Sonographic Measurement of the Quadriceps Muscle in Patients With Chronic Obstructive Pulmonary Disease

Functional and Clinical Implications

Carlos Cruz-Montecinos, PT, MSc, Carlos Guajardo-Rojas, PT, Eloísa Montt, PT, Felipe Contreras-Briceño, PT, MSc, Rodrigo Torres-Castro, PT, MSc, Orlando Díaz, MD, Antonio Cuesta-Vargas, PhD

Objectives—The purpose of this study was to determine the association between functionality as assessed by the 6-minute walking test (6MWT), maximal voluntary contraction of the quadriceps (MVCQ), and quadriceps thickness and echo intensity as measured by sonography, in patients with chronic obstructive pulmonary disease (COPD).

Methods—Maximal voluntary contraction of the quadriceps and the thickness and echo intensity of the rectus femoris and vastus intermedius were evaluated in 20 patients with COPD. Functionality was assessed by the 6MWT. Differences between the evaluated muscles were determined by the Student *t* test. Pearson and Spearman rank correlation coefficients were used to analyze relationships between variables of interest, according to data characteristics. Finally, multivariate regression models were applied.

Results—There was a positive correlation between MVCQ and rectus femoris and vastus intermedius thickness ($r = 0.427$; $P = .030$; $r = 0.469$; $P = .018$, respectively) and a negative correlation between MVCQ and rectus femoris and vastus intermedius echo intensity ($r = -0.500$; $P = .012$; $r = -0.482$; $P = .016$). No correlation was found between MVCQ and the 6MWT ($r = 0.319$; $P = .085$). Multivariate regression analysis showed that the rectus femoris echo intensity, vastus intermedius echo intensity, and vastus intermedius thickness explained 70% of the variance in the distance walked during the 6MWT.

Conclusions—These results indicate that, in patients with COPD, both quadriceps force and exercise capacity are associated with quantitative (thickness) and qualitative (echo intensity) characteristics of the quadriceps. Consequently, comprehensive assessments of peripheral muscles should simultaneously include both measurements.

Key Words—chronic obstructive pulmonary disease; echo intensity; musculoskeletal ultrasound; quadriceps; rectus femoris; sonography; vastus intermedius

The 6-minute walking test (6MWT) provides key functional indicators in patients with chronic obstructive pulmonary disease (COPD).[1,2] Moreover, this test is widely used to evaluate functional changes during pulmonary rehabilitation programs.[3] The functionality of the 6MWT in patients with COPD stems from its technical simplicity and ability to determine performance not only in terms of respiratory compromise but also in relation to extrapulmonary and psychological factors.[1] Of the extrapulmonary factors, recent studies associated the distance walked during the 6MWT with the strength[4] and thickness of the quadriceps muscle.[5,6]

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Address correspondence to Antonio Cuesta-Vargas, PhD, Department of Physiotherapy, School of Health Sciences, University of Malaga, Avenida Arquitecto Peñalosa, 29009 Malaga, Spain.

E-mail: acuesta@uma.es

Abbreviations

COPD, chronic obstructive pulmonary disease; CT, computed tomography; ICC, intraclass correlation coefficient; MRI, magnetic resonance imaging; MVCQ, maximal voluntary contraction of the quadriceps; ROI, region of interest; 6MWT, 6-minute walking test

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Current evidence indicates that decreased muscular strength and mass in the lower limbs significantly increases morbidity, mortality, and health care costs.[7–9] In noncachectic patients with COPD and a low body mass index, maximal voluntary contraction of the quadriceps (MVCQ) is 30% lower compared to healthy individuals.[7,9,10] Furthermore, change to MVCQ has a stronger prognostic value than age, body mass index, and forced expiratory volume in 1 second,[10] which are variables commonly used in the everyday clinical care of patients with COPD.

Several studies have previously shown direct associations between strength, thickness, and the cross-sectional area of the quadriceps in healthy individuals and patients with COPD.[11,12] Furthermore, patients with COPD have a significantly smaller muscle size and greater lipid infiltration in the knee extensors and plantar flexors compared to healthy individuals.[13]

The muscle mass of the quadriceps can be measured by a number of imaging techniques, such as computed tomography (CT),[14] magnetic resonance imaging (MRI),[15] and sonography.[11,14,16] In patients with COPD, MRI and CT can show changes in the muscle mass of lower limbs after a period of exercise.[7,16] Likewise, CT shows a high correlation between muscle thickness and the distance walked during the 6MWT.[5,6] Although CT is useful for evaluating the progression of muscular dysfunction in patients with COPD,[5] routine clinical use is limited because of economic costs.

One tool that provides a noninvasive, quick, and effective assessment of muscle quality is sonography.[11,17,18] It has been used in different studies to evaluate muscle quality in the elderly population.[19,20] Quantitative (thickness) and qualitative (echo intensity) aspects are taken into account when assessing muscle characteristics with sonography.[11,12,20,21] The echo intensity is obtained by a grayscale analysis of the muscle and reports the intramuscular amount of fat and fibrous tissue.[22,23] As supported by MRI results, there is a good correlation between the echo intensity and amount of intramuscular fat.[24] A recent study also described suitable consistency between rectus femoris measurements obtained by sonography and fat content as evaluated by dual-energy x-ray densitometry,[25] which is the reference standard for evaluating lean mass.[26]

Studies using MRI show that fat infiltration in the quadriceps is 74% greater in patients with COPD than in healthy individuals,[13] and this infiltration is inversely related to functionality, as determined by the 6MWT.[13] Although different imaging techniques have been used to evaluate muscle quality in patients with COPD, such as CT[14] and MRI,[13] little attention has been given to the usefulness of sonographic assessments in patients with COPD and the relationship of sonographic data with functionality. Therefore, the objective of this study was to examine the association between exercise capacity, as evaluated by the 6MWT, quadriceps strength, and muscle characteristics (ie, thickness and echo intensity) obtained by sonography in patients with COPD. We hypothesized that the strength of and ability to perform exercise in the quadriceps would concomitantly depend on quantitative (thickness) and qualitative (echo intensity) muscle characteristics as evaluated by sonography.

Materials and Methods

Study Design and Population

The study group was selected by convenience sampling from a group of 24 patients recruited for a pulmonary rehabilitation program. All patients had a diagnosis of COPD, defined as a postbronchodilator 1-second forced expiratory volume-to-forced vital capacity ratio of less than 0.7.[27] Inclusion criteria were age of 45 years or older, smoking for 20 pack-years or longer, and no history of chronic lung diseases other than COPD. Exclusion criteria were use of supplemental oxygen, extreme obesity (body mass index >40 kg/m^2), history of severe or unstable chronic heart failure, cardiac arrhythmia, pulmonary hypertension, severe chronic renal failure, liver disease, and other comorbidities that would prevent patients from completing a 6MWT (eg, peripheral vascular disease, neuromuscular compromise after a stroke, and severe arthritis/arthrosis). Additional exclusion criteria included the use of β-blockers, angiotensin-converting enzyme inhibitors, or diuretics.[27] Of the 24 patients, 4 were ultimately eliminated from the sample group because of supplemental oxygen use (n = 2) and extreme obesity (n = 2). Ethical approval was obtained from the Northern Metropolitan Health Service of Santiago, Chile, and informed consent was required from each participant.

Measurements

Pulmonary Function

Patients completed spirometry tests before and after the administration of 400 μg of albuterol (a β_2 agonist bronchodilator), according to international guidelines.[28] Spirometric measurements were standardized as percentages of the predicted values by using established Chilean prediction equations.[29]

Quadriceps Strength

Isometric MVCQ was evaluated by an FMON-1 analog-to-digital load cell (ArtOficio, Santiago, Chile) at a resolution of 0.25 N and sampling frequency of 500 Hz. The load cell was connected near the ankle of the patient with a rigid strap. Measurements were taken with the patient sitting, with the hips and knees at 90°. To familiarize patients with the measurement process, 3 submaximal tests were initially performed. The best of the 3 tests was selected for posterior analyses. Maximal voluntary contraction of the quadriceps was expressed in terms of torque (newton meters), as calculated from the force through a lever arm. This type of evaluation is highly reliable, with intraclass correlation coefficients (ICCs) of 0.92 to 0.95.[12,30]

Muscle Mass Assessment

Muscle mass assessments were performed by a physical therapist with more than 5 years of experience in sonographic measurements and sonogram analysis. The tissue thickness of the anterior compartment of the right thigh was measured by B-mode sonography. Transverse images were obtained with a B-mode ultrasound device (SonoSite 180 Plus; SonoSite Japan, Tokyo, Japan) and a linear transducer (5–10 MHz). Measurements were taken with the patient in a supine, semi-Fowler position with the knees completely extended. The transducer was placed perpendicular to the axis of the limb (Figure 1) and was located two-thirds of the way between the anterior superior iliac spine and the lateral condyle of the knee. Coupling gel was abundantly applied to minimize distortion generated by underlying tissues. Shaving was not needed. The thickness of the rectus femoris and of the vastus intermedius were measured (Figure 2A). This measurement has high intra-rater and inter-rater reliability, with ICCs of 0.98 and 0.95, respectively.[31]

Muscle Quality Assessment

For recording the echo intensity of the rectus femoris and vastus intermedius, a computational code was implemented with MATLAB 2014 (The MathWorks, Inc, Natick, MA). This code contained the following 3 steps: (1) determining a region of interest (ROI) representing two-thirds of the visible thickness and width of the muscle, where the ROI size was determined in proportion to the muscle thickness for each patient; (2) locating the ROI within the muscle (Figure 2B) without including fascial tissue; and (3) determining the average grayscale value by histogram analysis (Figure 3). This type of evaluation has a high test-retest reliability score (0.963).[20] To measure the grayscale image of the ROI, tones varied from 0 (black) to 255 (white), where a higher value represented a greater amount of infiltrated fat in the muscle.

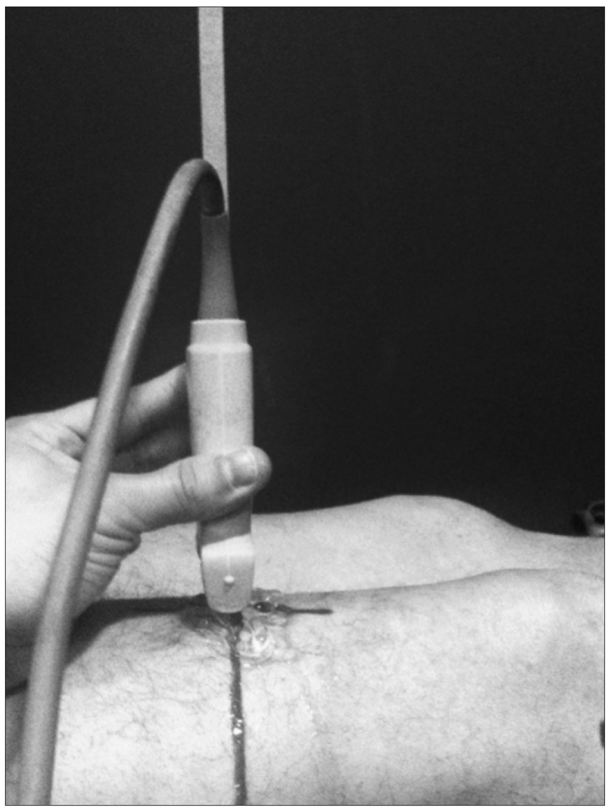
Six-Minute Walking Test

The 6MWT was performed according to recommendations by the American Thoracic Society.[32] The patients were asked to walk at maximum speed down a 30-m-long hallway, covering the most distance possible in 6 minutes without running. The distance walked was expressed as an absolute value and as a percentage of the reference value.[33]

Statistical Analysis

Values are shown as mean ± standard deviation or median and interquartile range according to the distribution. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to check for a normal distribution. To determine whether differences existed between the evaluated muscles, a Student *t* test was used. To assess the reliability of the sonographic variables, the ICC was calculated for 10 patients after 3 consecutive measurements. One evaluator

Figure 1. Perpendicular location of the transducer, two-thirds of the way between the superior anterior iliac spine and the lateral condyle of the knee.



performed all measurements, which included image acquisition and subsequent analysis. To analyze correlations between variables of interest, the Pearson and Spearman correlation indices were used according to data characteristics. Finally, a multivariate analysis was applied using forward selection to evaluate the sonographic variables that would best predict the distance walked during the 6MWT. The sample size was calculated by assuming a correlation coefficient between both the strength and cross-sectional area of the quadriceps and the 6MWT of about $r = 0.60$.[5,34] This calculation determined the inclusion of at least 18 patients for $P = .05$ and $\beta = 0.20$. Statistical significance was established at $P < .05$.

Figure 2. **A**, Muscular thickness of the rectus femoris (RF) and vastus intermedius (VI). **B**, Selected ROI in the rectus femoris and vastus intermedius.

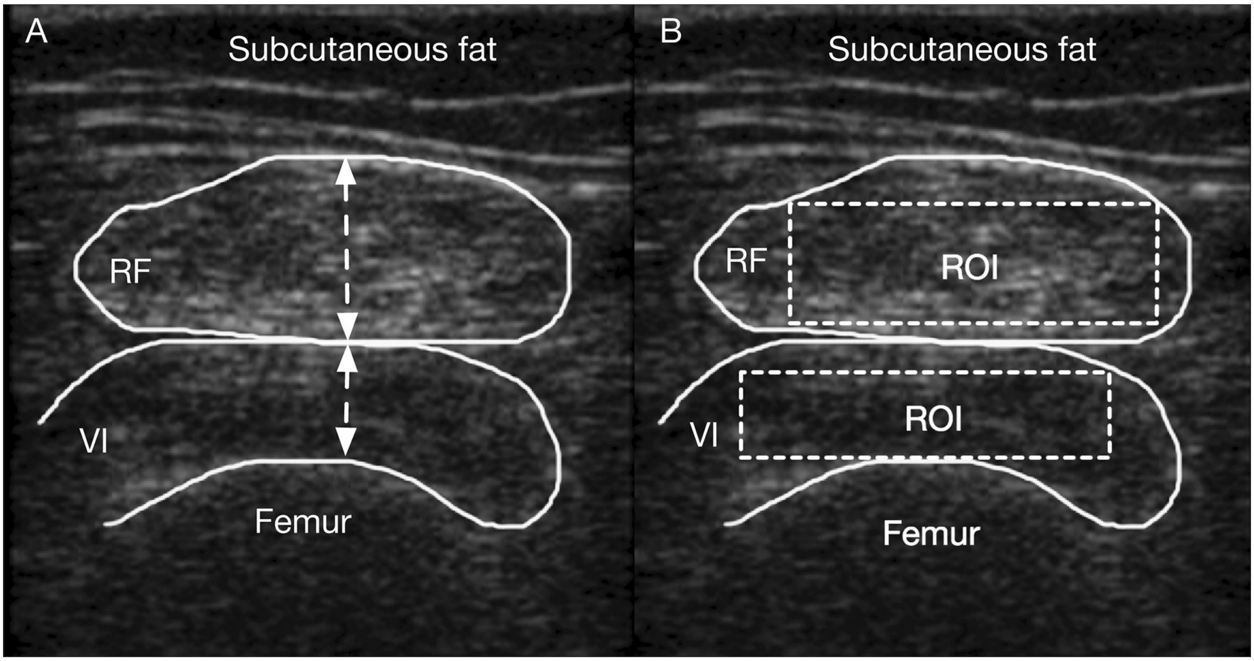
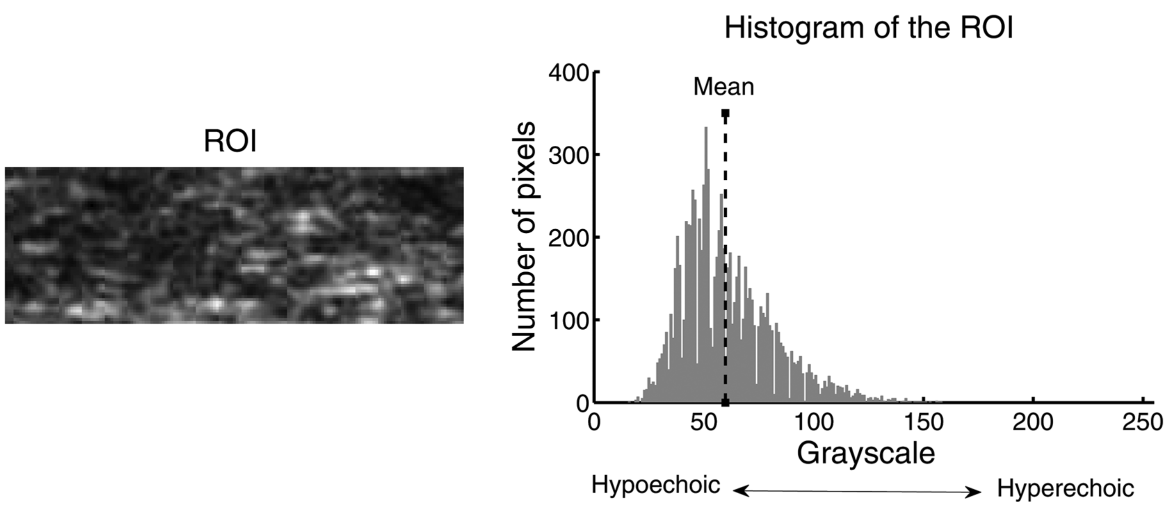


Figure 3. Grayscale analysis of the selected ROI (0, black; 255, white).



Results

Clinical Characteristics

The characteristics of the 20 patients with COPD evaluated in this study are presented in Table 1. According to the Global Initiative for Chronic Obstructive Lung Disease, 7 patients had mild COPD; 8, moderate; 3, severe; and 2, very severe disease.

Quadriceps Strength, Muscle Mass, Muscle Quality, and Exercise Capacity

The mean MVCQ was 48.82 ± 18.22 N-m. Intrasubject reliability was high for sonographic measurements of thickness and echo intensity, with an ICC of greater than 0.95 for all data. There was a significant difference between rectus femoris and vastus intermedius thickness (1.20 ± 0.24 versus 1.01 ± 0.28 cm, respectively; P = .003) as well as between rectus femoris and vastus intermedius echo intensity (51.91 ± 9.54 versus 46.18 ± 9.34; P = .048).

Relationship Between Quantitative and Qualitative Characteristics of the Quadriceps

Elevated MVCQ values of were associated with greater rectus femoris and vastus intermedius thickness (r = 0.427; P = .030; r = 0.469; P = .018, respectively) as well as decreased rectus femoris and vastus intermedius echo intensity (r = –0.500; P = .012; r = –0.482; P = .016). The 6MWT showed a strong association with vastus intermedius thickness (r = 0.701; P = .001) and echo intensity (r = –0.762; P = .001), but there was no significant correlation with rectus femoris thickness (r = 0.377; P = .051), rectus femoris echo intensity (r = 0.100; P = .337), or MVCQ (r = 0.319; P = .085).

Table 1. Characteristics of Patients With COPD

Characteristic	Value
Age, y	70 ± 7[a]
Male/female, n	11/9
Forced expiratory volume in 1 s, L	0.91 ± 0.30
Predicted forced expiratory volume, %	45 ± 10[a]
Forced vital capacity, L	1.65 ± 0.61[a]
Predicted forced vital capacity, %	65 ± 20
Forced expiratory volume/vital capacity %	56 ± 15[a]
6MWT, m	369 ± 90[a]
Predicted 6MWT, %	71 ± 24[a]
Body mass index, kg/m^2	31.4 ± 4.8[a]
Saint George Respiratory Questionnaire score	54.5 ± 13[a]
Medical Research Council dyspnea score	2

Values are expressed as the mean ± SD where applicable.
[a]Normal distribution.

Analysis of the regression model including vastus intermedius thickness, vastus intermedius echo intensity, rectus femoris thickness, and rectus femoris echo intensity as explanatory variables showed all to be independent determinants of the distance walked, except for rectus femoris thickness (P = .250). Thus, a model constructed with vastus intermedius thickness, vastus intermedius echo intensity, and rectus femoris echo intensity explained 70% of the variance of the distance walked (Table 2 and Figure 4). Including MVCQ values did not modify the predictive value of the model. Similar results were obtained when using the absolute and reference values of the 6MWT.

Discussion

The main finding of this study is that, in patients with COPD, simultaneous assessments of qualitative and quantitative characteristics of the quadriceps most accurately predict muscle performance. In effect, quadriceps strength was directly associated with rectus femoris and vastus intermedius thickness and inversely associated with rectus femoris and vastus intermedius echo intensity, whereas the 6MWT was directly and closely related to vastus intermedius thickness and negatively affected by vastus intermedius echo intensity. Finally, quadriceps strength did not show a relationship with the 6MWT.

The echo intensities of the selected variables were negatively associated with MVCQ, which is in line with observations by other authors.[20] With regard to quadriceps thickness as measured by sonography, some authors have observed a correlation in healthy individuals between electrical activity, measured via surface electromyography, and rectus femoris thickness (r = 0.68).[35] However, other authors have found the vastus intermedius to be a better predictor of maximum force,[36] as in this study. Moreover, during submaximal contraction, 50% of total knee extension movement is explained by vastus intermedius activity.[37] It has also been reported that vastus intermedius fascicles

Table 2. Summary of Models A, B, and C

Model	r	R^2	Adjusted R^2	SE	F	P
A	0.762	0.581	0.558	68.19	24.94	<.001
B	0.822	0.676	0.637	61.73	17.70	<.001
C	0.868	0.754	0.708	55.43	16.32	<.001

Model A included the variable vastus intermedius echo intensity; model B included the variables vastus intermedius echo intensity and vastus intermedius thickness; and model C included the variables vastus intermedius echo intensity, vastus intermedius thickness, and rectus femoris echo intensity.

change independently of the knee joint angle, which could influence force production at different joint angles.[38] These characteristics would help explain the close relationships observed between functionality, thickness, and vastus intermedius echo intensity in this study.

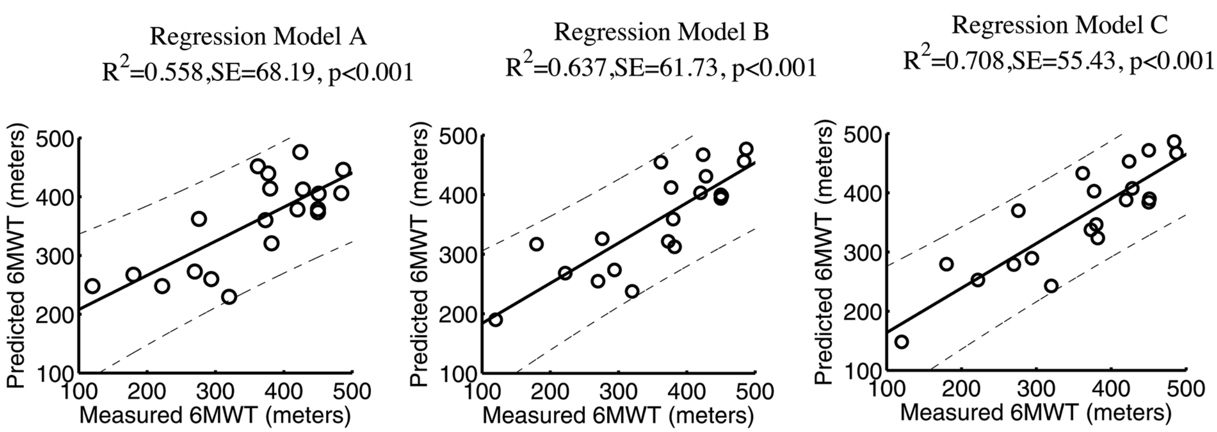
Incorporating a regression model based on vastus intermedius echo intensity, rectus femoris echo intensity, and vastus intermedius thickness explained 70% of the variance of the 6MWT ($P < .001$). These results support previous studies that found a positive relationship ($r = 0.62$) between the cross-sectional area of the quadriceps, evaluated by CT, and the distance walked during the 6MWT.[5] These data also substantiate the strong negative correlation ($r = -0.722$) observed between the amount of MRI-measured intramuscular fat[13] and the distance walked during the 6MWT.

No significant associations were observed between rectus femoris thickness, MVCQ, and the 6MWT, although the *P* values were very close to reaching statistical significance. The determined associations and regression model also could have been influenced by the sample size, particularly for rectus femoris thickness. On the other hand, previous studies assessing the relationships between MVCQ and the 6MWT have produced conflicting results.[39] Some, which agreed with our findings, failed to show a relationship between MVCQ and the 6MWT in patients with moderate to severe COPD,[39] but other studies reported a relationship between these variables.[4,34] These divergent results may be explained by a type II error in studies that did not find an association, such as this study. Additionally, this study mainly included patients with mild to moderate COPD, which differed from the COPD severity in other cohorts.[4] Apart from these statistical considerations, thickness measurements could be influenced by intramuscular edema, in which concomitant muscle atrophy[40] and edema may lead to spurious interpretations. Further studies are needed to corroborate this assumption.

In terms of methodology, it is important to mention that the echo intensity analysis focused on an ROI that included two-thirds of the muscle thickness respective to each patient to incorporate the most muscle tissue possible, excluding the fascia and surrounding bone (Figure 2B). This method has previously shown excellent test-retest reliability (0.963), with an average coefficient of variation of 4.2%,[20] which is in agreement with our results. Although other authors have used grayscale analysis methodologies, these normally encompass a smaller ROI.[36] In contrast, this study used a methodology encompassing the entire muscle, thereby facilitating the designation of the ROI in the muscle. Based on a small 64 × 64-pixel ROI, there was a coefficient of variation of 14% between 3 ROIs in the rectus femoris as well as the vastus intermedius. Furthermore, grayscale measurements can be modified if the ultrasound transducer is not perpendicular to the segment being evaluated, since the angle of the instrument can change the echo intensity of the measurement.[41]

With regard to clinical implications, muscle dysfunction has been specifically recognized as an important factor in reduced physical activity, with a consequent impact on the quality of life, morbidity, and mortality of patients with COPD.[9] The infiltration of intramuscular fat is a key component to consider, not only because of altered force as a result of the metabolites and cytokines derived from adipose tissue[34,42] but also because of the concomitant impacts on functionality.[13,34] Therefore, assessment of peripheral muscles should be considered a crucial component in the evaluation of patients with COPD, particularly because muscle dysfunction could be treated to optimize the functional capacities of patients.[16]

Figure 4. Linear regression models.



For the clinical application of echo intensity analysis in patients with COPD, it is important to consider that this method can be influenced by ultrasound system settings. It is therefore critical to maintain the same ultrasound system parameters during all measurements. Moreover, some methodological limitations need to be considered. In particular, muscle fat infiltration, fibrous tissue, and edema can all increase echo intensity,[22,43] thus affecting echo intensity analysis in these conditions. To overcome this limitation, a model has been proposed for detecting collagen content in the extracellular matrix by brightness anlysis.[44] Another possible solution is to statistically analyze the texture features of the ROI based on spatial pixel intensity variation.[45] This method can even differentiate between sex and muscle types.[45] However, further clinical studies are needed to improve the development of these methods in patients with COPD.

Despite the fact that various studies have tried to explain the causes and physiopathologic mechanisms of the muscle weakness associated with COPD,[9] there is little information relating function with muscle atrophy.[5,13] The findings of this study are clinically relevant, especially when considering that the 6MWT can predict both patient functionality and mortality.[2,3] Due to this factor, incorporating additional tools, such as sonography, could be useful in evaluating the quality of peripheral muscles in patients with COPD. Importantly, previous studies have reported that assessing muscle thickness with sonography requires training,[46] which will need to be considered when training pulmonary rehabilitation teams.

In consideration of the strong relationships reported here between qualitative and quantitative muscle characteristics and both muscle strength and the 6MWT, we think that a larger sample would probably not affect the main conclusions of this study. However, because of sampling methodology, care should be taken in extrapolating these results to the entire population of patients with COPD.

Regarding the variables obtained by sonography, this study only analyzed the quadriceps, but other muscle groups could be assessed in future investigations. Considering that poor 6MWT results in patients with COPD also include pulmonary and nonpulmonary factors,[1] muscle sonography could be incorporated into assessments of electrophysiologic variables, such as muscle fatigue, or variables regarding breathing and cardiac function, which could provide an integral view for treatment and rehabilitation.

In conclusion, sonographic quadriceps analysis in patients with COPD is a simple and reproducible method for clinical assessment. Our results indicate that quadriceps strength and exercise capacity are associated with quantitative (thickness) and qualitative (echo intensity) characteristics in the muscles of patients with COPD. Future studies should place greater focus on image-processing analysis to achieve better interpretations of muscle function.

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