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ASSESSMENT OF PERIPHERAL SKELETAL MUSCLE FUNCTION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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INTRODUCTION

It is now universally accepted that chronic obstructive pulmonary disease (COPD) is associated with a number of manifestations that extend beyond the lungs and contribute to disease severity [1]. Dysfunction of the peripheral skeletal muscles is one systemic manifestation that is linked to a variety of clinically relevant adverse outcomes. Although the lung function impairment in COPD is essentially irreversible, peripheral muscle dysfunction may be amenable to therapy as evidenced by the positive responses to muscle training. It is, therefore, important to identify, characterise and quantify these muscle abnormalities in order to institute appropriate therapy. In this review, we discuss the significance of, and methodologies for, measuring peripheral skeletal muscle function in COPD. The function of the respiratory muscles, which are also skeletal muscles, may also be abnormal in COPD. However, these muscles are subject to different influences, as they are chronically overworked and are also affected by the effects of hyperinflation. Assessment of respiratory muscle function is a large topic and beyond the scope of this review.

SIGNIFICANCE OF PERIPHERAL MUSCLE DYSFUNCTION IN COPD

There is a substantial body of evidence to show that peripheral skeletal muscle dysfunction exists in COPD [2]. At the cellular level, reductions in the proportion of type I muscle fibres and oxidative enzymes, and reduced capillary density suggest impaired aerobic function. At a macroscopic level, reductions in muscle mass and muscle strength have been observed. In addition, there is evidence for abnormal muscle energy metabolism and early onset of lactic acidosis during exercise at low relative external work loads, suggesting the presence of intrinsic abnormalities of the exercising muscles. Moreover, even when lung function is restored by transplantation, exercise performance does not usually return to normal [3, 4]. Similarly, improving lung function by drug therapy results in only modest improvements in exercise capacity [5], particularly when compared with rehabilitation.

The clinical significance of peripheral muscle dysfunction in COPD is illustrated by its

association with a number of adverse outcomes, independent of lung function. Muscle weakness, which is mainly due to a loss of muscle mass [6] is independently associated with reduced exercise capacity [7] and increases in healthcare utilisation [8] and mortality [9]. Peripheral muscle strength is also related to performance in functional tests, such as the incremental shuttle walking test (ISWT) [10]. Furthermore, reduced quadriceps mass measured by computed tomography (CT) is a better predictor of mortality than body mass index [11]. Most of the evidence for peripheral muscle dysfunction in COPD comes from work performed on the lower-limb muscles, especially the quadriceps, since this is an important muscle of locomotion. However, the upper-limb muscles may also be affected, although, when compared to the ambulatory muscles, this is more likely to be a result of systemic factors rather than disuse.

Peripheral muscle strength training in the context of pulmonary rehabilitation leads to clear improvements in muscle performance, without any demonstrable change in lung

function [12]. Muscle dysfunction in COPD is therefore potentially reversible and strategies to identify these abnormalities are clinically relevant.

The main objectives of measuring peripheral muscle function in COPD are as follows:

1. To assess physical impairment
2. To assess the outcome of interventions, such as rehabilitation or nutritional therapy
3. To allow prescription of resistance training

There is potential for muscle function assessment to be used as a diagnostic tool to identify the aetiology of muscle dysfunction in COPD, although, at present, this is speculative because the underlying pathophysiology of skeletal muscle dysfunction has not been fully understood. There is also good evidence to show that mortality in these patients can be predicted from measures of peripheral muscle mass and strength [9, 11]. Therefore, measurement of peripheral muscle function can potentially be used as a guide to prognosis in this disease.

METHODS OF ASSESSING PERIPHERAL MUSCLE FUNCTION

Clinically relevant aspects of muscle function in COPD include measures of muscle strength, muscle mass and muscle performance during cardiopulmonary exercise testing.

1. Muscle strength

Strength refers to the force-generating capacity of a muscle and can be determined using volitional or nonvolitional methods. Volitional methods of strength testing require maximum effort and are therefore subject to patient and operator motivation. Volitional strength can

Types of muscle strength assessments
Volitional Testing
<i>e.g.</i> tensiometry, 1-rm testing, dynamometry (mechanical or electric), computer assisted dynamometry
Nonvolitional Testing
<i>e.g.</i> magnetic femoral nerve stimulation
Types of muscle contractions
Static (isometric) contraction: the length of muscle fibres remain constant during the muscle contraction, and there is no movement of associated joints
dynamic contraction: joint movements occur during this type of muscle contraction, and consist of either isotonic or isokinetic contractions
Isotonic: there is shortening (concentric action) and lengthening (eccentric action) of a muscle throughout its range of motion around a joint
Isokinetic: the speed of muscle contraction is fixed within a range of motion, and the force generated by the muscle encounters an opposing force relative to that applied to the testing device

be measured during static or dynamic muscle contractions using different types of equipment (table 1). Conversely, nonvolitional testing is effort-independent but technically demanding and not in routine clinical use. Both volitional and nonvolitional techniques of muscle strength testing have been used in COPD.

Volitional methods

Tensiometry

Cable tensiometers can be used to measure isometric muscle strength. For measuring quadriceps muscle force, a cable is strapped to the lower leg and connected to a tensiometer. When the knee is forcibly extended, increased tension on the cable leads to depression of the riser over which the cable passes. This leads to deflection of the pointer on the instrument to indicate the subject's isometric strength. This technique can measure strength at different joint angles and the equipment is light and portable. It has been used to measure quadriceps strength in COPD [13], although, at present, it

is not routinely employed in clinical practice.

One-repetition maximum

This is a form of isotonic strength measurement that measures the maximum amount of weight that can be lifted during one repetition of a standard weight-lifting exercise. It can be tested using standard gym equipment. When properly conducted, one-repetition maximum (1-RM) testing has been shown to be a reliable and safe testing tool in most subjects including those with COPD [14]. It can also be used to prescribe muscle strength training programmes and to measure changes in muscle strength after training [13, 15, 16]. When compared with other methods, 1-RM testing may have some practical advantages and may be more aligned with habitual physical tasks. However, no normative data exist for these tests and the values obtained depend on the equipment used. 1-RM testing may be contraindicated in frail elderly subjects and in those with pre-existing cardiac disease. In these patients, submaximal multiple repetition tests may be performed ►



Figure 1. Handheld dynamometer

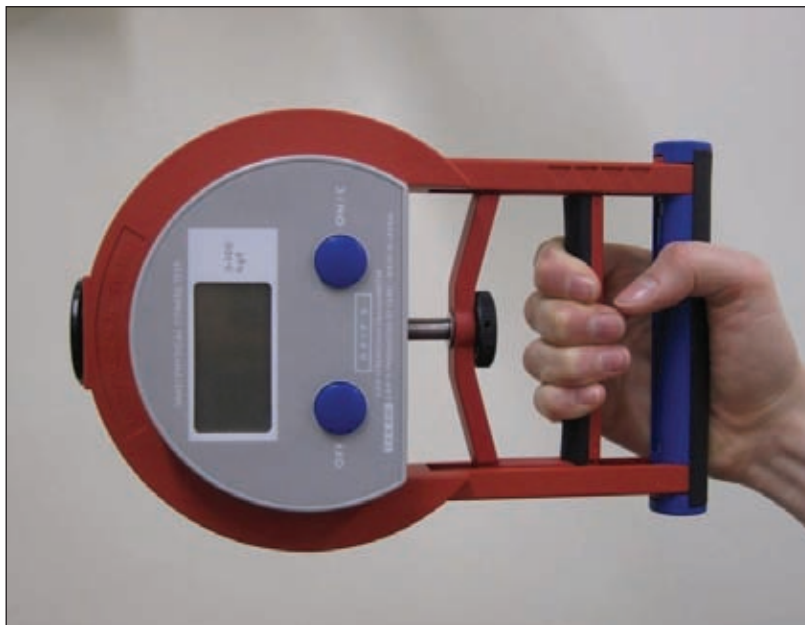


Figure 2. Handgrip dynamometer

and 1-RM can be estimated using validated equations [17].

Dynamometry

Dynamometers are used to measure isometric muscle force. Application of an external force leads to either compression of a steel spring

(mechanical dynamometer) or movement of an electronic force transducer (electronic dynamometer), to give an estimate of isometric muscle strength.

Handheld dynamometers (fig. 1) can be used to test the strength of specific upper and lower limb

muscles. As an example, for the assessment of the knee extensors, the subject is seated with hips and knees flexed at 90°, the shoulders are stabilised by an assistant, and the dynamometer is placed over the lower leg, proximal to the malleoli [18]. The force applied by the subject will give an estimate of isometric quadriceps strength. Various other muscle groups can also be tested by positioning the subject accordingly. However, in order to get reliable readings, the assessor's strength should be greater than the specific muscle group being tested [19]. Therefore, there is potential for greater operator variability with this technique. Reference values are available [18, 20, 21] and this device has been used to test peripheral muscle strength in COPD [22].

Handgrip dynamometers (fig. 2) are available to measure grip strength [23] and they have been used in several studies involving COPD patients [7, 24–26]. Reference ranges are also available for various age groups [27].

Handheld devices are portable, easy to use, and cheaper than some of the more sophisticated instruments for measuring isometric strength. However, a number of errors can occur with these measurements. These can be avoided by ensuring that subjects are positioned in a standardised manner during testing. Sufficient training in the use of these devices is also needed to minimise variability of measurements.

Computer-assisted dynamometer (isokinetic dynamometer)

This is considered to be the gold standard method for muscle strength testing. Isokinetic testing uses the force–velocity characteristics of muscle contraction and allows the measurement of maximal muscle strength over a wide range of joint positions and velocities. An isokinetic dynamometer (fig. 3) contains a



Figure 3. Isokinetic dynamometer

speed control mechanism that accelerates to a preset constant velocity with the application of force. Once a speed is attained, the device automatically adjusts to provide a force that opposes the force generated by the muscle through the range of motion. It can be used to measure isokinetic and isometric muscle strength of various muscle groups.

For example, in order to test the strength of the quadriceps using an isokinetic dynamometer (Cybex II Norm), the subject is seated in a chair with lumbar support and straps at the level of the shoulders, pelvis and thighs to minimise unnecessary movements. The padded lever arm of the dynamometer is attached with a strap to the shin of the leg to be tested, while the contralateral leg is immobilised with padded support. The chair is positioned so that the axis of rotation of the knee joint is aligned with the axis of rotation of the dynamometer. The maximal range of movement at the knee joint is set with safety stops placed at the extremes of extension and flexion. Testing can be done using various protocols. At our institution,

isometric quadriceps strength is measured during a maximal static contraction with the knee at 70°, while isokinetic strength is measured during a dynamic knee extension at 60°·s⁻¹. In addition, it is also possible to determine both peak and total work performed during a set number of repetitions. For instance, if the number of repetitions is set at 30, peak isokinetic work will be calculated as the greatest amount of work done during any single knee extension over the course of the 30 contractions. Total isokinetic work is determined as the sum of the peak work done for each of the 30 contractions.

In healthy subjects, a good correlation exists between isometric and isokinetic measurements using this device [28, 29], and reference values are also available [30, 31].

There is evidence to show that both isokinetic [16, 32] and isometric muscle strength [7, 33] are significantly lower in COPD when compared with healthy subjects.

Although isokinetic tests give accurate assessments of muscle

strength, the equipment required is expensive, not widely available and the measurements may not be related to functional ability of patients. Moreover, the clinical utility of the additional data that is provided by this method, including measures of torque and isokinetic work, remains uncertain.

Nonvolitional methods

Motivation, which is an important issue in task performance, may influence muscle strength measured by maximal voluntary contraction (MVC) manoeuvres. Other issues, such as functional ability and patient cooperation may also affect these measurements. Therefore, it is not uncommon to get submaximal muscle activation during MVC testing [34]. Nonvolitional methods of assessing muscle contractility overcome some of these limitations.

A technique using supramaximal magnetic stimulation of the femoral nerve has been developed as a nonvolitional method of assessing quadriceps strength [35]. This technique works on the principle that magnetic stimulation of the motor nerve results in a muscle twitch, and the ensuing tension or pressure generated has a constant relationship with maximal tetanic tension, or the true MVC, and, therefore, accurately reflects strength. A figure-of-eight coil is placed over the femoral nerve high in the femoral triangle and a single supramaximal magnetic stimulus is applied. This results in femoral nerve depolarisation and yields isometric twitch tension (TwQ). The procedure is independent of patient effort but may be uncomfortable, although most patients taking part in studies will accept it. Quadriceps strength using this technique has been shown to be lower in COPD patients when compared with age-matched controls [36]. In addition, a drop in TwQ following exercise has been used as an indicator of muscle fatigue [37, 38]. ▶

Nonvolitional testing is effort-independent and is particularly useful when detailed information about muscle physiology is required. Currently, its main application is in the research laboratory and further evaluation is required to establish its role as an assessment tool during pulmonary rehabilitation.

2. Muscle mass

Other than cadaver analysis, there is no true gold standard method to directly measure human muscle mass. Measures of body composition, which divide the body into different compartments depending on the method used, can be used to indirectly estimate muscle mass. Of particular interest is the fat-free mass (FFM) compartment which contains functional muscle tissue. Depletion of FFM in COPD is associated with a number of adverse outcomes. In addition, FFM depletion has been shown to occur even in patients with normal body weight [39]. Measurement of FFM, therefore, gives better functional and prognostic information compared with simple measures of body



Figure 5. Bioelectric impedance

weight. Moreover, increasing muscle mass is an important therapeutic goal for rehabilitation and nutritional support programmes, emphasising the importance of FFM measurement in COPD.

The choice of method for assessment of body composition

will depend on the purpose for which the measurement is intended, in addition to the cost and availability of equipment. Furthermore, age-specific normal ranges for FFM have not been established, making the identification of wasted patients difficult. FFM can be measured at the whole body or regional level, and the techniques that have found clinical applications in COPD are discussed.

Whole-body measurements

Skin fold anthropometry

Skin fold anthropometry (SFA) is a cheap and simple bedside method that can be used to estimate body composition in routine clinical practice. By means of special callipers (fig. 4), the thickness of the skin and underlying fat is measured at specific sites in the body, including the biceps, triceps, subscapular and suprailiac areas. The sum of the skin fold measurements at the four sites is then placed in a regression equation that has been previously validated [40], using hydro densitometry as the reference method, to give an estimate of body fat. FFM is then ►



Figure 4. Skinfold caliper

obtained by subtracting fat mass from total body weight. This technique works on the assumption that the amount of subcutaneous fat in the sites chosen for measurement is proportional to total body fat.

There are equations available to estimate regional quadriceps muscle cross-sectional area from measures of thigh circumference and skin fold thickness [41]; however, these have been developed in young men and may not accurately represent true muscle size in the elderly or in COPD patients [42].

Bioelectric impedance

Bioelectric impedance (BIA) (fig. 5) is probably the most frequently used method for measuring body composition in clinical practice. It has the advantage of being relatively inexpensive, easy to use and portable. It is based on the differential conductance of an electric current through the body compartments, with FFM, which contains all body fluids and electrolytes, being a better conductor of electricity than fat mass. With subjects in the supine position, ipsilateral self-adhesive electrodes

are attached; two at the wrist and two at the ankle. In the single frequency method, a weak alternating current of 800 μ A at 50 kHz is passed through the outer electrodes and the voltage drop across the body is measured by the inner pair of electrodes, which gives a measure of whole-body impedance. This information is then converted to a volume estimate based on the principle that the impedance (or resistance) of a conducting system (the human body, in this instance) is related to its length and cross-sectional area. This relationship is expressed as follows:

$$V=L^2/R$$

where V is volume, L is length and R is resistance. In biological systems conduction of electricity occurs predominantly through water and so V represents total body water (TBW). Since TBW lies almost entirely within FFM rather than fat mass, FFM can be estimated from the following relationship:

$$\text{FFM} \propto \text{Height}^2/R$$

Regression equations for calculating FFM by this method have been

derived for a number of different populations including patients with COPD, using a variety of reference methods for measuring body water [43, 44].

Dual energy X-ray absorptiometry

Dual energy X-ray absorptiometry (DEXA) (fig. 6) measures the differential attenuation of two low-energy X-ray beams by body tissues to provide a three-compartment model of body composition: fat mass, bone-free lean mass and bone mineral mass. Bone mass is measured directly from its X-ray absorption and soft tissue mass, at each point, is derived by subtracting bone mass from total mass. Lean and fat mass are distinguished by water content and their attenuation of X-ray beams is known from *in vitro* measurements. The subject is scanned longitudinally in the supine position using X-rays at two different energies. The differential attenuation of the X-ray beams as they pass through the body is measured and reconstructed by computer software to provide quantitative information about the three body compartments. The entire scan takes <10 min to perform and analysis of regional limb and trunk FFM can also be done.



Figure 6. Dual energy X-ray absorptiometry

DEXA has been suggested as a suitable reference method for the measurement of body composition and has been validated against deuterium dilution in COPD [45]. It can be performed quickly, involves minimal radiation exposure and also gives information about bone mineral loss. It has the added advantage of being able to provide regional FFM measurements. Although this technique assumes constant intracellular hydration of bone-free lean mass [46], changes in hydration status do not seem to affect the accuracy of measurements [47].

In COPD, significant intermethod differences have been

demonstrated for FFM measured using the various body composition techniques [48]. In a group of patients with moderate-to-severe COPD, FFM was estimated using SFA, BIA and DEXA prior to the commencement of pulmonary rehabilitation. Relative to DEXA, FFM was overestimated by SFA whereas it was underestimated by BIA. There was a systematic increase in bias with mean FFM for both DEXA *versus* BIA and DEXA *versus* SFA; although this was almost eliminated when FFM was corrected for height (FFM index (FFMI)). Moreover, the sensitivity and specificity of BIA to identify nutritional depletion was superior to SFA, when they were both compared against DEXA as the reference method. These differences need to be borne in mind when choosing a method to assess FFM in clinical practice.

It is important to note that there are a number of limitations to whole-body FFM measurements. These techniques are based on the assumption that intracellular hydration remains constant, which may not be the case in the elderly or in disease states. Therefore, the true precision of these methods remain uncertain. SFA is subject to inter-observer variability and sufficient experience is required by the operator to minimise this. Also, the inherent assumptions regarding the distribution of body fat may not hold true in COPD. Single frequency bioelectric impedance cannot reliably distinguish between extra cellular water (ECW) and intracellular water (ICW) and will therefore be affected by fluid shifts (*e.g.* oedema and diuretic therapy) [49]. In addition, it may not be sensitive enough to detect changes in FFM in response to interventions, such as resistance training [50, 51].

In the case of DEXA, the equipment is expensive and not readily accessible and, despite its ability to determine regional limb FFM, it cannot reliably measure the size of individual muscles. It is also important to note that soft tissue mass measured using DEXA scanners from different manufacturers can give different results [52].

Regional muscle mass measurements

CT and magnetic resonance imaging

These two radiographic techniques can be used to measure regional body composition and are considered to be the closest to a gold standard method for estimating human muscle mass. They can accurately measure the size and cross-sectional areas of individual muscles or muscle groups. In CT, collimated X-ray ►

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beams from an X-ray source are passed through the region of interest and the transmitted radiation is detected on the other side by an array of detectors. The difference in X-ray attenuation from different body structures is related to the physical density of tissues, and a cross-sectional image of the scanned area is generated.

Magnetic resonance imaging (MRI), on the other hand, does not involve ionising radiation and provides better contrast between fat and muscle tissue. It is based on the principle that when the human body is placed in a strong magnetic field, hydrogen atoms in water can behave like magnets and attempt to align with the external magnetic field [53]. If a radiofrequency wave is then directed at the body tissues, the atoms tend to absorb energy and change their orientation in the magnetic field. When this radio wave is then turned off, the absorbed energy is emitted and the intensity of the signal is used to measure the number of hydrogen nuclei in the tissues, which is then used to create an image.

Reduced quadriceps cross-sectional area measured by CT has been shown to be a better predictor of mortality than body mass index in COPD [11]. Recent studies, using MRI, have shown that quadriceps mass, cross-sectional area and volume are lower in COPD patients when compared with age-matched controls [42, 54]. CT and MRI have both been used to detect changes in quadriceps size in response to resistance training in COPD [55, 56]. However, it is difficult to access these techniques in routine clinical practice due to the high cost of equipment and the need for technical expertise. Moreover CT involves exposure to ionising radiation, which makes it unsuitable for repeat measurements.

Ultrasound

This noninvasive method can be used to measure thickness and cross-sectional areas of superficial muscles.

It is based on the reflection of high-frequency sound waves from tissue interfaces, which are used to construct an image. The advantage of ultrasound is that it is portable, quick to perform and involves no exposure to ionising radiation. Although ultrasound has been used extensively to measure muscle size in various populations [57], its application in COPD has so far been limited.

A recent study has shown a good correlation between quadriceps strength and ultrasound-measured cross-sectional area of the rectus femoris in COPD patients [58]. This technique can also potentially be used to quantify the muscle response to training. Nevertheless, a number of measurement errors can occur with this method as it is more operator dependent than other imaging techniques. This can be minimised by avoiding excessive tissue compression during scanning and ensuring that the probe is placed perpendicular to the long axis of the limb being measured.

3. Muscle performance during cardiopulmonary exercise testing

In COPD, resting quadriceps muscle biopsies show impaired aerobic function, as evidenced by reductions in oxidative enzymes and the proportion of type I fibres [59–61]. However, the primary role of the skeletal muscles is to maintain activity and body movements and, therefore, from a functional point of view, important information regarding muscle performance can be obtained in the context of cardiopulmonary exercise testing (fig. 7). In fact, there is evidence to show that abnormal metabolic response to exercise may contribute to impaired whole-body exercise performance in COPD [62]. The measurements of relevance will include maximal oxygen uptake ($\dot{V}O_{2,max}$), metabolic threshold, lactate and ammonia.

$\dot{V}O_{2,max}$

$\dot{V}O_{2,max}$ is the highest value for oxygen uptake that is attained

during a standard incremental exercise testing protocol and is the best available index for the assessment of aerobic capacity [63]. It usually requires the use of large muscle groups and is influenced by many factors, including age, gender, body weight and the platform used for exercise testing. Since muscle metabolism is a major determinant of oxygen uptake during exercise, abnormal muscle function is usually accompanied by a reduction in $\dot{V}O_{2,max}$. However, reduced $\dot{V}O_{2,max}$ on its own is not diagnostic for muscle dysfunction and examination of other physiological data, including cardiovascular and ventilatory responses to exercise are required to make a proper assessment. In addition, COPD patients are more likely to show abnormal cardiopulmonary responses to exercise, thus making the interpretation of muscle dysfunction difficult. Nevertheless, $\dot{V}O_{2,max}$ provides a useful index of muscle aerobic function during exercise.

Metabolic Threshold, Lactate and Ammonia

During steady state exercise at low intensities, the energy for muscle contraction is provided predominantly from aerobic (oxygen dependent) sources. However, as intensity increases, anaerobic (oxygen independent) energy provision rises. In exercise testing terms, the metabolic or anaerobic threshold is defined as the point at which anaerobic metabolism becomes sufficient to cause lactate to appear in the blood. Exercise above the metabolic threshold cannot be sustained because the accumulation of lactate results in a metabolic acidosis and is an important cause of muscle fatigue. Although the transition from a predominantly aerobic to a predominantly anaerobic mode of exercise is not an abrupt process within the muscle, the metabolic threshold can usually be identified either directly, from measurement



Figure 7. Cardiopulmonary exercise testing

of blood lactate, or noninvasively, from gas exchange measurements during incremental exercise testing.

The metabolic threshold is interpreted in relation to the predicted $\dot{V}O_{2,max}$ and normally occurs at ~50–70% of $\dot{V}O_{2,max}$. Physical deconditioning and muscle abnormalities can result in low metabolic thresholds relative to $\dot{V}O_{2,max}$, while it is increased with physical training. As with $\dot{V}O_{2,max}$, metabolic threshold and lactate on their own cannot be used to diagnose muscle disease but have to be interpreted in conjunction with other variables

obtained during cardiopulmonary exercise testing. In COPD, an early rise in lactate and/or a premature metabolic threshold may be seen as a result of deconditioning although some patients may be unable to exercise sufficiently to reach the metabolic threshold if severe ventilatory limitation or lack of motivation is present.

A rise in ammonia levels during exercise is an indicator of the efficiency of energy provision during muscular contraction and has been associated with fatigue in healthy subjects. It has also been used to assess the skeletal muscle metabolic response to exercise in

COPD but its role in the wider assessment of skeletal muscle function in clinical practice remains uncertain [64]. ^{31}P -magnetic resonance spectroscopy (^{31}P -MRS) is another technique that can provide useful information about skeletal muscle metabolic function during exercise. This technique can provide information about energy metabolism but remains mainly a research tool.

CONCLUSION

Skeletal muscle dysfunction is an important extra-pulmonary manifestation of COPD that adversely affects exercise capacity, quality of life and prognosis. Muscle function can be improved by interventions such as physical training. Measurement of peripheral muscle function is becoming an important tool in the clinical assessment of disability and for monitoring response to therapeutic interventions. A number of techniques are available for assessing various aspects of muscle function. The choice of method will depend on the purpose for which the measurement is intended, in addition to the availability and cost of equipment. ■

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