

Components of physical capacity in patients with chronic obstructive pulmonary disease: relationship with phenotypic expression

Eduardo Márquez-Martín¹
Pilar Cejudo Ramos¹
José Luis López-Campos¹
María del Pilar Serrano
Gotarredona²
Silvia Navarro Herrero²
Rodrigo Tallón Aguilar¹
Emilia Barrot Cortes¹
Francisco Ortega Ruiz¹

¹Medical-Surgical Unit of Respiratory Diseases, University Hospital Virgen del Rocío, Seville, Spain; ²Radiodiagnostic Unit, University Hospital Virgen del Rocío, Seville, Spain

Background: More accurate phenotyping of COPD is of great interest since it may have prognostic and therapeutic consequences. We attempted to explore the possible relationship between the extent of emphysema, as assessed by high-resolution computed tomography (HRCT), and COPD severity. We also included some study variables involving exercise tolerance evaluation and peripheral muscle strength (PMS) measurement.

Methods: Sixty-four patients with COPD (mean age 64 ± 7 years) were enrolled in a prospective observational cross-sectional study. All patients underwent clinical and functional evaluations: assessment of dyspnea, body mass index (BMI), health status assessment, spirometry testing, and arterial blood gas analysis. The extent of emphysema was graded using HRCT. Functional capacity was evaluated by a cardiopulmonary maximal exercise testing (CPET), the shuttle walking test, and by estimation of PMS.

Results: Half of the study patients had an emphysematous phenotype. There was a significant correlation between the score derived from analysis of HRCT images and BMI and respiratory functional parameters, as well as VO_2 max (maximal oxygen uptake) and chest pull 1RM (1 rep max). Compared with subjects with a nonemphysematous phenotype, those with an emphysematous phenotype showed a lower BMI, a reduced PMS, and displayed a lower power at CPET. Significant differences in lung function tests were found for diffusing capacity and hyperinflation. No significant differences in quality of life were observed between the two study groups.

Conclusions: Compared with subjects with a nonemphysematous phenotype, subjects with an emphysematous phenotype has a different profile in terms of BMI, lung function, PMS, and exercise capacity.

Keywords: chronic obstructive pulmonary disease, exercise tolerance, emphysema, phenotypes, lung function

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible and usually progressive.¹ This airflow limitation may be caused by both inflammation and wall thickening in small airways, which is responsible for the narrowing of the airway lumens, and in some but not all cases, parenchymal destruction of the lungs (emphysema), leading to loss of the elastic lung recoil.² Traditionally, on the basis of determined clinical, functional, and radiologic features, patients with COPD used to be classified into 2 different biotypes: the “blue boater”, in association with a predominant chronic bronchitis condition, and the “pink puffer”, identified as predominant emphysema.³ However these are only the

Correspondence: Eduardo Márquez-Martín
Medical-Surgical Unit of Respiratory
Diseases, University Hospital Virgen del
Rocío, Seville, Spain
Tel +34 955013164
Fax +34 955013167
Email eduardo.marquez.sspa@juntadeandalucia.es

two extreme phenotypes among the broad variety of clinical presentations in COPD.

Studies conducted in recent years have revealed that patients with the same stage of disease may offer different pathological changes,⁴⁻⁶ and classic COPD phenotypes clearly differ from these based on severity of emphysema as assessed by high resolution computed tomography (HRCT) scanning.⁴

Based on studies with HRCT support, some authors find that patients with the phenotype in which emphysema predominates have more severe lung function impairment but more intense airway inflammation and a higher BODE index (body mass index, airflow obstruction, dyspnea, exercise capacity) and subsequently, a possible more serious systemic dysfunction.⁷ In contrast, other studies show that the severity of emphysema is highly variable even among subjects with the same functional stage of COPD, which does not support emphysema as the major cause of airflow limitation in COPD.⁴

In COPD patients, health-status measurement and the BODE score predicts mortality better than FEV₁ (forced expiratory volume in the first second of expiration) since FEV₁ is a component of BODE.^{8,9} These multidimensional tools may be more valuable because they can reflect the systemic nature of the disease. Other parameters, such as physical activity and exercise tolerance as measured by cycle ergometry, have been demonstrated to be strong independent predictors of COPD mortality.^{10,11} In addition, peripheral muscle strength¹² and muscle mass depletion,¹³ which do reflect the skeletal muscle dysfunction present in COPD patients, also offer prognostic information. Some authors state that these comorbid manifestations are more frequent in patients with predominant emphysema, what would imply a poorer prognosis.¹⁴

Consequently more accurate phenotyping of COPD is of great interest since it may have prognostic and therapeutic consequences. We attempt to explore the possible relationship between emphysema extension as assessed by HRCT, and COPD severity. Our hypothesis is that patients with predominant emphysema have a greater systemic dysfunction, and then show evidence of lower exercise capacity and peripheral muscle strength than those with COPD not associated with emphysema. To clarify the differences between the morphological phenotypes and clinical features of COPD, we classified patients into 2 phenotypes according to the dominance of emphysema on chest HRCT and examined the clinical characteristics, including exercise and muscle function, in each phenotype.

Material and methods

Study participants

Sixty-four male patients with age-related COPD were enrolled in a prospective, observational, cross-sectional study. The study was approved by the Institutional Review Board and written informed consent was obtained from all participants. Patients were recruited from the outpatient clinic. Inclusion criteria were: 1) being an adult patient with a diagnosis of COPD according to international guidelines,⁹ and 2) being clinically stable during the previous 3 months. The exclusion criteria were: 1) unwillingness to participate in the study, 2) a history of recent exacerbation (<3 months) requiring systemic corticosteroids or antibiotics, and 3) any contraindication or inability to perform the study tests.¹⁵

All patients underwent clinical and functional evaluations that included assessment of dyspnea, body mass index (BMI),¹⁶ health status assessment, spirometry testing, and arterial blood gas analysis. These were followed by assessments of physical function and radiological examinations consisting of HRCT scans. The functional capacity of the study participants was evaluated by cardiopulmonary maximal exercise testing (CPET), the shuttle walking test (SWT),¹⁷ and by estimation of peripheral muscle strength (PMS).

Dyspnea scale

Basal dyspnea was measured using the modified Medical Research Council scale (mMRC)¹⁸ which classifies the degree of dyspnea ranging from 0 to 4.

Pulmonary function tests

Spirography was performed using a pneumotachograph spirometer (Masterlab, Erich Jaeger GMBH, Wuerzburg, Germany) following the SEPAR¹⁹ and the ATS²⁰ recommendations. Static lung volumes were determined plethysmographically.²¹ Arterial blood gas analysis was carried out according to the SEPAR²² recommendations.

Health-related quality of life

For the assessment of quality of life, we used a specific questionnaire for patients with COPD, the Chronic Respiratory Disease Questionnaire (CRDQ) proposed by Guyatt, which has been previously validated and translated into Spanish.²³ It consists of 20 items rated from 1 to 7 (so that the higher the score better quality of life) and divided into 4 sections: dyspnea (questions 4a–4e), fatigue (questions 7, 10, 14, 16), emotional functioning (questions 5, 8, 11, 13, 15, 17, 19), and mastery (questions 6, 9, 12, 18). Normal range should be the maximum amount for all items, which means 7 points

in each section and 28 in total (the maximum amount of the 4 sections). The changes are considered clinically significant when the score for each question increased by at least 0.5 points on the overall score for each of the paragraphs (0.5–1: slight change; 1–1.5: moderate; ≥ 1.5 : excellent).

Peripheral muscle strength

Weight-lifting capacity was measured as the heaviest weight that could be lifted once throughout the complete range of movement (1RM test, 1 rep max test).²⁴ Typical PMS values were described by Hamilton et al.²⁵

Shuttle walking test

The SWT was conducted as described by Singh et al.,²⁶ which requires patients to walk a 10 m course marked out by 2 cones with progressive levels. The maximum distance to walk is 1020 m.

Maximal cardiopulmonary exercise test

Maximal cardiopulmonary exercise testing was performed on a cycle ergometer (Collins Respiratory Ergomed, USA) according to international standards.^{15,27} Typical values were described by Wasserman et al.²⁸ The following variables were measured: oxygen consumption; carbon dioxide production; an indirect assessment of anaerobic threshold, and the respiratory pattern (maximal breathing capacity, tidal volume, respiratory rate).²⁹ The exercise was performed on electrocardiographic, heart rate and pulseoxymetric monitoring. All measurements were integrated into the cycle ergometer device (Collins Respiratory Ergomed, USA) and evaluated simultaneously during the test. After the exercise, we assessed heart rate, blood pressure, leg fatigue, chest pain, and dyspnea using the modified Borg's scale.³⁰

High-resolution computed tomography

HRCT was used to distinguish between emphysematous and non-emphysematous phenotypes. Acquisition parameters were as follows: 1 mm collimation, 120 to 140 kV, 75 to 350 mA, 0.75 to 1 seconds scanning time, and field of view 350 to 400 mm. HRCT images were selected at 3 levels, including the aortic arch, the main carina, and 1 to 2 cm above the highest hemi-diaphragm. A window level of -700 to -900 Hounsfield units (HU) with a 600 to 1600 HU window width were used for image interpretation.³¹ Two readers visually and independently assessed the severity of emphysema according to a modified scoring system adopted from previous studies with no knowledge of the patients' clinical information.³² We analyzed 6 images in 3 slices in the lungs; the total score

from all images was considered as a representative value of the severity of emphysema in each person. Each image was classified as normal (score 0), up to 25% affected (score 1), up to 50% affected (score 2), up to 75% affected (score 3), and more than 75% affected (score 4), giving a minimum score of 0 and maximum of 24. Disagreement between the two radiologists was resolved by consensus. Emphysema was defined as the presence of a score >6 , which means 25% of total area, according to Nakano et al.³³

Data analysis

Quantitative variables were summarized with means and standard deviations. For descriptive purposes, variables are presented first for the entire study sample and thereafter according to the GOLD stages.¹ Differences across different GOLD stages were assessed on the basis of analysis of variance (ANOVA). Qualitative variables were compared between emphysematous and nonemphysematous patients using the chi-square test. The correlation between the study variables was estimated using Pearson's correlation coefficient (*r*). Quantitative variables were compared by Student's *t* test. Data were analyzed by SPSS (SPSS Inc., Chicago IL, USA), version 14.0.

Results

Clinical and functional characteristics of the 64 patients are described in Table 1. Globally, our patients had a severe obstruction, hyperinflation, and hypoxemia. They had a mildly impaired pulmonary diffusion, and showed decreased exercise capacity and low HRQL and dyspnea indexes.

From the analysis of the HRCT images, we obtained scores ranging between 0 and 24 points. Based on these scores, half of the study participants ($n = 32$) were classified as emphysematous phenotype and half ($n = 32$) as nonemphysematous phenotype; median score for the whole group was 8.5 ± 6.05 points. By groups, emphysematous patients' score was significantly higher than that of nonemphysematous patients (12.4 ± 5.1 vs 4.65 ± 4.075 points; $P < 0.05$). The mean attenuation values for the emphysema and nonemphysema groups were -889 (32.3) HU and -865 (25) HU, respectively. The correlation study (Table 2) showed a significant relation between the HRTC score and BMI, dyspnea indexes, respiratory function parameters, VO_2 max (maximal oxygen uptake), and chest pull 1RM.

When we separated patients into GOLD stages (Table 3), they were homogeneously distributed across the study groups. Patients with GOLD stages I and II were grouped

Table 1 Baseline characteristics of the 64 male study participants

Parameter	Mean \pm SD or %
Age, yr	64 \pm 7
BMI, kg/m ²	29 \pm 5
CRDQ dyspnea	2.8 \pm 0.7
CRDQ fatigue	4.2 \pm 0.9
CRDQ emotional function	4.7 \pm 0.9
CRDQ mastery	4.9 \pm 1.2
CRDQ total	16.7 \pm 2.9
FEV ₁ % predicted	42 \pm 12
TLC % predicted	110 \pm 15
RV % predicted	158 \pm 37
KCO % predicted	84 \pm 28
PaO ₂ , mmHg	72 \pm 11
PaCO ₂ , mmHg	42 \pm 5.5
CPET power, W	61 \pm 25
VO ₂ max, mL/min/kg	14.5 \pm 3.7
PMS neck press, kg	24 \pm 6.5
PMS chest pull, kg	42 \pm 9.1
PMS butterfly, kg	19 \pm 6.8
PMS flexion, kg	16.7 \pm 6
PMS extension, kg	39 \pm 11.7
SWT, m	380 \pm 147

Abbreviations: BMI, body mass index; CRDQ, chronic respiratory disease questionnaire; FEV₁, forced expiratory volume in the first second of expiration; TLC, total lung capacity; RV, residual volume; KCO, Krogh coefficient; PaO₂, arterial oxygen partial pressure at rest; PaCO₂, arterial carbon dioxide partial pressure at rest; CPET, cardio-pulmonary exercise test; VO₂ max, maximal oxygen uptake; PMS, peripheral muscle strength; SWT, shuttle walking test.

together since only 1 patient had stage I disease. Our results showed that the presence of emphysema is roughly equal across all levels of obstruction. PMS was similar in the three groups, but increasing GOLD stages were associated with a worsening of exercise capacity.

We differentiated COPD phenotypes according to HRCT findings (Table 4). Compared with nonemphysematous patients, emphysematous patients had a lower

Table 2 Significant relationships between HRCT emphysema score and clinical variables in patients with COPD

Clinical variable	r value	P value
Dyspnea, mMRC	0.282	0.028
BMI, kg/m ²	-0.4	0.001
PaCO ₂ , mmHg	-0.346	0.01
IRM chest pull, kg	0.3	0.032
VO ₂ max, mL/min/kg	-0.274	0.03
FVC, %	0.346	0.01
FEV ₁ /FVC, %	-0.431	0.001
TLC, %	0.5	0.001

Abbreviations: BMI, body mass index; PaCO₂, arterial carbon dioxide partial pressure; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second of expiration; TLC, total lung capacity; KCO, Krogh coefficient; mMRC, modified Medical Research Council; IRM, 1 rep max; VO₂ max, maximal oxygen uptake.

BMI (26.5 [3.5] vs 31.4 [5.2]; $P < 0.001$), a reduced PMS (Figure 1), and displayed a significantly lower power at CPET (54 [21.5] vs 67.9 [26.7] W; $P < 0.05$) (Figure 2). Both groups reached a similar distance in the SWT and there were no significant differences in HRQL indexes. It is important to note that because the grade of obstruction was not associated with a determined phenotype, both groups had a similar FEV₁. Emphysematous patients showed a lower CO diffusion, lower FEV₁/FVC ratio, and higher FVC, functional residual capacity (FRC), and total lung capacity (TLC) than nonemphysematous patients (Table 4).

Discussion

In this study, we have provided evidence that patients with an emphysematous phenotype have a different profile in terms of BMI, some measures of lung function, PMS, and exercise tolerance compared with nonemphysematous phenotype patients. Although lung function is required to diagnose COPD and classify its severity, FEV₁ values are not generally associated with symptom intensity or exercise capacity.³⁴ Moreover, the usefulness of FEV₁ as a prognostic factor for clinical outcomes and mortality in COPD has been questioned. Accordingly, numerous other factors including dyspnea or acute exacerbations have been shown to significantly affect survival.^{35,36} In recent years, there has been growing interest for patient-related outcomes in subjects with COPD, including clinical symptoms, the number of acute exacerbations, exercise tolerance, functional ability, and general well-being.^{37,38}

Recent evidence has shown that different COPD phenotypes may be significantly associated with differences in BMI, health-related HRQL,⁴ small airway obstruction,³⁹ responsiveness to bronchodilators,⁵ and systemic inflammation.⁴⁰ To our knowledge, however, there is a paucity of information on the differences in physical function between emphysematous and nonemphysematous COPD patients.

Some authors have found no clinical or pulmonary functional differences between emphysematous and nonemphysematous patients.⁴¹ Other authors describe that patients with the phenotype in which emphysema predominates in HRCT are characterized by a severe pulmonary functional affect and a high airway inflammation.⁷ In our results, the severity of the emphysema varies even in patients with the same level of COPD. The grade of obstruction is not associated with a determined phenotype as both groups showed a similar FEV₁. Emphysematous patients had lower CO diffusion,

Table 3 Clinical and functional characteristics of the 64 male study participants

Characteristics	GOLD I-II (n = 18)	GOLD III (n = 29)	GOLD IV (n = 17)	P value*
Age, yr	62 ± 6	65 ± 7	65 ± 7	NS
FEV ₁ , %	57 ± 7.3	40 ± 5.6	25 ± 3.2	<0.001
FEV ₁ /FVC, %	48 ± 7.7	39 ± 6.5	28 ± 5	<0.001
RV, %	141 ± 28.5	159 ± 34.9	189 ± 35	<0.001
FRC, %	136 ± 18.8	148 ± 26	169 ± 30	<0.001
TLC, %	109 ± 10.6	109 ± 17.4	112 ± 16	NS
Dyspnea, mMRC	2.3 ± 0.9	2.2 ± 0.7	2.7 ± 1	NS
BMI, kg/m ²	29 ± 3.8	29 ± 5.5	27.8 ± 5.5	NS
PMS neck press, kg	25 ± 7	24 ± 7	22 ± 5	NS
PMS chest pull, kg	44 ± 11	41.7 ± 9	41 ± 6	NS
PMS butterfly, kg	19.5 ± 6.6	19.8 ± 7.6	17.5 ± 5.4	NS
PMS flexion, kg	17.4 ± 7.7	17 ± 4.7	15.6 ± 6.1	NS
SWT distance, m	39.5 ± 11.7	38.2 ± 12.6	40.4 ± 10.4	NS
SWT level	7.8 ± 2	7.1 ± 1	5.7 ± 1.7	0.001
CPET power, watts	76.3 ± 27	61 ± 20.5	44.7 ± 20.4	<0.001
VO ₂ max, mL/min/kg	17.2 ± 2.9	14 ± 3.3	12.5 ± 3.7	<0.001
VO ₂ max, %	62 ± 11	54 ± 15.5	46.6 ± 13	0.007
Emphysematous phenotype	9 (50%)	13 (44.8%)	10 (58.8%)	NS

Notes: *Calculated by ANOVA or chi-square tests. Data are expressed as means and standard deviations or as absolute and relative frequencies for each group.

Abbreviations: CPET, cardio-pulmonary exercise test; NS, not significant; mMRC, modified Medical Research Council scale; BMI, body mass index; PMS, peripheral muscle strength; SWT, shuttle walking test; CPET, cardio-pulmonary exercise test; VO₂ max, maximal oxygen uptake; FEV₁, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity.

Table 4 Clinical and functional characteristics of the 64 male study participants according to COPD phenotype

Characteristics	Non-emphysema (n = 32)	Emphysema (n = 32)	P value*
BMI, kg/cm ²	31.4 ± 5.2	26.5 ± 3.5	<0.001
FVC, %	78.3 ± 12.9	90.8 ± 16.1	0.002
FEV ₁ , %	43.3 ± 10.9	41.2 ± 13.9	NS
FEV ₁ /FVC, %	43.2 ± 9.6	36.9 ± 8.5	0.006
RV, %	152 ± 28	165 ± 45	NS
FRC, %	138 ± 21	158 ± 29	0.006
TLC, %	104 ± 12	117 ± 16	0.003
KCO, %	103 ± 25	65 ± 14	<0.001
PaCO ₂ , mmHg	44 ± 5.6	40 ± 4.9	0.013
PaO ₂ , mmHg	70.6 ± 10.6	73.1 ± 11.9	NS
PMS neck press, kg	25 ± 7.5	23 ± 5	NS
PMS chest pull, kg	44.4 ± 10.2	39.9 ± 7.1	0.048
PMS butterfly, kg	21.3 ± 8.2	16.9 ± 3.9	0.010
PMS flexion, kg	18 ± 7	15.3 ± 4.3	0.089
PMS extension, kg	41.6 ± 12.9	36 ± 9.9	0.076
SWT distance, m	401 ± 142	359 ± 153	NS
CPET power, watts	67.9 ± 26.7	54 ± 21.5	0.026
VO ₂ max, mL/min/kg	14.8 ± 3.9	14.3 ± 3.6	NS
VO ₂ max, %	57 ± 15.8	51.5 ± 13.2	NS

Notes: *Calculated by Student's t-test. Data are expressed as means and standard deviations.

Abbreviations: CPET, cardio-pulmonary exercise test; NS, not significant; mMRC, modified Medical Research Council scale; BMI, body mass index; CRDQ, chronic respiratory disease questionnaire; PMS, peripheral muscle strength; SWT, shuttle walking test; CPET, cardio-pulmonary exercise test; VO₂ max, maximal oxygen uptake; FEV₁, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; PaCO₂, arterial carbon dioxide partial pressure; PaO₂, arterial oxygen partial pressure at rest.

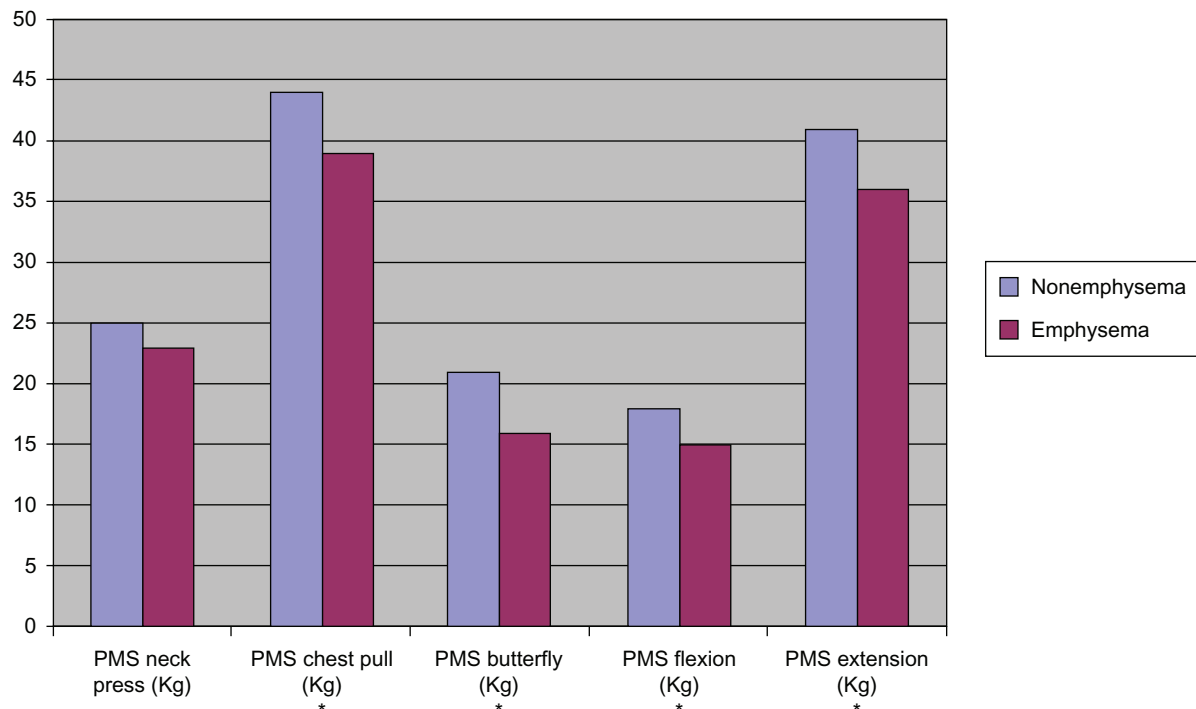


Figure 1 Differences in peripheral muscle strength between emphysema and nonemphysema patients.

Note: *Statistically significant.

Abbreviation: PMS, peripheral muscle strength.

lower FEV₁/FVC ratio, and higher FVC, FRC, and TLC than nonemphysematous patients. Equally, BMI was significantly lower in emphysematous patients. However these parameters did not vary by GOLD stages, which shows that they are related more to the grade of emphysema than to the grade of airway obstruction of the patients. In these subjects, the distance walked in the SWT was lower, which could be an expression of a greater affect on exercise capacity in emphysematous patients. This was confirmed in the maximum exercise capacity test, as emphysematous patients had lower CPET power.

Peripheral muscle weakness is commonly found in patients with COPD. Compared with normal subjects of

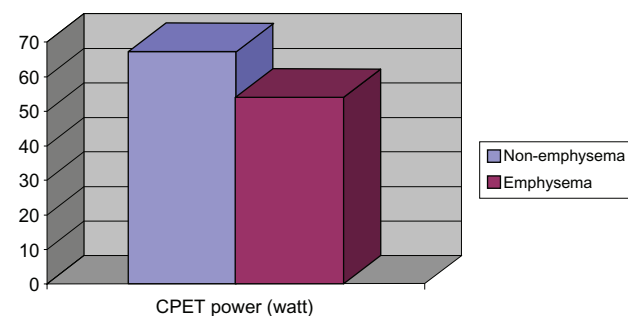


Figure 2 Differences in cardio-pulmonary exercise test power between emphysema and nonemphysema patients.

Abbreviation: CPET, cardio-pulmonary exercise test.

similar age, the reduction in quadriceps strength averages 20% to 30% in patients with severe to moderate disease.⁴² In this study, PMS was significantly more impaired in emphysematous than in nonemphysematous patients in the majority of 1RM maneuvers. In COPD, there is a loss of muscle mass and a muscle fiber-type shift from type I to type II accompanied by reduced activities of enzymes involved in oxidative energy metabolism.⁴³ These changes have been associated with disease severity and BMI, but it is unclear whether fiber type redistribution is comparable between the COPD subtypes emphysema and chronic bronchitis.⁴⁴ These modifications might affect impairment of muscle function, which we found to be associated with the emphysematous phenotype. Among COPD patients, upper limb strength is in general relatively well preserved compared with the lower limbs.⁴⁵ The uneven distribution of muscle weakness between upper and lower limbs could be related to differences in accustomed level of activity between the different muscle groups. In this study, we found significant differences according to COPD phenotypes in both upper and lower body strength.

Peripheral muscle abnormalities and lung hyperinflation may play a major role in the pathogenesis of exercise intolerance among COPD patients.⁴⁶ Lung hyperinflation has been related to a systemic inflammatory response, as resistive

breathing per se is an “immune challenge” for the body, elevating plasma cytokines and activating lymphocyte subpopulations.⁴⁷ It also has been shown that inspiratory fraction as an index of increased lung volumes is an independent predictor of maximal exercise capacity in patients with COPD.⁴⁸ Moreover, inflammatory markers play an important part in muscle dysfunction and exercise intolerance.⁴⁹ We have found a relationship between hyperinflation (total lung capacity and residual volume) and emphysematous patients, who have impaired exercise capacity. This could be due to the inflammation caused by hyperinflation, which is related to peripheral muscle dysfunction.

It is worth noting that the physical capacity parameters – including exercise capacity and PMS – are patient-centered measurements which significantly affect patient health status.⁵⁰ Makita et al⁴ found that subjects with severe emphysema had poorer quality of life scores, evaluated using the St. George’s Respiratory Questionnaire, than those without emphysema. In our study, however, we were unable to find an association between HRQL and severity of emphysema. In turn, a significant negative relationship was found between emphysema score and the mMRC dyspnea scale.

A limitation of the study is that we used visual scoring to assess emphysema severity rather than objective quantification. However, all HRCT images were thin-slice (<2 mm) and we carefully optimized the parameters for data analysis to obtain ideal images for assessment of emphysema. We were able to assess the overall percentage of emphysema and many investigators have demonstrated that a visual emphysema score for computer tomography images was highly correlated with objective volume-based computerized assessment.^{4,14} Moreover, the sample size was not calculated by what we cannot say that the results have not reached statistical significance are not due to a small sample size.

In summary, we have shown that compared with subjects with a nonemphysematous phenotype, subjects with an emphysematous phenotype have a different profile in terms of BMI, lung function, PMS, and exercise tolerance. The severity of emphysema is highly variable, even in patients with the same GOLD stage. Our results point to major differences among distinct phenotypes within COPD that should be taken into account in future studies.

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Disclosure

All the authors declare that they do not have a conflict of interest and that they do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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