The added value of ultrasound muscle measurements in patients with COPD

Nijholt, Willemke; ter Beek, Lies; Hobbelen, Johannes S. M.; van der Vaart, Hester; Wempe, Johan B.; van der Schans, Cees P.; Jager-Wittenaar, Harriet

Published in:
Clinical Nutrition ESPEN

DOI:
10.1016/j.clnesp.2019.01.001

Clinical Nutrition ESPEN 30 (2019) 152–158

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

The added value of ultrasound muscle measurements in patients with COPD: An exploratory study

Willemke Nijholt [a, b, *], Lies ter Beek [a, c], Johannes S.M. Hobbelen [a, d], Hester van der Vaart [c], Johan B. Wempe [c], Cees P. van der Schans [a, b, e], Harriët Jager-Wittenaar [a, f]

[a] Hanze University of Applied Sciences, Research Group Healthy Ageing, Allied Health Care and Nursing, Groningen, the Netherlands
[b] University of Groningen, University Medical Center Groningen, Department of Rehabilitation Medicine, Groningen, the Netherlands
[c] University of Groningen, University Medical Center Groningen, Department of Pulmonary Diseases and Tuberculosis, Center for Rehabilitation, Haren, Groningen, the Netherlands
[d] University of Groningen, University Medical Center Groningen, Department of General Practice and Elderly Care Medicine, Groningen, the Netherlands
[e] University of Groningen, University Medical Center Groningen, Health Psychology Research, Groningen, the Netherlands
[f] University of Groningen, University Medical Center Groningen, Department of Maxillofacial Surgery, Groningen, the Netherlands

ARTICLE INFO

Article history:
Received 9 April 2018
Accepted 3 January 2019

Keywords:
Ultrasonography
Skeletal muscle
Muscle strength
Muscle function
COPD

SUMMARY

Background and aims: Malnutrition and sarcopenia are common nutrition (-related) disorders in patients with COPD and are associated with negative health outcomes and mortality. This study aims to correlate ultrasound measured rectus femoris size with fat-free mass and muscle function in patients with COPD.
Methods: Patients with COPD, at the start of a pulmonary rehabilitation program, were asked to participate in this study. Rectus femoris (RF) size (thickness in cm, cross-sectional area [CSA] in cm^2) was determined by ultrasound. Fat-free mass index (FFMI in kg/m^2) was estimated with bioelectrical impedance analyses, using a disease-specific equation. Handgrip strength (HGS) was measured in kilograms and the five times sit to stand test (in seconds, higher scores indicating decreased strength) was performed to assess leg muscle power. The Incremental Shuttle Walk Test (ISWT, in m) was used to assess maximal exercise capacity.
Results: In total, 44 patients with COPD (mean age 59.8 ± 8.6 years, 43% male, median FEV1%pred 37 [IQR = 23–52]) were included. Greater RF-CSA and thickness were associated with higher FFMI ($r = 0.57$, $p < 0.001$; $r = 0.53$, $p = 0.003$, respectively) and HGS (CSA $r = 0.58$, $p < 0.001$, thickness $r = 0.48$, $p = 0.009$). No significant correlations between RF-thickness, CSA, and leg muscle power were found ($r = -0.33$, $p = 0.091$; $r = -0.35$, $p = 0.073$, respectively). Furthermore, no correlation between RF size and maximal exercise capacity was observed (thickness $r = 0.21$, $p = 0.297$, CSA $r = 0.22$, $p = 0.274$).
Conclusions: This exploratory study shows that in patients with COPD, rectus femoris size is moderately correlated with FFMI and HGS. Future studies should focus on the role of ultrasound in evaluating nutritional status.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a complex disease, involving more than airflow limitation [1–3]. The disease burden is largely determined by extra-pulmonary impediments, such as impaired muscle function. Loss of muscle mass and impaired muscle function are key characteristics of both malnutrition and sarcopenia [4,5]. In patients with COPD, both malnutrition and sarcopenia are highly prevalent, with estimates ranging from 11% to 62% for malnutrition [6–9], and from 9% to 35% for sarcopenia [2,9–11]. In this population, in particular the assessment of lower extremity muscle mass has become of interest, since

* Corresponding author. Hanze University of Applied Sciences, Research Group Healthy Ageing, Allied Health Care and Nursing, Petrus Driessenstraat 3, 9714 CA, Groningen, the Netherlands.
E-mail address: w.nijholt@pl.hanze.nl (W. Nijholt).

https://doi.org/10.1016/j.clnesp.2019.01.001

depletion of lower extremity muscle mass is associated with poorer physical function [12,13].

Methods used for the assessment of lower extremity muscle mass are, for example, dual-energy absorptiometry (DXA) and segmental bioelectrical impedance analysis (BIA). DXA is a valid and reliable method, however, high costs and limited access to the equipment may preclude its use in clinical practice [14]. BIA, on the other hand, is a reliable method, but its validity is limited and strongly relies on the type of equation that is used [15,16]. Alternatively, ultrasound is a valid and reliable method that facilitates quantification of peripheral muscles [17,18]. In general, little is known about the relationship between peripheral muscle size and (whole body) muscle mass, but also about the association between muscle size and muscle function. A few studies in patients with COPD, have shown that ultrasound measured rectus femoris size is moderately related to fat-free mass [19,20], and muscle function, e.g., quadriceps strength [19–22], and physical performance [21,22]. However, the measurement methods used for the assessment of muscle function in these studies are not used in clinical practice. In clinical practice, handgrip strength, the five times sit to stand test, and the Incremental Shuttle Walk Test (ISWT) are commonly used for the assessment of muscle function [23,24]. To the best of our knowledge, no studies have focused on the relationship between ultrasound measured muscle size and these tools used in daily practice for the assessment of muscle function. Therefore, this study aims to study the relationship between ultrasound measured muscle size and fat-free mass and muscle function in patients with COPD.

2. Materials and methods

2.1. Design and setting

This study was part of a larger observational study on disease-related malnutrition, frailty, and disability in patients with COPD. For this study, data collected between March 2015 and January 2017 were used. Recruitment, written informed consent, and study procedures were approved by the Medical Ethical Committee of the University Medical Center Groningen (reference 2014/432). This study was registered in the Dutch Trial register (NTR5107).

2.2. Population

Adult patients with COPD starting a pulmonary rehabilitation program of nine weeks were recruited from the University Medical Center Groningen, Center for Rehabilitation. Participants were included if they were aged 40 years and older, were able to understand and speak the Dutch language, were diagnosed with COPD by a pulmonary physician, if they were attending the full rehabilitation program, and were not wheelchair bound. Participants with a pacemaker, undergoing palliative treatment, or having skin problems, or with any contra-indication for physical activities or severe cognitive disabilities were excluded from participation in the study.

2.3. Measurements

2.3.1. Ultrasound

Ultrasound measurements were performed by two dietitians and one undergraduate dietitian, who were trained in muscle ultrasound. Portable B-mode ultrasound (Philips, VISIQ) with a 5.0 MHz curved-array transducer was applied to obtain transverse images of the rectus femoris. All measurements were performed on the right leg, with the participant in a supine position. During the measurements, the participants were instructed to relax their leg muscles. Measurements were taken at half point of length between epicondylus lateralis and trochanter major of the femur. Minimal transducer pressure was applied to avoid compression of the muscle. Two independent ultrasonographers subsequently analyzed the ultrasound images. Rectus femoris size was assessed in two ways: thickness (in cm) and cross-sectional area (CSA, in cm^2). The measurements were performed from the frozen ultrasound on-screen images using the inbuilt software. Rectus femoris thickness was defined as the distance between the superficial and the deep aponeurosis. For the assessment of the CSA, the fascial borders of the rectus femoris were identified and an automatic ellipse/-region of interest was used. The mean value of three consecutive measurements of rectus femoris thickness and CSA was recorded.

2.3.2. FFM

Fat-free mass was measured using multi-frequency BIA (Quadscan 4000,Bodystat) [25]. FFM was estimated using the disease-specific Rutten equation [26]:

1. FFM (kg) = −11.81 + 0.245 x weight + 0.298 x height [2]/ impedance + 0.148 x height + 5.248 x gender (1 for male, 0 for female)
2. Fat-free mass index (FFMI) (kg/m^2) = total fat free mass/height [2].

2.3.3. Muscle function

2.3.3.1. Handgrip strength. Handgrip strength was determined with a JAMAR handheld dynamometer. Measurements were performed three times per side. The best performance of either the right-hand or the left-hand side was used and defined as the maximum handgrip strength in kilograms [27].

2.3.3.2. Leg muscle power. The five times sit to stand test was used to determine leg muscle power (seconds) [28]. Participants were asked to stand up five times from a height-adjustable chair without armrests as fast as possible, without using the arms for support. During the test, the participants were asked to cross their arms across their chest. The five times sit to stand test was completed after the participants' final stand-up. Leg muscle power was measured as the amount of time taken to rise from the chair and was expressed in seconds, with higher scores indicating decreased power.

2.3.3.3. Maximal exercise capacity. The Incremental Shuttle Walk Test (ISWT) was used to measure maximal exercise capacity (meters) [29]. Participants were instructed to walk a 10 m course for as long as possible. The walking speed was progressively increased and was externally controlled with acoustic signals. Participants had to reach the end of the course in time before the audio signal. The test was ended if they failed to do so, or when they indicated they were exhausted. Maximal exercise capacity was expressed in meters.

2.4. Statistical analyses

The Shapiro–Wilk test was used to evaluate data for normal distribution. Categorical variables were expressed as relative frequencies and continuous variables were presented as the means ± standard deviations (SD) or median and interquartile range (IQR) for non-normally distributed variables. Correlations were tested using Pearson coefficients (normally distributed data) or Spearmans rho (not-normally distributed data). For the ultrasound measurements, the inter-rater *measurement reliability*, i.e., reliability of solely the analyses of the ultrasound images, was determined by Intra-class Correlation Coefficients (ICC) and Bland-Altman plots. Rater 1 had more than four years, and Rater 2 had one year experience in muscle ultrasound. Excellent agreement between the raters is defined as an ICC score of ≥0.81 [30]. In case of excellent agreement, the measurements of Rater 1 were used for further analyses. All statistical analyses were performed using the Statistical Package for Social Sciences version 23.0 (SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at $p < 0.05$.

3. Results

Of the 84 patients who agreed to participate in the larger observational study and met the inclusion criteria, ultrasound was performed in 44 patients (Table 1). The mean age of the study population was 60.2 ± 9.0 years of which 19 (43%) were men, and the median FEV_1 was 0.96 L (IQR = 0.80–1.49). No participants were classified as GOLD stage I, 34% were classified as GOLD stage II, 34% as GOLD stage III and 32% as GOLD stage IV.

Ultrasound measured rectus femoris thickness (ICC = 0.94, 95% CI: 0.91–0.94) and CSA (ICC = 0.87, 95% CI:0.73–0.94), showed excellent inter-rater measurement reliability. Bland–Altman analysis demonstrated a small systematic error of 0.11 cm between the observers and 0.09 cm^2 for measuring muscle thickness and muscle CSA, respectively (Fig. 1).

Of the 44 patients with available ultrasound images, 30 ultrasound images (68%) were used for the analysis. Fourteen ultrasound images could not be interpreted, because the visibility of the borders of the rectus femoris was insufficient. No statistical significant differences in age, BMI, FFMI, triceps skinfold, or severity of COPD were found between the patients of whom ultrasound images could be interpreted and patients of whom images could not be interpreted ($p = 0.787$, $p = 0.812$, $p = 0.885$, $p = 0.903$ and $p = 0.693$, respectively).

3.1. Muscle size in relation to FFM and muscle function

Mean muscle thickness was 1.81 ± 0.40 cm for males and 1.58 ± 0.28 cm for females ($p = 0.086$) (Table 1). Patients with (very) severe COPD did not have lower rectus femoris CSA (8.15 ± 2.89 cm^2) and thickness (1.66 ± 0.36 cm) compared to patients with moderate COPD (CSA: 8.66 ± 2.74 cm^2; thickness: 1.72 ± 0.35 cm) ($p = 0.65$ and $p = 0.68$). Higher FFMI was associated with greater rectus femoris CSA and thickness ($r = 0.57$, $p < 0.001$ and $r = 0.53$, $p = 0.003$, respectively). The correlation did not differ between males and females (Figs. 2 and 3). In patients with moderate COPD, the correlation between rectus femoris thickness and FFMI ($r = 0.70$, $p = 0.015$), was stronger than in patients with (very) severe COPD ($r = 0.40$, $p = 0.087$). Furthermore, rectus femoris CSA and thickness were correlated with handgrip strength ($r = 0.58$, $p < 0.001$; $r = 0.48$, $p = 0.009$, respectively). Rectus femoris CSA and thickness were not significantly correlated with leg muscle power ($r = -0.35$, $p = 0.073$ and $r = -0.33$, $p = 0.091$, respectively). Furthermore, we did not observe a correlation between rectus femoris muscle size and maximal exercise capacity (thickness: $r = 0.21$, $p = 0.297$; CSA: $r = 0.22$, $p = 0.274$) (Table 2). Consistent with the results for rectus femoris size, a correlation between HGS and FFMI was observed ($r = 0.50$, $p = 0.007$). No correlations between leg muscle power, maximal exercise capacity, and FFMI were found ($r = -0.10$, $p = 0.616$; $r = 0.23$, $p = 0.265$, respectively).

Table 1
General characteristics of the study population (N = 44).

Male	19 (43)
Age (y), mean (SD)	60.2 (9.0)
Smoking	
No	1 (2)
Former	28 (64)
Current	15 (34)
Most prevalent comorbidities	
Diabetes mellitus	6 (20)
Congestive heart failure	5 (17)
Pulmonary function	
FEV_1 (L)	0.96 (0.80–1.49)
FEV_1 (% predicted)	38.0 (27.0–55.8)
FEV_1/FVC (%)	39.0 (30.3–48.0)
GOLD 2011 classification	
Mild	0 (0)
Moderate	15 (34)
Severe	15 (34)
Very severe	14 (32)
Body water (l), mean (SD) N = 43	
Total body water	38.0 (7.5)
Intracellular water	20.9 (5.3)
Extracellular water	17.4 (2.9)
BMI (kg/m^2), mean (SD)	26.3 (6.5)
Obesity (BMI ≥30)	8 (27)
FFMI (kg/m^2), mean (SD) N = 37	17.2 (2.8)
FMI (kg/m^2), mean (SD) N = 37	9.2 (3.7)
Five times sit to stand (sec) N = 39	14.9 (11.2–18.7)
Handgrip strength (kg) N = 42	34.1 (11.7)
ISWT (m)	190 (97.5–307.5)
Sarcopenia[a] N = 42	
No	18 (43)
Low muscle mass	22 (52)
Low muscle mass and function	2 (5)

Data are presented as N (%) or median (interquartile range), unless otherwise stated. BMI, body mass index; FEV, forced expiratory volume; FMI, fat mass index, FFMI, fat free mass index; ISWT, Incremental Shuttle Walk Test.
[a] Using the EWGSOP criteria and cut-off points [4].

4. Discussion

This study demonstrated that in patients with COPD starting a pulmonary rehabilitation program, ultrasound measured rectus femoris size, i.e. thickness and CSA, is correlated with fat-free mass and handgrip strength. However, no significant correlation was found between rectus femoris size and leg muscle power, probably due to insufficient power.

In our study, we did not find any difference between rectus femoris thickness and CSA in their relations with FFMI and function. Furthermore, we did not observe any systematic differences in the reliability of both measurements. These findings indicate that the measurements of the CSA and thickness can both be used. The advantage of assessing the CSA of the rectus femoris, is that it reflects the size of the entire muscle. However, in larger muscles the entire CSA cannot be determined due to the limited size of the image. Moreover, visualization of the anatomical borders of the muscle may be challenging in a clinical population [19]. Muscle thickness, on the other hand, can be obtained more easily and, therefore could be a more feasible measurement for use in practice.

We observed that both rectus femoris thickness and CSA are moderately correlated with FFMI. These findings are in line with previous studies in patients with COPD, that observed that rectus femoris CSA is associated with FFMI [19,20]. Interestingly, we found that the correlation between rectus femoris thickness and FFMI is less strong in patients with (very) severe COPD, as compared to patients with moderate COPD ($r = 0.70$, $r = 0.40$, respectively). This might be explained by the fact that in patients with (very) severe COPD, in particular muscle mass of the lower limbs is depleted [19,20]. However, it is more likely that other factors contribute to this finding since patients with (very) severe COPD did not have a significant lower mean thickness, which is in line with a previous study.19 A possible explanation for this result could be that in

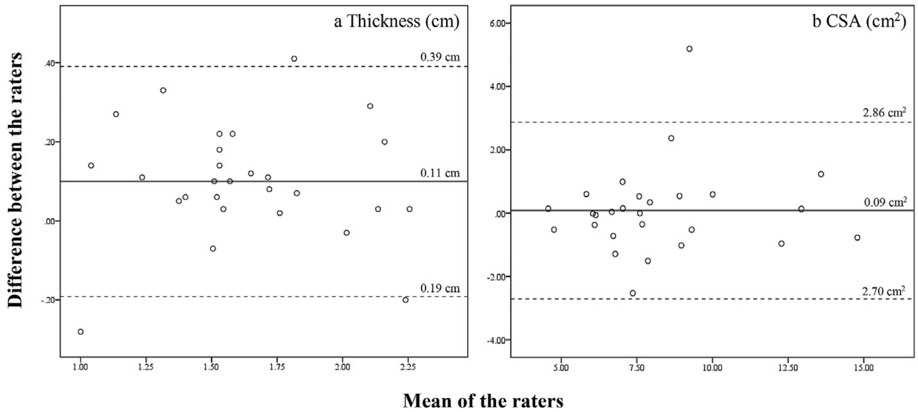

Fig. 1. Bland-Altman plots illustrating the inter-rater measurement reliability for both rectus femoris thickness (Fig. 1a) and CSA (Fig. 1b).

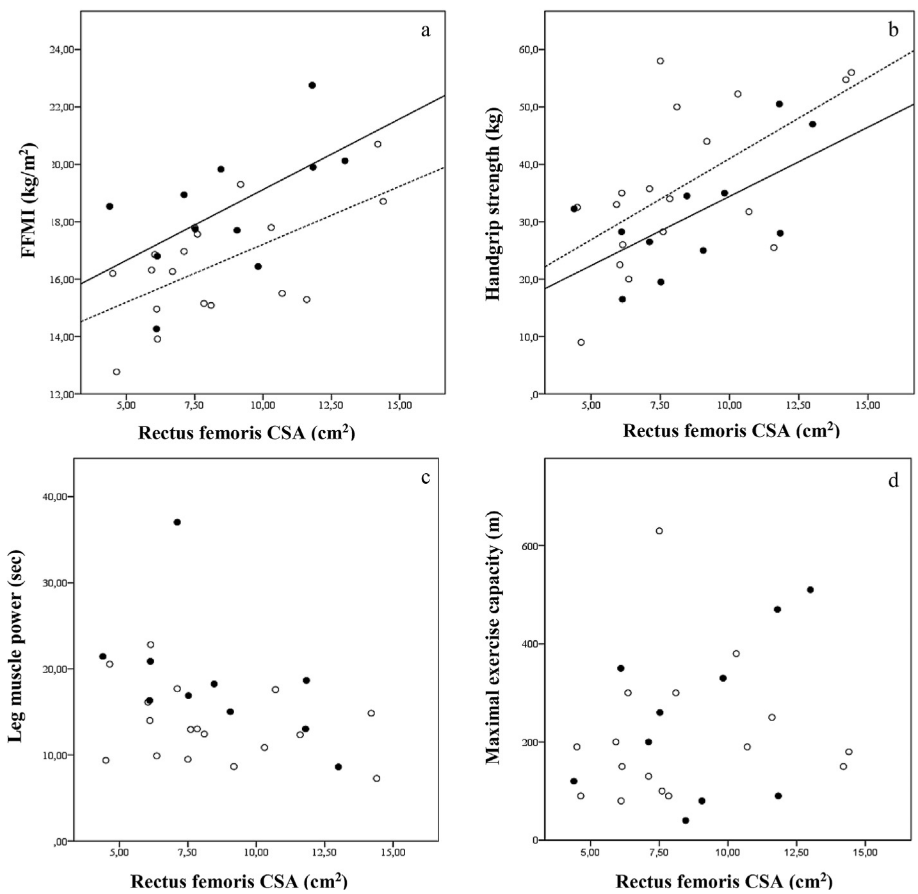

Fig. 2. Illustration of the relationship between rectus femoris CSA and FFMI (Fig. 2a), handgrip strength (Fig. 2b), leg muscle power (Fig. 2c) and maximal exercise capacity (Fig. 2d). Patients with moderate COPD are presented by *closed* dots and patients with severe to very severe COPD are presented by *open* dots.

patients with (very) severe COPD, muscle size remains stable, but intramuscular fat increases which may lead to muscle dysfunction [31]. Another explanation could be an overestimation of the FFMI in patients with (very) severe COPD, due to edema [32].

This study also demonstrates that muscle size is moderately correlated with handgrip strength. Besides being an indicator of overall strength [33], there is strong evidence that handgrip strength is a predictor for disability and mortality [34–37]. Although handgrip strength is also influenced by non-nutritional factors such as inflammation [38], in clinical practice, handgrip strength is often used as a marker for nutritional status [36]. In this study, we found a moderate correlation between muscle size and handgrip strength, suggesting that peripheral muscle size might be related to overall strength as well. Future studies should assess concurrent and predictive validity of ultrasound in relation to malnutrition, to elucidate the role of ultrasound measured muscle size in the assessment and monitoring of nutritional status in daily practice.

Similar to findings in previous research [21], rectus femoris size was not related to leg muscle power and exercise capacity in our

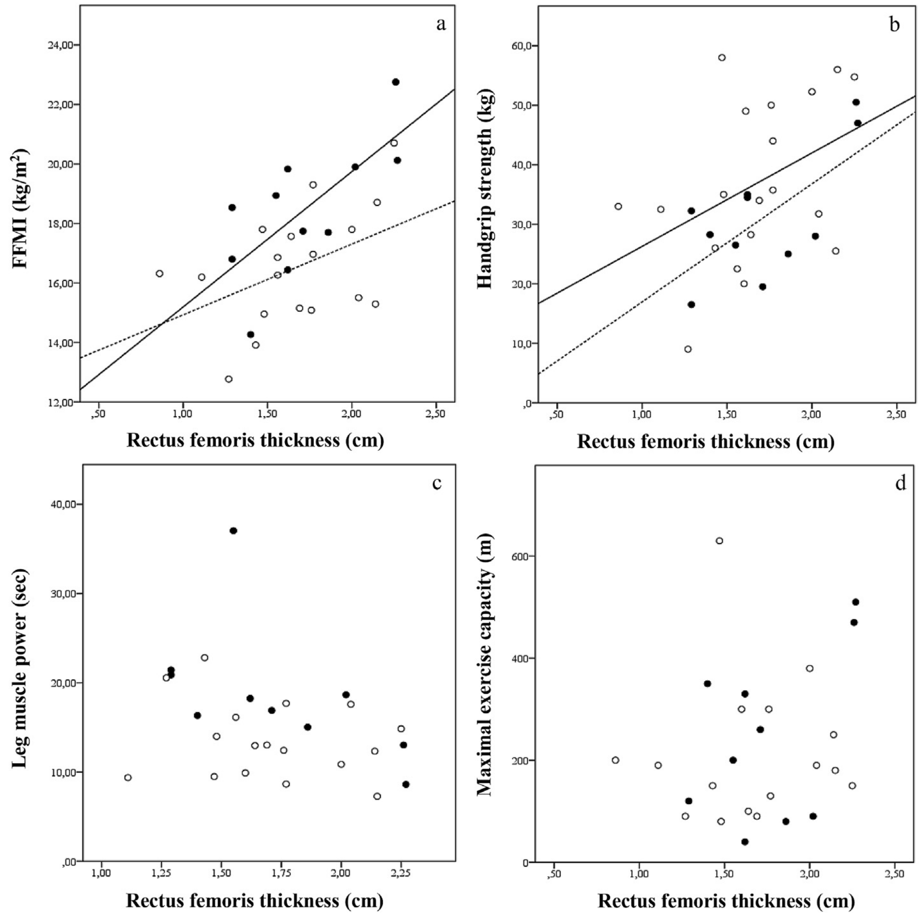

Fig. 3. Illustration of the relationship between rectus femoris thickness and FFMI (Fig. 3a), handgrip strength (Fig. 3b), leg muscle power (Fig. 3c) and maximal exercise capacity (Fig. 3d). Patients with moderate COPD are presented by *closed* dots and patients with severe to very severe COPD are presented by *open* dots.

Table 2
Correlations of rectus femoris thickness and CSA with muscle strength and mass.

	Muscle thickness (in cm)		Muscle CSA (in cm^2)	
	r	p-value	r	p-value
FFMI (kg/m^2)	0.53	0.003[a]	0.57	<0.001[a]
Handgrip strength (kg)	0.48	0.009[a]	0.58	<0.001[a]
Five times sit to stand test (sec)	−0.33	0.091	−0.35	0.073
Maximal exercise capacity (m)	0.21	0.297	0.22	0.274

FFMI, fat-free mass index
[a] Significant correlation ($p < 0.05$) Expressed as Pearson correlation coefficient (r).

study. A possible explanation for the fact that muscle size was not related to exercise capacity, is that exercise capacity is determined by many other factors both inside and outside the lung [39]. Rectus femoris size, together with other parameters of muscle mass and function, might predict exercise capacity, however we cannot conclude this based on this exploratory study. The absence of a correlation between muscle size and power might be a result of the small sample size, which might have led to low statistical power and possibly resulted in a type II error, since the observed p-values are close to significance. Therefore, more studies are needed to investigate the association between (loss of) of muscle size and maximal exercise capacity.

An unexpected observation of this study is that ultrasound images are not always interpretable. Although this study suggests that ultrasound is a reliable tool for the assessment of muscle size, we also observed that the interpretation of ultrasound might be challenging in patients with (severe) COPD. In 14 out of 44 ultrasound images, we were unable to measure both rectus femoris CSA and thickness because the borders of the rectus femoris could not be interpreted. There are two possible explanations for the non-interpretable ultrasound images. First, it has been previously observed that anatomical definitions might be decreased due to edema and the amount of subcutaneous fat [19,21]. Second, an increased echogenicity, i.e. a brighter appearance of the muscle which reflects intramuscular fat, may lead to non-interpretable images for the size of the muscle [40]. In our study, we did not find significant differences on any health related variables between the patients with and without interpretable ultrasound images. Therefore, future research should focus on the validity and reliability of ultrasound in patients with (severe) COPD, by taking the assessment of subcutaneous fat, edema, and intramuscular fat into consideration.

In this study, we link ultrasound data with tools used in daily practice for the assessment of muscle mass and function in patients with COPD. Our study shows that peripheral muscle size is associated with whole body fat-free mass, showing that rectus femoris size is a moderate reflection of fat-free mass. Nevertheless, since the loss of muscle mass is not uniform across all muscles [41], and nutritional depletion preferentially affects the upper limbs whilst chronic inactivity is associated with loss of muscle mass of the lower limbs [42], it is of great interest to evaluate peripheral muscles. Superficial muscles can be obtained easily with ultrasound, although training on the use and interpretation of ultrasound images is needed before health-care professionals can use it for evaluating muscles.

Besides the small sample size and the cross-sectional study design, some limitations should be taken into account when interpreting our results. First, BIA was used to estimate FFMI, which is not a gold standard for the assessment of muscle mass and, therefore, could possibly have led to an over- or underestimation of FFMI due to for example an altered hydration status [25]. Nevertheless, BIA is frequently used in clinical practice and therefore it is of great interest to assess the correlation between peripheral muscle size by ultrasound and whole body fat-free mass by BIA. Second, a handheld ultrasound machine that predominantly was developed for abdominal scans was used in this study. Although we optimized the standard abdominal protocol for the assessment of muscles, we used the built-in ellipse shape for the assessment of the CSA. As the muscle is not a perfect ellipse, this might have led to an overestimation of the true CSA of the rectus femoris. Furthermore, the echogenicity of the muscle cannot be assessed with this type of ultrasound machine, and therefore we could not assess whether (increased) echogenicity is associated with fat-free mass and function in this sample of patients with COPD. Third, in this study, we used a curved transducer for the assessment of muscles which has a large field of view. However, a disadvantage of this transducer is the limited resolution, which could have resulted in spurious interpretations of the ultrasound image. Nevertheless, a previous study showed that a curved-array transducer is valid and reliable for the assessment of muscles compared to a linear array transducer [43]. Lastly, the outcomes were measured by different individuals, which may have caused bias.

In conclusion, this study shows that ultrasound measured muscle size is related to FFMI and strength in patients with COPD. Disease severity might influence the relationship between muscle size and FFMI, implicating that peripheral assessment of muscles is important in a clinical situation. Ultrasound might play an important role in the assessment of peripheral muscles, however, the echogenicity of the muscle should be taken into consideration, as this might be increased in patients with COPD.

Statement of authorship

WN: methodology, data analyses, visualization, writing original draft, review and editing, data curation; LTB: conceptualization, methodology, resources, data analyses, review and editing, data curation; JSMH: conceptualization, supervision, review and editing; HVDV: conceptualization, methodology, resources, review and editing; JBW: conceptualization, methodology, resources, review and editing; CPVDS: conceptualization, methodology, resources, supervision, review and editing; HJW: conceptualization, methodology, resources, supervision, review and editing.

Conflict of interest statement

The authors declare that they have no competing interests.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

The authors gratefully acknowledge Margot Broeze for the analysis of the ultrasound images. We would also like to thank all participants for their participation in this study.

References

[1] Donaldson AV, Maddocks M, Martolini D, Polkey MI, Man WD. Muscle function in COPD: a complex interplay. Int J Chronic Obstr Pulm Dis 2012;7:523–35.
[2] Maddocks M, Kon SS, Canavan JL, Jones SE, Nolan CM, Labey A, et al. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. Thorax 2016;71(11):988–95.
[3] Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009;33(5):1165–85.
[4] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: european consensus on definition and diagnosisReport of the european working group on sarcopenia in older PeopleA. J. cruz-gentoft et al. Age Ageing 2010;39(4):412–23.
[5] Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr 2017;36(1):49–64.
[6] Luo Y, Zhou L, Li Y, Guo S, Li X, Zheng J, et al. Fat-free mass index for evaluating the nutritional status and disease severity in COPD. Respir Care 2016;61(5):680–8.
[7] Ng MGS, Kon SSC, Jane JL, Clark AL, Nolan CM, Jones SE, et al. Prevalence and effects of malnutrition in COPD patients referred for pulmonary rehabilitation. 2013.
[8] Ingadottir AR, Beck AM, Baldwin C, Weekes CE, Geirsdottir OG, Ramel A, et al. Two components of the new ESPEN diagnostic criteria for malnutrition are independent predictors of lung function in hospitalized patients with chronic obstructive pulmonary disease (COPD). Clin Nutr 2017. https://doi.org/10.1016/j.clnu.2017.05.031.
[9] de Blasio F, Di Gregorio A, de Blasio F, Bianco A, Bellofiore B, Scalfi L. Malnutrition and sarcopenia assessment in patients with chronic obstructive pulmonary disease according to international diagnostic criteria, and evaluation of raw BIA variables. Respir Med 2018;134:1–5.
[10] Jones SE, Maddocks M, Kon SSC, Canavan JL, Nolan CM, Clark AL, et al. Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. Thorax 2015;70(3):213–8.
[11] van de Bool C, Rutten EP, Franssen FM, Wouters EF, Schols AM. Antagonistic implications of sarcopenia and abdominal obesity on physical performance in COPD. Eur Respir J 2015;46(2):336–45.
[12] Takahashi T, Sugie M, Nara M, Koyama T, Obuchi SP, Harada K, et al. Femoral muscle mass relates to physical frailty components in community-dwelling older people. Geriatr Gerontol Int 2017 Oct;17(10):1636–41.
[13] Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debigaré R, et al. An official american thoracic society/european respiratory society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2014;189(9):e15–62.
[14] Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, et al. Pitfalls in the measurement of muscle mass: a need for a reference standard. J Cachexia Sarcopenia Muscle 2018 Apr;9(2):269–78.
[15] Buchholz AC, Bartok C, Schoeller DA. The validity of bioelectrical impedance models in clinical populations. Nutr Clin Pract 2004;19(5):433–46.
[16] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al. Bioelectrical impedance analysis—part I: review of principles and methods. Clin Nutr 2004;23(5):1226–43.
[17] Arts IM, Pillen S, Schelhaas HJ, Overeem S, Zwarts MJ. Normal values for quantitative muscle ultrasonography in adults. Muscle Nerve 2010;41(1):32–41.
[18] Nijholt W, Scafoglieri A, Jager-Wittenaar H, Hobbelen JSM, van der Schans CP. The reliability and validity of ultrasound to quantify muscles in older adults: a systematic review. J Cachexia Sarcopenia Muscle 2017 Oct;8(5):702–12.
[19] Seymour JM, Ward K, Sidhu PS, Puthucheary Z, Steier J, Kolley CJ, et al. Ultrasound measurement of rectus femoris cross-sectional area and the relationship with quadriceps strength in COPD. Thorax 2009;64(5):418–23.
[20] Shrikrishna D, Patel M, Tanner RJ, Seymour JM, Connolly BA, Putchucheary ZA, et al. Quadriceps wasting and physical inactivity in patients with COPD. Eur Respir J 2012;40(5):1115–22.
[21] Cruz-Montecinos C, Guajardo-Rojas C, Montt E, Conreras-Briceño F, Torres-Castro R, Díaz O, et al. Sonographic measurement of the quadriceps muscle in patients with chronic obstructive pulmonary disease. J Ultrasound Med 2016;35(11):2405–12.
[22] Rozenberg D, Martelli V, Vieira L, Orchanian-Cheff A, Keshwani N, Singer LG, et al. Utilization of non-invasive imaging tools for assessment of peripheral skeletal muscle size and composition in chronic lung disease: a systematic review. Respir Med 2017;131:125–34.
[23] Eaton T, Young P, Nicol K, Kolbe J. The endurance shuttle walking test: a responsive measure in pulmonary rehabilitation for COPD patients. Chron Respir Dis 2006;3(1):3–9.
[24] Brouillard C, Pepin V, Milot J, Lacasse Y, Maltais F. Endurance shuttle walking test: responsiveness to salmeterol in COPD. Eur Respir J 2008;31(3):579–84.
[25] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr 2004;23(6):1430–53.

[26] Rutten EP, Spruit MA, Wouters EF. Critical view on diagnosing muscle wasting by single-frequency bio-electrical impedance in COPD. Respir Med 2010;104(1):91–8.
[27] Bohannon RW. Grip strength: a summary of studies comparing dominant and nondominant limb measurements. Percept Mot Skills 2003;96(3):728–30.
[28] Csuka M, McCarty DJ. Simple method for measurement of lower extremity muscle strength. Am J Med 1985;78(1):77–81.
[29] Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. Thorax 1999;54(3):213–22.
[30] Mota P, Pascoal AG, Sancho F, Bø K. Test-retest and intrarater reliability of 2-dimensional ultrasound measurements of distance between rectus abdominis in women. J Orthop Sports Phys Ther 2012;42(11):940–6.
[31] Games Robles P, Sussman MS, Naraghi A, Brooks D, Goldstein RS, White LM, et al. Intramuscular fat infiltration contributes to impaired muscle function in COPD. Med Sci Sports Exerc 2015;47(7):1334–41.
[32] Wouters E. Management of severe COPD. Lancet 2004;364(9437):883–95.
[33] Rantanen T, Era P, Kauppinen M, Heikkinen E. Maximal isometric muscle strength and socioeconomic status, health, and physical activity in 75-year-old persons. J Aging Phys Act 1994;2(3):206–20.
[34] Rantanen T, Guralnik JM, Foley D, Masaki K, Leveille S, Curb JD, et al. Midlife hand grip strength as a predictor of old age disability. JAMA 1999;281(6):558–60.
[35] Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol (1985) 2000;89(2):465–71.
[36] Norman K, Stobaus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. Clin Nutr 2011;30(2):135–42.
[37] Celis-Morales CA, Welsh P, Lyall DM, Steell L, Petermann F, Anderson J, et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK biobank participants. BMJ 2018;361:k1651.
[38] Norman K, Stobäus N, Kulka K, Schulzke J. Effect of inflammation on handgrip strength in the non-critically ill is independent from age, gender and body composition. Eur J Clin Nutr 2014;68(2):155.
[39] Jobin J, Maltais F, Doyon J, et al. Chronic obstructive pulmonary disease: capillarity and fiber-type characteristics of skeletal muscle. J Cardpulm Rehabil Prev 1998;18(6):432–7.
[40] Pillen S, Tak RO, Zwarts MJ, Lammens MMY, Verrijp KN, Arts IMP, et al. Skeletal muscle ultrasound: correlation between fibrous tissue and echo intensity. Ultrasound Med Biol 2009;35(3):443–6.
[41] Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. J Appl Physiol (1985) 2000;89(1):81–8.
[42] Heymsfield S. Nutritional assessment by anthropometric and biochemical methods. Mod Nutr Health Dis 1994;1:812–41.
[43] Hammond K, Mampilly J, Laghi FA, Goyal A, Collins EG, McBurney C, et al. Validity and reliability of rectus femoris ultrasound measurements: comparison of curved-array and linear-array transducers. J Rehabil Res Dev 2014;51(7):1155–64.