energy X-Ray Absorptiometry (DEXA)

DEXA is an imaging technique used for estimating total-body and
regional skeletal muscle mass. It also can be used for quantifying
lean soft tissue, fat and bone mineral density.43

The different studies consistently show that the different tests for
quantifying muscle mass in COPD patients are useful and provide reliable
inter-individual measurements over time. Evidence: GRADE 1A.

Local MM Study Techniques

Although measuring thigh circumference is simple and cheap,
it is not a good measure of local muscle mass.44 Alternatives
include computed tomography (CT),44 magnetic resonance imaging
(MRI),45 and ultrasound,46 particularly for measuring quadriceps
size. In COPD, the amount of local MM measured by these techni-
cues has been correlated with parameters as diverse as muscle
strength47 and mortality.44 Muscle biopsy is a morphological
technique that provides data on the structural and biochemical
properties of the muscles,48 but its invasive nature means that use
is essentially limited to research studies, even when fine needle
microbiopsies are obtained.47

Numerous studies consistently show that obtaining a muscle biopsy
from COPD patients is highly useful and provides reliable and com-
parable inter-individual measurements over time. Evidence: GRADE
1A.

Physical Activity

Physical activity can be measured by questionnaires or, more
reliably, by accelerometers that record activities performed by a
subject over a prolonged period.49

Exercise Testing

Both the walk test and ergometry are discussed in detail in the
specific section of these guidelines.

Electromyography (EMG)

EMG consists of recording the electrical activity of muscles
at rest and during both voluntary and externally stimulated
contraction50–53 (see below).

The various studies consistently show that physical activity, exercise
capacity and electromyography are useful and provide reliable

50–53
Indications

Evaluation of the functional status of patients with different chronic diseases, such as COPD, asthma, obesity, interstitial lung diseases, pulmonary hypertension and various cardiovascular diseases and measurement of the effect of interventions, such as training, lung transplantation, lung parenchyma resection, and pharmacological treatments for pulmonary hypertension, COPD and heart failure were done. Although this is a very safe exercise protocol, since the patients themselves determine the speed of the walk, it should not be performed in patients with unstable angina, recent myocardial infarction (within 1 month), tachycardia of over 120 bpm, or high blood pressure spikes. Safety measures and training by professionals are essential for any form of exercise testing.

Variables

The variables measured in the test are the following: (i) distance walked expressed in meters; (ii) heart rate and oxygen saturation measured by pulse oximetry at the beginning and end of the test; and (iii) symptoms, dyspnea (Borg scale) and discomfort in the lower limbs at the beginning and end of the walk. The walk test should be performed twice, with approximately 1 h between assessments; the longest distance walked should be used. If the patient requires oxygen therapy, the test should be performed with the prescribed oxygen regimen in place.

Interpretation of Results

For comparison of the results obtained before and after an intervention, the minimum clinically important difference, set at 25–30 m, must be identified after an intervention. Although results in terms of distance walked are usually interpreted as absolute values (meters), reference values are also used, such as those of Enright et al. In short, the 6-minute walk test is highly recommendable in clinical practice as a simple exercise test for evaluating functional status and the effect of certain interventions in patients with chronic respiratory and cardiac diseases. The simplicity, safety, reproducibility and high predictive value of the test make it a simple reference protocol for studying aerobic capacity in clinical practice.

The various studies consistently show that the 6-minute walk test is very useful and provides highly reliable and comparable inter-individual measurements over time. It is of great benefit in routine clinical practice and in clinical studies. Evidence: GRADE 1A.

Evaluation of Exercise Tolerance: Cycloergometry

Incremental Exercise Testing

Incremental exercise testing can be used for evaluating the sub-maximal and maximal response, and can often help identify the mechanisms underlying exercise intolerance. It can also be used to adapt interventions for exercise intolerance to the source of the limitation, and for ruling out other medical interventions (such as physical training) that may be a risk factor, thus increasing patient safety.

The procedure is highly standardized. Cycle ergometry is the most commonly used test, because it is cheap and compact, and the work rate can be accurately determined. Most patients can perform the test without practicing first.

Variables

Most currently available software programs can generate large numbers of variables, but the most commonly used in clinical studies are maximum oxygen consumption (VO2 max) and maximum work rate (WRmax), both of which are symptom-limited. VO2 max is a highly reproducible variable, with coefficients of variation ranging from 3% to 7%, when maximum work rate criteria are reached. Consistent measurements have been obtained in multicenter clinical studies when appropriate quality controls are in place. Moreover, in cardiac patients at least, improved VO2 max after interventions leads to improved survival.

The advantage of maximum work rate (WRmax) over VO2 max is that it can be determined without the need for a metabolic cart. It should be remembered that, unlike VO2 max, WRmax depends on the rate of the previous incremental protocol (ΔWR/Δt), so it cannot be equated with the VO2 max. Moreover, exactly the same protocol must be used before and after the intervention or exposure.

High-Intensity Constant-Power Tests

Although moderate-intensity constant-power tests can be performed to characterize the kinetics of the response of the oxygen transport system, these tests require complex analysis, so their use is limited to research studies. In contrast, high-intensity constant-power (HCP) tests have been used widely in studies for assessing interventions targeting the muscles. The variable that defines exercise tolerance is time until the patient can no longer continue (Tlim, expressed in seconds). Tlim has been shown in multicenter trials to be reproducible and consistent (Fig. 4). The clinically important difference for these tests is in the order of 100 s (95% confidence interval: 50–150 s). The different studies consistently show that cycle ergometry is very useful and provides highly reliable and comparable inter-individual measurements over time. It is of great benefit in routine clinical practice and in clinical studies. Evidence: GRADE 1A.

Muscle Training in COPD Muscle Dysfunction

Muscle training, a fundamental component of Pulmonary Rehabilitation (PR) programs, has been widely shown to be effective for improving exercise tolerance, muscle strength, dyspnea, fatigue, and quality of life. Hence, it is an essential intervention in the treatment of muscle dysfunction in COPD patients.

In patients with chronic respiratory disease, general muscle training must be aimed at improving both the aerobic limitations and muscle dysfunction often seen in these diseases. Choice of training type will not only depend on the needs of the patient and planned objectives, but also to a large extent on the resources available in the rehabilitation clinic.

The various studies consistently show that muscle training is the best treatment for muscle dysfunction in COPD patients. It is of benefit in routine clinical practice and in clinical studies. Evidence: GRADE 1A.

Types of Training

Aerobic or Endurance Training

This is the type of training most often used in PR, and the evidence for recommendation is the highest (Grade 1A). Aerobic exercise is a submaximal exercise involving the large
muscle groups, sustained for a prolonged length of time. In COPD patients, aerobic training not only achieves better cardiovascular adaptation, it also improves limb muscle function. This leads to increased muscle endurance, with adaptive phenomena in the bioenergetics of the quadriceps \(^{3,15,120}\) and skeletal muscles. \(^{3,121}\)

Cycloergometry and treadmill training are the most common aerobic exercises prescribed in PR, especially in outpatient and inpatient rehabilitation programs. Training intensity is very important when prescribing exercise therapy. An intensity of around 60%–80% of the maximal exercise capacity (previously evaluated with cardiopulmonary exercise testing) for a minimum of 8 weeks \(^{118}\) is recommended for achieving a substantial benefit, while 12 weeks is considered the optimal duration \(^{114}\) (Table 3). Longer exercise programs can achieve greater, longer-lasting effects, particularly on quality of life indices. \(^{122}\)

*The various studies consistently show that aerobic endurance muscle training is one of the best treatments for muscle dysfunction and restoring exercise capacity in COPD patients. It is of benefit in routine clinical practice and in clinical studies. Evidence: GRADE 1A.*

**Interval Training**

This is a modification of standard aerobic training, in which short periods (1–2 min duration) of high-intensity exercise (80%–120% maximum capacity) are regularly alternated with similar periods of rest or lower intensity exercise. In this way, patients achieve high levels of output, but with less dyspnea and fatigue. The benefits are equivalent to those of conventional aerobic training. \(^{121,123,124}\)

*The different studies consistently show that interval training is one of the best treatments for muscle dysfunction and restoring exercise capacity in more severe COPD patients. It is of benefit in routine clinical practice and in clinical studies. Evidence: GRADE 1A.*

**Strength Training**

Following the “specificity principle”, muscle strength training is potentially better for increasing the strength and mass of the exercised muscle than conventional aerobic training. \(^{125}\) Available evidence supports the use of strength training in combination with general aerobic training (1A), since this achieves further increases in limb muscle strength.\(^{114,118}\) In PR, this type of exercise is often applied with weight-lifting exercises for the lower and upper limbs, performed on gym apparatus with heavy loads, equivalent to 70%–85% of the maximum weight lifted by the individual in a previous single maneuver (or one repetition maximum testing, 1 RM), with few repetitions, \(^{118}\) in 2–3 sessions per week for 8–12 weeks. \(^{114,118}\)

*The different studies consistently show that muscle strength training is one of the best treatments for muscle dysfunction and restoring exercise capacity in more severe COPD patients. It is of great benefit in routine clinical practice and in clinical studies. Evidence: GRADE 1A.*

**Other Types of Training**

Very promising alternatives for limb muscle training in PR programs include transcutaneous electrical nerve stimulation (TENS) \(^{2,128,129}\) and electromagnetic stimulation, \(^{128}\) which is better tolerated but less well studied.
Respiratory Muscle Training

Inspiratory muscle training (IMT) has been shown to improve muscle strength and endurance in COPD patients, with benefits in dyspnea, functional capacity and quality of life. The efficacy of specific expiratory muscle training with abdominal muscle exercises remains in doubt. In general, IMT should be performed twice a day, at an intensity of at least 30% of the MIP and in sessions lasting about 15 min. IMT is indicated mainly in patients with respiratory muscle dysfunction.

The various studies consistently show that respiratory muscle training may be of benefit in COPD patients with significant respiratory muscle dysfunction, in routine clinical practice and in clinical studies. Evidence: GRADE 1B.

Other Non-Training-Based Treatments for Muscle Dysfunction

Nutritional Supplements and Hormone Treatment

Nutritional disorders are found in 20%–40% of patients with severe respiratory disease. The causes appear to be multifactorial, and include imbalance between energy intake and output, hypoxemia, and the systemic inflammatory component often observed with this disease. Results from the use of high-energy nutritional supplements in these patients (anabolic steroids and growth hormones, antioxidants and other protein compounds) have been contradictory as regards weight gain and, in particular, their impact on functional recovery.

Nutritional Supplements

Nutritional supplements are commonly used in COPD patients, but there is very little evidence to support this approach. While some authors have reported weight gain and increased fat-free mass, along with improvements in exercise tolerance, these data are not supported by other studies. The most recent Cochrane review includes a meta-analysis of 17 randomized clinical trials, performed mainly in undernourished patients, that provide little evidence that patients receiving nutritional supplements show improvements in weight, fat-free mass, respiratory muscle strength and distance walked during the 6-minute walk test.

Studies do not consistently show that the benefits outweigh the risks of treatment administration. It is hoped that better quality research in the future will contribute to improved understanding in this area, and provide more reliable results than those currently available, to help introduce this type of treatment into routine clinical practice for the management of COPD patients. Evidence GRADE 2B.

Anabolic Steroids

Androgen deficiency, often associated with loss of muscle mass, occurs in up to 40% of COPD patients. Administration of anabolic steroids has been associated with weight gain and increased muscle mass, supporting the use of these products as adjuvant treatment in rehabilitation programs. However, the results have not been sufficiently corroborated, and this approach is not recommended by ERS/ATS rehabilitation guidelines. Several published studies have shown that despite weight gain and increased fat-free mass, no improvements were reported in lung function parameters, exercise tolerance or respiratory (MIP) or limb (handgrip strength) muscle function. However, the meta-analysis included not only treatment with androgenic derivatives, but also a study on growth hormone and another on ghrelin (a growth hormone secretagogue), as well as other studies that may or may not have included training, with no subgroup analyses. All these factors limit the interpretation of the above-mentioned meta-analysis. In reality, the combination of nutritional or androgeneic supplements with muscle training has led to increases in weight, fat-free muscle mass, MIP, quadriceps force, maximum work load and exercise endurance time.

The studies do not consistently show that the benefits outweigh the risks of treatment administration. It is hoped that better quality research in the future will contribute to improved understanding in this area, and provide more reliable results than those currently available, to help introduce this type of treatment into routine clinical practice for the management of COPD patients. Evidence GRADE 2B.

Growth Hormone and Ghrelin

The use of recombinant human growth hormone (GH) has also been studied in malnourished COPD patients, in rehabilitation programs, but results have been inconclusive. More recently, the use of ghrelin has been studied in these patients, also in the rehabilitation setting. Ghrelin is polypeptide hormone that acts by binding to GH-stimulating hypothalamic receptors, stimulating secretion of GH. It also stimulates the release of orexigenic factors, increasing appetite. Paradoxically, malnourished COPD patients may have elevated ghrelin levels. Results published to date on the exogenous administration of this substance are inconclusive.

The studies do not consistently show that the benefits outweigh the risks of treatment administration. It is hoped that better quality research in the future will contribute to improved understanding in this area, and provide more reliable results than those currently available, to help introduce this type of treatment into routine clinical practice for the management of COPD patients. Evidence GRADE 2C.

Other Nutrients

The ability of other products to improve the muscle and physical function of COPD patients, including antioxidants, vitamins and high-calorie compounds, has been investigated. However studies are generally isolated and uncontrolled, or conducted in small numbers of patients, and results are difficult to reproduce.

The studies do not consistently show that the benefits outweigh the risks of treatment administration. It is hoped that better quality research in the future will contribute to improved understanding in this area, and provide more reliable results than those currently available, to help introduce this type of treatment into routine clinical practice for the management of COPD patients. Evidence GRADE 2C.

Non-Pharmacological Treatments: Non-Invasive Ventilation and Heliox

It is well known that non-invasive mechanical ventilation (NIV) allows the respiratory muscles to rest, explaining improved lung function, evidenced by increased MIP, Pdimax and pressure-time product. A few studies have even associated the use of NIV with better limb muscle function, demonstrated by increased quadriceps strength and endurance. This is probably a consequence of improved oxygen supply to the peripheral muscles, as a result of the reduction in work-of-breathing. This same mechanism has been cited to explain the effect of breathing heliox (a mixture of helium and oxygen) on limb muscle function. A recent Cochrane review, based on a meta-analysis of 6 clinical trials evaluating the results of NIV during a physical exercise program, concluded that the slight differences in exercise capacity and tolerance were inconsistent. In line with the latest consensus recommendations from the ERS/ATS, the use of NIV during muscle training is not recommended.

This intervention should be limited to hypercapnic patients on nighttime NIV programs.

The studies consistently show that the benefits outweigh the risks of treatment administration. Research in the future may contribute to improved understanding in this area, to help introduce this type of...
treatment into routine clinical practice for the management of COPD patients. Evidence GRADE 2A

Conclusions

In summary, good respiratory and limb muscle function is essential for sustaining life and an acceptable quality of life. Muscle function is affected in many respiratory diseases and may lead to problems for the patient's social life and for maintaining an adequate level of ventilation. Muscle function can and must be evaluated in these patients, so that the appropriate therapeutic measures can be implemented. In view of the current evidence, muscle training, with or without nutritional supplements, is clearly the best therapeutic strategy for increasing muscle mass and function and improving quality of life in COPD patients.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbr.2015.04.027.

References


Society for Cardiovascular Angiography and Interventions, and Society of Tho-


dibility of cardiopulmonary exercise measurements in patients with pulmonary

102. McKone EF, Barry SC, Fitzgerald MX, Gallagher CG. Reproducibility of max-

103. Noseda A, Carpiaux JP, Prigogine T, Schmerber J. Lung function, maximum and
submaximal exercise testing in COPD patients: reproducibility over a long in-

104. Sittig KE, Brawner CA, Ehrman JK, Ivanhoe R, Boehmner WT. Reproducibility of peak oxygen uptake and other cardiopulmonary ex-
cise parameters: implications for clinical trials and clinical practice.

of ventilatory endpoints during cycle ergometry in multicentre trials in COPD.


exercise lactacid and ventilation as a function of exercise training in pa-


109. De Jong W, Grevink RG, Roorda RJ, Kaptein AA, van der Schans CP. Effect of


111. Andrianopoulos V, Klijn P, Franssen FM, Spruit MA. Exercise training in pul-

112. Benzo RP, Paramesh S, Patel SA, Slivka WA, Sciurba FC. Optimal proto-
col selection for cardiopulmonary exercise testing in severe COPD. Chest.

113. Newell JT, Noye BJ, Silva AC, Cabral AL, Fernandes AL. Short-term effects of
aerobic training in the clinical management of moderate to severe asthma in

114. PuentedeMaestuL,SanzML,SanzP,CubillosJM,MayolJ,CasaburiR.Comparison of
effects of supervised versus self-monitored training programmes in patients

115. Benzo RP, Paramesh S, Patel SA, Slivka WA, Sciruba FC. Optimal proto-
col selection for cardiopulmonary exercise testing in severe COPD. Chest.

core of constant power exercise duration changes in COPD. Eur Respir J.

cial American Thoracic Society/European Respiratory Society statement: key
concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med.
2013;188:E13–64.

118. Andrianopoulos V, Klijn P, Franssen FM, Spruit MA. Exercise training in pul-


123. Vogiatzis I, Terzis G, Stratagkis G, Cherroneuvin E, Athanasopoulos D, Spetsioti S,
et al. Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in
patients with COPD in GOLD stages II to IV. Chest. 2011;140:744–52.

etal muscle adaptations to interval training in patients with advanced COPD.

125. Beaucamp MK, Janauvais-Ferreira T, Goldstein RS, Brooks D. Optimal duration of
pulmonary rehabilitation for individuals with chronic obstructive pul-


127. Vogiatzis I, Nanas G, Roussos C. Interval training as an alternative modality to con-

128. Sillen MJ, Franssen FM, Gosker HR, Wouters EF, Spruit MA. Metabolic and
motoric changes in lower-limb skeletal muscle following neuromuscular electrical stimulation: a systematic review. PLOS ONE. 2013;8:e69391.

129. Sillen MJ, Franssen FM, Delhove JM, Vaes AW, Wouters EF, Spruit MA. Efficacy of lower-limb muscle training modalities in severely dyspnoic indi-
viduals with COPD and quadriplegia muscle weakness: results from the DI-


