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Quality of Life and Exercise Performance in COPD – is there a Link?

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a debilitating disease. The severity of airflow limitation alone is not strongly correlated with quality of life (QoL) and, therefore, exercise testing is employed to measure functional performance objectively, which is generally believed to correlate with QoL.

Objectives: Understand the relation between exercise capacity and quality of life.

Methods: Prospective study. Stable COPD patients were consecutively recruited. We analysed demographic, clinical, functional and exercise performance data. Patients answered symptoms and quality of life questionnaires - modified Medical Research Council (mMRC) dyspnoea scale, COPD Assessment Test (CAT), COPD Clinical Questionnaire (CCQ).

Results: 124 subjects - 13% female, mean age 66 ± 9years. Most patients were GOLD B or D (36% and 33%). Median FEV1 was 47%, (38-65%). Forty subjects (32%) had mMRC ≥ 2, CAT was ≥ 10 in 35% and CCQ ≥ 1.5 in 40% of patients. FEV 1 and hyperinflation, measured by IC/TLC, correlated with mMRC and CCQ but not with CAT. DLCO correlated better with mMRC and CCQ than CAT. The median peak VO2, in CPET, was 15.5 mL/min/kg (13.6-17.8 mL/min/kg). The 6MWD median was 479 meters (404-510 m), with median ∆SpO2 5% (3-9%). Patients with mMRC ≥ 2 had worse performance in both 6MWT and CPET - lower 6MWD, peak workload and peak VO2 and higher ∆SpO2 and ∆Borg. The 6MWD, peak workload and peak VO2 also correlated with quality of life (CAT and CCQ). Higher mMRC and CCQ were associated with dynamic hyperinflation, but not CAT.

Conclusion: Symptoms and QoL can estimate exercise performance.

Keywords: QoL; PRO; 6-min walk test; 6MWD; CPET; Peak VO_2

Introduction

Exertional dyspnoea and reduced exercise capacity are typical features of chronic obstructive pulmonary disease (COPD) [1]. Lung function parameters evaluated at rest cannot accurately predict exercise capacity, thus exercise testing is a precious tool to evaluate these patients [2].

Dyspnoea is the most common exercise-limiting symptom in COPD [3, 4] and a better explanatory factor for exercise inactivity than FEV1 [5]. Dyspnea correlates with patient's performance during the 6-minute walk test (6MWT) [6] better than FEV1 [7]. Nonetheless, characterizing COPD only according to breathlessness does not achieve a full vision of the disease and the patient`s daily limitations as it is recognized that COPD has multiple symptomatic effects on health-related quality of life (HRQoL) [8]. Several patient-reported outcome (PRO) measures are used to assess HRQoL [9-12]. The severity of airflow limitation alone is not strongly correlated with HRQoL in COPD patients and exercise testing is believed to better assess functional performance and overall HRQoL [13, 14]. Nonetheless, the extent to which laboratory and field-based exercise test correlate with PROs in not fully understood. Since 2011, Global Initiative for Chronic Obstructive Lung Disease strategy (GOLD) adopted St. George's Respiratory Questionnaire (SGRQ) [15] as a new assessment tool for COPD patients. SGRQ is the most widely used and valid tool to evaluate the health status of COPD patients [9] but it is composed of 50 items with 76 weighted responses which may be difficult to use in clinical practice. The COPD Assessment Test (CAT) was developed to minimize the complexity of SGRQ, and it is associated with clinically important variables in COPD patients – dyspnoea measured by mMRC, exacerbations and lung function [11]. The clinical COPD Questionnaire (CCQ) is a simple questionnaire; it is easy to apply in daily routine and correlates well with SGRQ, CAT and lung function [12, 16-18]. CCQ also seems to be a good instrument for assessing health status and predict mortality in COPD patients [19]. GOLD recommends a comprehensive approach to adequately manage symptoms in COPD and proposes the mMRC, CAT and CCQ as interchangeable instruments for evaluation health status [17, 20].

The easiest and most used exercise test in COPD is the 6MWT [21]. It provides important data such as the walked distance and desaturation during the test and it is a crucial parameter of the BODE index [22]. The variation in the distance covered during the 6MWT correlates with changes in spirometry [23] and it is also a better predictor of mortality than FEV1 [24, 25]. Still, the cardiopulmonary exercise test (CPET) is considered the gold standard in these patients, due to its ability to determine the level of exercise limitation and its causes [26]. CPET indexes, such as peak oxygen uptake (VO_2 peak), ventilatory equivalents for carbon dioxide production (VE/VCO_2) and arterial oxygen saturation (SpO2) provide important functional information and are better prognostic predictors than lung function measurements obtained at rest [27-29].

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In clinical practice, exercise testing is not always available or is not used by clinicians and the severity of symptoms or QoL impairment should be a stimulus for further investigation. Only limited evidence is available to support an association between exercise test outcomes and PRO in patients with COPD [30]. The limited data available for CPET suggests that it may be more closely associated with the SGRQ and other HRQoL outcomes than the 6MWT [30-32], but more studies are needed. The aim of the present study is, therefore, as primary outcome to investigate if breathlessness, measured by mMRC, and respiratory symptoms and QoL, measured by CAT and CCQ, can predict maximal exercise capacity assessed by CPET and 6MWT, using a large cohort of COPD patients across all severity stages and the scope of this association.

Material and Methods

Study design and participants

Single-centre, prospective studies to evaluate the impact of PRO in exercise capacity in COPD patients. We included patients with stable COPD defined by GOLD. Patients were selected consecutively after reference to the lung function department for respiratory function assessment between October 2018 and March 2019, if they could complete exercise tests (Cyclergometer – incremental protocol and 6MWT) and QoL questionnaires, irrespectively of their age, smoking history and GOLD stage. All bronchodilators and corticosteroid medication were allowed in the study. Patients were classified as non-exacerbators if they did not have moderate to severe exacerbations in the past 12 months.

Exclusion criteria included: Diagnosis of asthma; Severe emphysema requiring endobronchial interventions within 6 months prior to screening; Pregnancy; History of myocardial infarction within 6 months; Life-threatening cardiac arrhythmia; Diagnosis of thyrotoxicosis; Known active tuberculosis. A total of 8 participants were excluded (132 subjects screened): 6 subjects had physical limitations that impaired the ability to perform exercise tests and 2 subjects missed the scheduled exams (Figure 1).

Procedure

Ethical approval for this study was obtained from the Ethics Committee (CHVNG – 199/2018). The study was conducted according to the ethical principles of the Declaration of Helsinki. The purpose of the study was explained to prospective participants and informed consent form was obtained before any assessment was performed.

Data were collected by the authors and respiratory function tests were performed by the Pulmonary Function Testing Laboratory cardiopulmonary technicians. Sociodemographic characteristics and medications prescribed were recorded and anthropometric characteristics were measured. CAT, CCQ and mMRC dyspnoea scale were collected before respiratory testing. In assessment of COPD, An mMRC value<2, a CAT value<10 or a CCQ value<1.5 suggest stable health status [1].

Patients performed pulmonary function testing following ATS/ERS guidelines [33] including routine post-bronchodilator spirometry [34] and lung volumes measurement with plethysmography [35]. The 6MWT followed the ATS recommendations [36-37]. Participants were encouraged to resume walking as soon as possible but they were allowed to stop during the test if their symptoms became intolerable. A single operator monitored and recorded the 6MWD simultaneously. The distance walked in the test was reported in meters and as a percentage of predicted value using reference equations previously developed for healthy population [38]. Oxygen desaturation and dyspnoea and leg discomfort measured by BORG scale in the beginning and end of the test [39] were recorded. Desaturation was defined as ≥ 4% reduction between arterial oxygen saturation measured by Pulse oximetry pre- and post-test ($\Delta SpO_2 \geq 4\%$) and post-test SpO_2<90% [24,40]. Use of oxygen during the test was standardised, if required (patients with long term oxygen therapy (LTOT) completed the test with oxygen). Due to practical reasons (time and staff constrains), each patient performed only one 6MWT. Incremental CPET followed ATS/ACCP standards

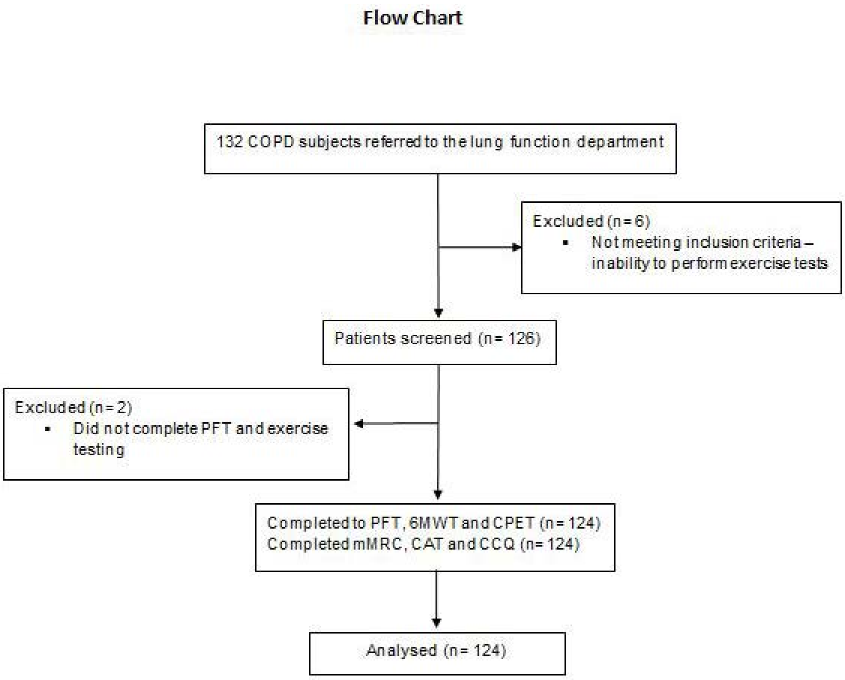

Figure 1: Flow chart (COPD- Chronic Obstructive Pulmonary Disease; PFT- Pulmonary Function Tests; 6MWT- 6 Minute Walking Test; CPET- Cardiopulmonary Exercise Test; mMRC- modified Medical Respiratory Council Dyspnoea Scale; CAT- COPD Assessment Test; CCQ- Clinical COPD Questionnaire).

[41]. Patients were subjected to symptom-limited incremental exercise with progressively increasing work rate until fatigue was reached (increment selected to maintain exercise for 8–10 min). We performed breath-by-breath monitoring of cardiopulmonary variables [Minute ventilation (V_E), Pulmonary O2 uptake (VpO_2), Pulmonary CO_2 output (VCO_2), Heart Rate (HR)]. Dynamic hyperinflation was assessed by measuring IC repetitively during CPET as patients were required to take a deep inspiration, after normal expiration, at predetermined intervals of 2 min [42]. Ventilatory limitation at peak exercise was defined by VE/maximum voluntary ventilation (MVV) above 85% [43,44].

Statistical analysis

Data are presented as frequency (%) and mean ± SD or median and interquartile range. The normality of the data distribution was checked by the Kolmogorov–Smirnov test. Unpaired t-test, Mann-Whitney test and Chi square test were used for comparisons when appropriate. Relationships between variables were assessed by Pearson correlation coefficient (r) or by Spearman's rank correlation coefficient (rho), depending on the data distribution. A statistical analysis was undertaken using SPSS 28.0. p<0.05 was considered significant.

Results

Main clinical and functional characteristics of the 124 study participants included in the study are presented in (Table 1). Our cohort was mostly male (87%) with a mean age of 66 years (±9). Only 6% of our patients were non-smokers. Most patients were GOLD B or D (36% and 33%, respectively) and had moderate or severe airflow limitation (median FEV1 was 47% of predicted, interquartile range (IQR) 38-65%). Static hyperinflation (TLC>120%) was present in 43% of patients. Forty-nine patients (40%) were enrolled in pulmonary rehabilitation (PR) programs. Forty patients (32%) had mMRC ≥ 2, CAT was ≥10 in 35% of our cohort and CCQ ≥1.5 in 40% of patients (Table 1).

In our group of patients, PR was associated with less symptoms measured by lower mMRC<2 (p=0.02) and improved QoL with CCQ<1.5 (p<0.01). CAT was not associated with PR. Non-exacerbators had less symptoms and lower QoL, according to all questionnaires (p<0.01). Having heart diseases (6 patients had cardiac arrythmias, 2 had valvular disease, 3 had ischemic heart disease and 10 had heart failure) or sleep apnoea did not influence the presence of symptoms or patient´s QoL (p>0.05).

We found a strong correlation between CAT and CCQ. mMRC correlated moderately with both CCQ and CAT. DLCO correlated with both symptoms (mMRC) and QoL (CCQ and CAT) but the correlation with CAT was weak. FEV 1 and hyperinflation, measured by IC/TLC, correlated with mMRC and CCQ but not with CAT (Table 2a and 2b).

The median workload in CPET was 64 watts (46-88 W) with median peak VO2 15.5 mL/min/kg (13.6-17.8 mL/min/kg), corresponding to 65% predicted (56-74%) Table 3. Median peak VE was 40 L/min (31-49 L/min) and 71% of patients had ventilatory limitation in cyclergometry (76% presented with dynamic hyperinflation during the exam). In

Table 1: Baseline characteristics of study participants.

Sex - female, n (%)	**16(13)**	**Exacerbator, n (%)**	**54(44)**
Age (years-old)	66 (±9)*	Respiratory Rehabilitation, n (%)	49(40)
BMI (Kg/m^2)	27 (±4)*	LTOT, n (%)	8(7)
Smoking history		OSA, n (%)	13(11)
Current smokers, n (%)	37(30)	Heart disease, n (%)	21(17)
Former smokers, n (%)	79(64)	mMRC, median (P25-P75)	1 (1-2)#
GOLD stage n (%)		mMRC ≥2, n (%)	40 (32)
A	26(21)	CAT, median (P25-P75)	8 (5-12)#
B	44(35)	CAT ≥10, n (%)	43 (35)
C	13(11)	CCQ, median (P25-P75)	1.2 (0.6-2.0)#
D	41(33)	CCQ ≥1.5 n (%)	52 (42)
Data presented as mean and standard deviation* or median and quartiles# and n(%) for qualitative variables abbreviations			
BMI: Body Mass Index; **GOLD**: Global Initiative for Chronic Obstructive Lung Disease; **LTOT**: Long Term oxygen Therapy; **OSA:** Obstructive Sleep Apnoea; **mMRC**: modified Medical Respiratory Council Dyspnoea Scale; **CAT**: COPD assessment test; **CCQ**: Clinical COPD Questionnaire.			

Table 2(a and b): Correlations between PRO, Lung function and exercise tests parameters.

	CAT	**mMRC**	**CCQ**	**FEV1 (L)**	**FEV1 (%)**	**IC/TLC**	**DLCO (%)**
CAT	1	**.515****	.819**	-0.175	-0.127	-0.137	**-.208***
mMRC	**.515****	1	**.592****	**-.180***	-0.143	**-.184***	**-.330****
CCQ	**.819****	**.592****	1	**-.235****	-0.161	**-.224***	**-.289****

	6MWT				**CPET**						
	Distance (m)	∆spO2 (%)	∆Borg dyspnea	∆Borg fatigue	Peak W (watts)	Peak VO_2 (%)	Peak VO_2 (ml/min/kg)	∆spO_2 (%)	Peak O_2/HR	Peak HR (%)	Peak VE (L/min)
CAT	**-.248****	-0,055	**.345****	**.332****	**-.294****	**-.179***	-0,147	-0,084	-0,096	**-.344****	**-.181***
mMRC	**-.370****	**.217***	**.512****	**.276****	**-.422****	**-.443****	**-.382****	**.238****	**-.315****	**-.339****	**-.260****
CCQ	**-.353****	0,027	**.428****	**.352****	**-.432****	**-.287****	**-.293****	-0,011	-0,153	**-.444****	**-.262****
(Significant correlations on **bold**, * p<0.05, ** p<0.01)											
Abbreviations: mMRC: modified medical respiratory council dyspnoea scale; **CAT**: COPD assessment test; **CCQ**: Clinical COPD Questionnaire; **FEV1**: Forced Expiratory Flow in 1sec; **IC**: inspiratory capacity; **TLC**: total lung capacity; **DLCO**: lung diffusion capacity for carbon monoxide; **L**: liters, **%**:percentage; **6MWT**: 6-minute walk test; **6MWD**: 6-minute walk distance; **SpO_2**: pulse oxygen saturation; **CPET**: Cardiopulmonary exercise test; **peak VO_2**: peak oxygen uptake; **peak W**: peak workload; **AT**: Anaerobic threshold; **VE/VCO_2**: minute ventilation/carbon dioxide production; **peak O_2/HR**: peak oxygen pulse; **VE**: minute ventilation; **MVV**: maximal voluntary ventilation; **HR**: heart rate; **bpm**: beats per minute; **W**: watt; **L**: liters, **% pred**: percentage predicted; **ml**: millilitre; **min**: minute; **n**: number.											

6MWD, median distance was 479 meters (404-510 m), with median ΔSpO_2 5% (3-9%) and ΔBorg dyspnoea 2 (0-3).

The mMRC scale correlated with exercise performance assessed by both tests as well as ΔSpO_2 and ΔBorg Table 2a and 2b. In fact, patients with mMRC≥2 had significantly worse performance in both 6MWT and CPET, namely lower 6MWD, peak workload and peak VO_2. ΔSpO_2 was significantly higher in both tests in patients with mMRC≥2 (Table 3).

The 6MWD, peak workload and peak VO_2 were also lower in more symptomatic patients measured by both CAT and CCQ but ΔSpO_2 was not different between groups with both questionnaires (Tables 2a, 2b and 3).

ΔBorg dyspnoea and ΔBorg fatigue during 6MWT were higher if patients were more symptomatic, using all questionnaires (Tables 2a, 2b and 3).

Higher mMRC and CCQ were associated with dynamic hyperinflation, but not CAT (Table 3).

Discussion

Our study found a significative relation between exercise capacity in COPD patients GOLD A-D using 6MWT and CPET and PRO, using mMRC, CAT and CCQ questionnaires. The CAT questionnaire and mMRC scale were previously identified has predictors of maximum exercise capacity in CPET (maximum VO_2 and maximum workload) [31, 32] but 6MWT performance was not evaluated in these studies. Higher mMRC and CCQ were associated with dynamic hyperinflation, but not CAT. High dyspnoea scores had already been associated with high minute ventilation (VE) and dynamic hyperinflation during exercise [32] but we did not find previous studies using CCQ, which a novelty of our findings.

Previously, Durr S et al. found a correlation between 6MWD and CAT [45] and Liu W et al. reported a correlation between both SGRQ score and MRC scale and the 6MWD, with lower MRC and SGRQ scores when patients walked >350 m [46]. To our knowledge there is no data available using the CCQ questionnaire to estimate exercise capacity in COPD with both CPET and 6MWT.

The ΔBorg dyspnoea and the ΔBorg fatigue during 6MWT were higher if patients were more symptomatic, using all questionnaires, which is in accordance with previous studies that analysed mMRC and CAT [31, 32]. The ΔSpO_2 measured during 6MWT and CPET was significantly higher in more dyspnoeic patients with (mMRC ≥ 2), but

Table 3: Lungs function and exercise characteristics of study participants according to mMRC, CAT and CCQ.

	All patients	mMRC			CAT			CCQ		
		mMRC<2	mMRC≥2	p-value	CAT<10	CAT≥10	p-value	CCQ<1.5	CCQ≥1.5	p-value
Lung Function										
FEV1 (%)	47 (38-65)	59 (38-69)	43 (31-50)	**0.01**	46 (38-68)	47 (39-63)	0.84	51 (38-59)	40 (34-51)	**<0.01**
IC (%)	88 (73-105)	89 (75-107)	86 (64-94)	0.08	89 (73-105)	86 (74-106)	0.89	90 (78-109)	85 (69-94)	**0.03**
TLC (%)	116 (106-130)	114 (106-124)	122 (106-135)	0.07	116 (106-128)	116 (106-134)	0.31	113 (105-125)	121 (110-134)	**0.04**
IC/TLC	0.32 (0.26-0.39)	0.34 (0.28-0.39)	0.28 (0.22-0.35)	**<0.01**	0.33 (0.26-0.39)	0.31 (0.26-0.39)	0.51	0.34 (0.29-0.40)	0.28 (0.23-0.35)	**<0.01**
RV (%)	161 (137-194)	154 (135-183)	173 (134-217)	**<0.01**	155 (132-192)	168 (142-195)	0.08	151 (126-159)	174 (148-213)	**<0.01**
DLCO (%)	57 (46-73)	63 (51-77)	51 (36-59)	**<0.01**	58 (48-76)	55 (42-69)	0.12	61 (50-77)	53 (40-68)	**<0.01**
6MWT										
6MWD (meters)	479 (404-510)	488 (431-524)	412 (332-480)	**<0.01**	480 (423-519)	430 (372-498)	**<0.01**	581 (519-581)	424 (373-489)	**<0.01**
ΔSpO2 (%)	5 (3-9)	5 (2-8)	8 (4-11)	**<0.01**	5 (3-10)	5 (3-8)	0.65	3 (2-3)	6 (4-9)	0.29
Supplemental oxygen (n/%)	8/7	3/4	5 /13	0.06	5/2	3/7	0.86	0	4(8	0.64
ΔBorg dyspnoea	2(0-3)	1 (0-2)	3 (2-5)	**<0.01**	1 (0-2)	2 (1-4)	**<0.01**	1 (0-2)	3 (1-4)	**<0.01**
ΔBorg fatigue	1 (0-3)	1 (0-2)	3 (0-4)	**<0.01**	1 (0-3)	2 (1-4)	**<0.01**	1 (0-2)	2 (0-4)	**<0.01**
CPET										
Peak Workload	64 (46-88)	71 (53-95)	47 (28-65)	**<0.01**	65 (49-92)	56 (35-75)	**<0.01**	73 (55-92)	50 (28-67)	**<0.01**
Peak VO_2 (mL/min)	1101 (889-1311)	1194 (1100-1411)	928 (792-1102)	**<0.01**	1160 (927-1372)	1030 (809-1205)	**0.01**	1112 (987-1411)	993 (800-1154)	**<0.01**
Peak VO_2 (mL/min/kg)	15.5 (13.6-17.8)	16.5 (14.9-18.7)	13.2 (11.4-15.0)	**<0.01**	16.1 (14.1-18.2)	15.5 (12.6-17-3)	0.34	16.5 (14.6-18.6)	13.8 (12.5-16.6)	**0.01**
Peak VO_2 (%)	65 (56-74)	67 (61-78)	54 (48-64)	**<0.01**	65 (59-72)	61 (52-71)	0.10	66 (60-78)	60 (50-67)	**<0.01**
ΔSpO_2 (%)	2 (1-6)	1 (0-4)	4 (1-9)	**0.01**	2 (1-6)	2 (0-6)	0.37	2 (1-5)	3 (0-7)	0.75
AT (%peakVO_2)	47 (42-54)	49 (43-55)	43 (37-48)	0.09	47 (43-55)	47 (40-53)	0.66	47 (43-54)	48 (40-54)	0.90
VE/VCO_2@AT	37 (34-42)	37 (33-41)	39 (34-44)	**<0.01**	37 (34-42)	38 (34-43)	0.64	37 (34-42)	38 (34-43)	0.40
Peak O_2/HR (mL/bpm)	9.2 (7.7-10.7)	9.7 (8.2-11.3)	8.2 (7.0-9.7)	**<0.01**	9.3 (7.9-10.3)	9.0 (7.2-10.1)	0.37	9.3 (8.0-11.2)	8.9 (7.1-10.1)	0.17
Peak HR (%pred)	79 (71-86)	82 (75-87)	74 (68-81)	**<0.01**	81 (75-87)	74 (68-82)	**<0.01**	83 (76-88)	73 (66-80)	**<0.01**
Peak VE (L/min)	40 (31-49)	43 (34-53)	34 (28-39)	**<0.01**	41 (32-52)	39 (30-45)	0.15	43 (35-53)	34 (28-42)	**<0.01**
Peak VE (%MVV)	89 (71-102)	891 (73-102)	91 (70-103)	0.89	90 (73-103)	87 (69-100)	0.35	88 (71-100)	91 (77-104)	0.33
Dynamic hyperinflation (n/%)	94 /76	58 /69	36/90	**0.01**	59/48	35/28	0.29	51/41	43/35	**0.02**
Number of patients (n/%)	124/100	84/68	40/32		81/65	43/35		74/60	50/40	

Data presented as median and quartiles and n/% for qualitative variables; p<0.05 in bold.

Abbreviations: **6MWT**: 6-minute walk test; **6MWD**: 6-minute walk distance; **%**: percentage; **SpO_2**: pulse oxygen saturation; **CPET**: Cardiopulmonary exercise test; **peak VO_2**: peak oxygen uptake; **AT**: Anaerobic threshold; **VE/VCO_2**: minute ventilation/carbon dioxide production; **peak O_2/HR**: peak oxygen pulse; **VE**: minute ventilation; **MVV**: maximal voluntary ventilation; **HR**: heart rate; **bpm**: beats per minute; **W**: watt; **L**: liters, **% pred**: percentage predicted; **ml**: millilitre; **min**: minute; **n**: number.

the CAT and CCQ did not correlate with desaturation in both exercise tests. Crisafulli E et al. had not been able to establish a relation between desaturation during CPET and mMRC [32].

PR is known to improve exercise capacity [42] and it was previously known that the CCQ, SGRQ, CRQ and CAT all significantly improved after PR [47-49] but in our group of patients, PR was associated with less symptoms (mMRC<2) and improved QoL measured by CCQ (CCQ<1.5) but not with CAT score, suggesting that CCQ may be a better choice to evaluate COPD patient's response to rehabilitation, despite the good correlation between them. CAT is recommended in clinical practice to follow patients under rehabilitation [18, 50] and our contradictory results may be related to the inclusion of GOLD A COPD patients in our cohort, who are less symptomatic, have no indication for PR and usually are not included in PR studies. We need further studies comparing both questionnaires.

Non-exacerbators had less symptoms and lower QoL, measured with the three questionnaires ($p<0.01$), as expected from previous literature [11, 16].

FEV 1 and hyperinflation, measured by IC/TLC, correlated with mMRC and CCQ but not with CAT. In fact, no difference was found for FEV1 and hyperinflation between patients with CAT<10 and CAT ≥ 10. Similarly, DLCO correlated with both symptoms (mMRC) and QoL (CCQ and CAT) but the correlation with CAT was weak and no difference was found when we compared patients with CAT<10 and patients with CAT ≥ 10. Previous studies had found weak to moderate correlations between FEV1 and both CCQ and CAT [12] and this difference from our cohort may be related to the broad inclusion of COPD patients of all severity stages. Hyperinflation and DLCO were previously associated with mMRC in one observational study [32] and IC (at rest and at exercise peak) correlated with both CAT and mMRC in another recent study [31]. Further investigation and sample enlargement may help to clarify the association between QoL and lung function, specifically in different GOLD stages.

We found a strong correlation between CAT and CCQ, consolidating the idea that these are good COPD specific health related QoL instruments, easier to use than SGRQ [16, 18, 49]. mMRC correlated moderately with both CCQ and CAT, also confirming previous findings [11, 12].

One limitation of our results is the lack of a duplicate 6MWT, but a second test is currently mainly recommended for pharmacological and non-pharmacological impact evaluation over time [36]. Also, 89% of our patients had previously performed the test, which reduces the potential impact of a lack of the learning effect.

The current study was based on a large set consisting of patients with clinically stable COPD in GOLD stages A-D and it represents a real-world setting, since we included non-smokers and smokers or former smokers, patients with heart diseases and both patients with and without PR. The sample size, the wide spectrum of disease severity, the analysis of several variables related to exercise response including dynamic hyperinflation and the use of mMRC, CAT and CCQ simultaneously are clear strengths of our study. To our knowledge, this is the first prospective study to consider the relation between several COPD HRQoL scales and exercise capacity measured with both field and laboratory studies. Our study was an observational study and, therefore, we cannot establish the contributing factors for exercise limitation. Further longitudinal studies evaluating maximum exercise capacity in COPD patients with varying degrees of dyspnoea and QoL over time may add valuable information.

Conclusion

Our study highlights the value of PRO, measured with the mMRC, CAT and CCQ questionnaires scales in the assessment of the daily living activity in patients with COPD and confirms that dyspnoea and QoL are associated with maximum exercise capacity was measured by 6MWT and CPET in this population. Along with mMRC and CAT, we state that the CCQ questionnaire is an important and frequently overlooked tool to estimate exercise capacity in COPD patients. Our findings suggest that both mMRC and CCQ correlate better with lung function and response to PR than CAT, contrarily to some previously available data which needs to be further evaluated and clarified in future investigations.

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