Cardiopulmonary and Gas-Exchange Responses during the Six-Minute Walk Test in Patients with Chronic Obstructive Pulmonary Disease

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Key Words

Oxygen uptake kinetics · Six-minute walk test · Mobile cardiopulmonary monitoring · Submaximal exercise · Cardiopulmonary exercise testing

Abstract

Background: The 6-min walk test (6MWT) is representative of daily life activities and reflects the functional capacity of patients with chronic obstructive pulmonary disease (COPD). Information on the cardiopulmonary and gas exchange responses to the 6MWT is limited. **Objectives:** We aimed to analyze the breath-by-breath cardiopulmonary and gas exchange responses of patients with COPD during the 6MWT. We also investigated the extent to which parameters reflecting cardiopulmonary and gas exchange function are associated with exercise capacity. **Methods:** The oxygen uptake (VO_2) kinetics of patients were obtained using mobile telemetric cardiopulmonary monitoring during a 6MWT. A new mean response time (MRT) index was developed to quantify VO_2 on-kinetics by correcting MRT for work rate (wMRT). Multiple linear regression analysis was performed to assess the association between variables reflecting cardiopulmonary and gas exchange function and exercise capacity [6-min walking distance (6MWD) and VO_2 at steady state ($\text{VO}_{2\text{SS}}$)]. **Results:** In 72 COPD patients (29 fe-

males) with a mean (SD) age of 65 (10) years, FEV_1 44 (14) % predicted exercise capacity as assessed by $\text{VO}_{2\text{SS}}$ ($p = 0.003$) was significantly reduced across the stages of COPD. The criteria for maximal effort during the 6MWT were fulfilled by 82% of the patients. After adjustment for covariates, wMRT was independently associated with 6MWD ($p = 9.7 \times 10^{-5}$) and $\text{VO}_{2\text{SS}}$ ($p = 5.5 \times 10^{-10}$). **Conclusions:** As wMRT mostly depends on the rate of increase of pulmonary blood flow, our results underline the fact that cardiocirculatory function may play a significant role in exercise tolerance in patients with COPD. Our findings imply that modification of cardiocirculatory function may be beneficial in the treatment of COPD patients and improve their outcome more than anticipated previously.

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Introduction

Chronic obstructive pulmonary disease (COPD) is associated with pronounced exercise intolerance resulting in an impaired health-related quality of life [1], greater health care requirements [2] and increased mor-

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tality [3]. Cardiopulmonary exercise testing (CPET) is used to identify the factors contributing to exercise intolerance by linking performance and physiological parameters to the underlying metabolic substratum in COPD patients [4]. It is routinely performed on a cycle-ergometer or motorized treadmill using a rapid ramped incremental protocol to the limit of tolerance [4]. Since most activities of daily living are performed in a nonincremental fashion and at a submaximal level of exertion, the 6-min walk test (6MWT) is representative of daily life activities and can therefore accurately reflect the functional capacity of patients [5].

The 6MWT is often used in clinical practice and research studies as it embodies an essential functional task and is inexpensive, reproducible and responsive to standardization [4]. The classic 6MWT can only be used as a nonspecific assessment of functional capacity because cardiopulmonary and gas exchange responses to exercise cannot be determined with this test [6]. In particular, the assessment of the change in oxygen uptake (VO_2) in the initial phase of the 6MWT (VO_2 on-kinetics) may provide important information because most of the activities of daily living require a repetitive transition from rest to submaximal exercise intensity. In several chronic diseases, it has been demonstrated that VO_2 on-kinetics have a higher prognostic value than peak VO_2 [7]. An additional disadvantage of the classic 6MWT is that it cannot be used to identify factors contributing to exercise performance. Improved knowledge of the cardiopulmonary and gas exchange responses during the 6MWT may lead to a better understanding of the pathophysiological mechanisms causing functional impairments in patients with COPD.

To address the above-mentioned issues, we aimed to analyze the breath-by-breath cardiopulmonary and gas exchange responses of patients with COPD, i.e. with Global Initiative on Obstructive Lung Disease (GOLD) stages II–IV, during the 6MWT using mobile telemetric cardiopulmonary monitoring (MOB). We investigated the extent to which parameters reflecting cardiopulmonary and gas exchange function are associated with exercise capacity. Given the vast pathophysiological heterogeneity of exercise limitation in COPD, it may be reasonable to presume that the determinants of exercise capacity vary among patients. Furthermore, we investigated whether the 6MWT assesses the submaximal or maximal level of functional capacity in COPD patients.

Material and Methods

Study Design

We performed a cross-sectional, observational study on patients with COPD (GOLD stages II–IV). Patients referred to the Pulmonary Division of the University Hospital, Basel, Switzerland, between August 2003 and June 2007, were considered for participation in the study (fig. 1). Exclusion criteria were the need for oxygen supply or a resting transcutaneous oxygen saturation (SpO_2) of <85% while breathing room air, an inability to walk, any acute coronary event during the previous month and conditions precluding the use of a face mask (e.g. an anatomic anomaly, claustrophobia or panic disorder). All patients gave their informed consent. Our local institutional review board approved the study. Some of the study population data were used in another study evaluating the feasibility, safety and clinical usefulness of a MOB-enhanced 6MWT [8].

Six-Minute Walk Test

All patients performed the 6MWT after pulmonary function testing. The 6-min walking distance (6MWD) was measured according to the guidelines of the American Thoracic Society (ATS) [9], with standardized encouragement [10], in a 30-meter corridor under supervision of an experienced technician. Before starting the 6MWT, patients were to rest seated for 3–5 min until stable VO_2 values had been recorded, i.e. VO_2 at rest (VO_2 rest). The 6MWT was followed by a recovery phase, where the patient rested on a chair.

6MWT with the MOB Device

Indirect calorimetry was performed using the Oxycon Mobile® (Viasys Healthcare, Conshohocken, Pa., USA) portable wireless CPET device in order to quantify breath-by-breath oxygen exchange kinetics during the 6MWT. Pulse rate was determined using an electrocardiogram-triggered belt (Polar T-61®, Polar Electro, Cuxhoe, UK). SpO_2 was measured using a finger clip. VO_2 and carbon dioxide output (VCO_2), tidal volumes and breathing frequency were assessed using a face mask (dead space <70 ml) with a flow sensor and a gas analyzer. The patient carried data storage and transfer units on a harness. Wireless transfer of breath-by-breath data to a laptop computer allowed real-time monitoring. The feasibility and safety of MOB had been tested in previous work by performing both 6MWT and MOB on consecutive days in random order [8]. The additional weight of the equipment (950 g) had no effect on the walking distance [8]. The exact 6MWT-MOB procedure has been described previously [8]. Exercise capacity was quantified by 6MWD and VO_2 at steady state ($\text{VO}_{2\text{SS}}$).

Exercise Limitation according to ATS Criteria

The different types of exercise limitation were determined based on the ATS/American College of Chest Physicians Statement on CPET recommendations: ‘the patients’ effort was considered to be maximal if either one or more of the following criteria were fulfilled; *ventilatory limitation*: ventilatory reserve <11 liters or <15%; *cardiocirculatory limitation*: maximal heart rate >90% predicted; *gas exchange limitation*: VO_2 peak >84% predicted’ [4]. VO_2 maximal predicted and maximal predicted heart rate (HR) were calculated using standard equations [11].

Pulmonary Function

Spirometry, whole-body plethysmography and diffusion capacity measurements were performed according to the ATS and European

Respiratory Society guidelines with a commercially available system (Body 500™, ZAN, Oberthulba, Germany) [12, 13]. Postbronchodilator spirometry was performed on the same day as the 6MWTs.

Curve Fitting of VO_2

Original breath-by-breath data were imported from the MOB device. Raw data were preprocessed by averaging the breath-by-breath measurements over consecutive periods of 30 s. VO_2 kinetics describe the rate of change in VO_2 during exercise. Curves were fitted using the following nonlinear logistic regression model:

$$\text{VO}_2 = c + (d-c)/(1 + \exp(b \times (\text{time} - c))) \quad (1)$$

with b representing the steepness of the curve, $\text{time} - c$ representing VO_2 rest, d representing $\text{VO}_{2\text{SS}}$ and e representing the position of the inflection point.

Mean Response Time Reparameterization

Following the onset of constant workload exercise, the VO_2 increase (i.e. on-kinetics) can be characterized by the time, i.e. the mean response time (MRT) required for VO_2 to achieve 63% of the $\text{VO}_{2\text{SS}}$ in response to physical stress. In this study, the MRT index was calculated to quantify VO_2 on-kinetics by correcting MRT for work rate (wMRT) during the first phase of the 6MWT. This method has been described in work published previously [8]. The difference between VO_2 rest and during effort ($\text{VO}_{2\text{SS}} - \text{VO}_2$ rest) was used as a proxy for work rate during the first phase of the 6MWT.

Statistical Data Analysis

Descriptive data for continuous variables are expressed as a mean $\pm$ SD, 95% CI and percentages for frequencies. Variables were tested for parametric distribution by applying the Shapiro-Wilk test (null hypothesis rejection set at $p < 0.25$). Between-group differences of continuous variables were tested using linear models (ANOVA F test). Univariate linear regression was performed to assess the association between variables reflecting cardiopulmonary and gas exchange function and exercise capacity (6MWD and $\text{VO}_{2\text{SS}}$). Variables significantly associated with 6MWD and $\text{VO}_{2\text{SS}}$ in the univariate analysis were included in a multivariate analysis. Mixed-effect nonlinear regression was used to fit the VO_2 curves. A p value of <0.05 was considered to indicate statistical significance. All the analyses were done using R statistical software [14], including the package drc for curve fitting [15] and medrc and nlme [16] for nonlinear mixed-effects modeling.

Results

Patients' Characteristics

Seventy-five patients with moderate to very severe COPD were included in our study. In 3 patients, curve fitting was unsatisfactory, leading to their exclusion from the analysis. Two distinct patterns of response to exercise were noticed in this group: in 2 patients, VO_2 did not show a plateau, and in 1 patient, it showed a marked variability after reaching a plateau. Variable walking speed and pauses during the 6MWT are the most likely explanations for this observation. The exclusion process is depicted in figure 1.

Fig. 1. Study synopsis.

Table 1. Anthropometrics, pulmonary function, respiratory symptoms and cardiopulmonary exercise capacity

Variable	
Anthropometrics	
Subjects, n	72
Female/male	29/43
Age, years	65.2 $\pm$ 10.1
BMI	24.5 $\pm$ 5.1
Pulmonary function	
FEV ₁ , liters	1.1 $\pm$ 0.4
FEV ₁ , % predicted	43.5 $\pm$ 14.4
FEV ₁ /IVC ratio	0.5 $\pm$ 0.1
DLCO, % predicted	51 $\pm$ 23
TLC, % predicted	116 $\pm$ 23
RV/TLC ratio	0.57 $\pm$ 0.12
Cardiopulmonary exercise capacity	
6MWD, m	328.1 $\pm$ 106.1
SpO ₂ at rest, %	93.3 $\pm$ 3.3
SpO ₂ after exercise, %	82.6 $\pm$ 7.2
SpO ₂ at desaturation, %	8.4 $\pm$ 6.5
Dyspnea ¹ at rest, 0–10	1.0 $\pm$ 1.1
Dyspnea after exercise, 0–10	5.0 $\pm$ 2.2
Leg fatigue at rest, 0–10	0.4 $\pm$ 0.4
Leg fatigue after exercise, 0–10	3.1 $\pm$ 2.2

Values are presented as mean $\pm$ SD. DLCO = Diffusion capacity for carbon monoxide; FEV₁/IVC ratio = FEV₁ expressed as a % of IVC; RV/TLC = residual volume/TLC ratio; TLC = total lung capacity. ¹ The rating of perceived exertion was assessed by the Borg scale, an 11-point scale (0–10).

Seventy-two patients were included in the final analysis. Data on their anthropometrical characteristics, lung function, respiratory symptoms and exercise capacity are presented in table 1. COPD was moderate (GOLD II) in 29.2% of the patients, severe (GOLD III) in 54.2% and very severe (GOLD IV) in 16.7%.

Fig. 2. **a** Curve fitting of VO_2 for patients in GOLD stages II–IV. **b** The sigmoidal shapes of the VO_2 curves of the patients in the different GOLD stages including prediction equations for VO_2 . At baseline, VO_2 (i.e. VO_2 rest) is different between the groups ($p =$

0.0024). Both the steepness of the curve ($p = 0.0302$) and $\text{VO}_{2\text{SS}}$ ($p = 0.0048$) show highly significant differences between GOLD stages II–IV.

Exercise Capacity and VO_2 Kinetics at Exercise Onset

Figure 2 shows the sigmoidal shapes of the VO_2 curves of the patients at the different GOLD stages. At baseline, VO_2 rest differs between groups ($p = 0.0024$; table 2). The resting period of 5 min is followed by a period of rapid growth at exercise onset (the steepness of the curve), settling into $\text{VO}_{2\text{SS}}$ after 3 min. Both the steepness of the curve ($p = 0.0302$) and $\text{VO}_{2\text{SS}}$ ($p = 0.0048$) show highly significant differences between the GOLD stages. wMRT also shows highly significant differences between these GOLD stages ($p = 0.0013$), with GOLD stage IV showing high wMRT values. $\text{VO}_{2\text{SS}}$ was significantly ($p = 0.003$) reduced across the stages of COPD (table 2).

Exercise Limitation according to ATS Criteria

Table 3 demonstrates that 81.9% of the patients with COPD reached the criteria for maximal effort as specified above, 59.7% had a ventilatory limitation, 12.5% had a cardiocirculatory limitation and 72.2% had a gas exchange limitation. Some patients fulfilled more than one criterion for maximal exercise.

Determinants of Exercise Capacity

The results of the univariate regression analysis are shown in table 4. There was a significant association between exercise capacity (6MWD), FEV_1 and wMRT. Exercise capacity as quantified by $\text{VO}_{2\text{SS}}$ was associated with BMI, FEV_1 , FVC, HR, dyspnea and wMRT. After adjusting for covariates in multiple regression analyses (table 5), wMRT was found to be independently associated with 6MWD and $\text{VO}_{2\text{SS}}$. We found no independent association with dyspnea. There was a significant association between SpO_2 at rest and 6MWD.

Discussion

The purpose of this study was to gain insights into the cardiopulmonary and gas exchange responses of patients with COPD in the different GOLD stages during the 6MWT. The VO_2 curves of the patients with different GOLD stages all have sigmoidal shapes. Patients with advanced airflow limitation (higher GOLD stages) have altered VO_2 kinetics during the transition from rest to work (wMRT) as well as a lower exercise capacity ($\text{VO}_{2\text{SS}}$).

Table 2. Characteristics of participants, grouped into 3 categories according to GOLD stage

	GOLD II	GOLD III	GOLD IV	p value
Number of patients	21	39	12	
Sex, female	10	14	5	
Age, years	67.3±11.6	66.0±7.6	58.8±12.7	0.050
BMI	28.3±5.5	23.7±4.2	20.4±2.2	<0.001
FEV ₁ , l/s	1.5±0.4	1.0±0.2	0.7±0.1	<0.001
FVC, liters	2.8±0.9	2.6±0.8	2.1±0.4	0.049
FEV ₁ /FVC	0.6±0.1	0.4±0.1	0.4±0.1	<0.001
VO _{2SS} , ml/min	986.0±268.4	844.7±235.8	677.7±203.2	0.003
b (steepness of the curve)	-0.039±0.0018	-0.039±0.0016	-0.030±0.0027	0.0302
c (lower asymptote)	281.8±4.4	286.2±3.3	261.9±6.4	0.0024
d (upper asymptote)	984.0±50.5	853.6±38.0	695.2±69.7	0.0048
Walking distance, m	359.1±110.2	327.5±90.1	275.5±133.0	0.093
Dyspnea (Borg scale)	4.2±1.8	5.4±2.3	5.0±2.4	0.112
MRT, min	1.16±0.42	1.19±0.41	1.51±0.69	0.075
wMRT, min ² /ml	1.99 × 10 ⁻³ ±1.19 × 10 ⁻³	2.56 × 10 ⁻³ ±1.59 × 10 ⁻³	6.86 × 10 ⁻³ ±10.88 × 10 ⁻³	0.0013

Data are presented as mean ± SD. FEV₁/FVC ratio = FEV₁ expressed as a % of FVC.

The criteria for maximal effort during the 6MWT were fulfilled by 81.9% patients. After adjusting for covariates in the multiple regression analyses, wMRT was found to be independently associated with both 6MWD and VO_{2SS}.

There is some debate in the literature as to whether the 6MWT in patients with COPD reflects maximal [17, 18] or submaximal [19, 20] sustainable exercise. Troosters et al. [19] compared the physiological responses of 20 patients with COPD during an encouraged 6MWT and maximal-cycle ergometer exercise testing. They demonstrated that encouraged 6MWT (in the 4th–6th min) and peak cycling showed identical VO₂ responses and similar HR responses. As the VCO₂ and ventilatory response were found to be lower during walking than at peak cycling, it was concluded that the 6MWT should be referred to as submaximal. Hill et al. [21] compared the peak and submaximal cardiopulmonary responses to the 6MWT with a ramp-cycle ergometer test in 24 patients with moderate COPD. In accordance with the results of Troosters et al. [19], they demonstrated that the 6MWT elicited a similar peak rate of VO₂ and HR as a cycle ergometer test. Turner et al. [22] observed similar peak exercise responses achieved in the 6MWT and CPET in 20 patients with moderate to severe COPD. Controversially, van Helvoort et al. [20] found that VO₂ and HR were lower after the 6MWT than at peak cycling. According to the ATS criteria [4] for the determination of test in-

Table 3. Exercise limitations according to ATS criteria

Limitations	Patients, n (%)
Ventilatory	43/72 (59.7%)
Cardiocirculatory	9/72 (12.5%)
Gas exchange	52/72 (72.2%)
At least one limitation	59/72 (81.9%)

ATS criteria for the determination of test intensity were applied [9]. The effort was considered to be maximal if ≥1 of the following criteria were fulfilled: ventilatory limitation, i.e. ventilatory reserve <11 liters or <15%, cardiocirculatory limitation, i.e. maximal heart rate >90% predicted and gas exchange limitation, i.e. VO₂ peak >84% predicted.

tensity, 81.9% of our patients reached at least one limitation; this being a substantial number, the 6MWT could be considered as maximal sustainable exercise.

The multifactorial character of exercise limitation in patients with COPD was underlined by the fact that our patients experienced ventilatory, cardiocirculatory and/or gas exchange limitations. The number of patients who experienced one or more limitations is compelling and provides a rationale that, at least in some patients, exercise capacity is limited by several mechanisms as well as that a single mechanism does not necessarily dominate in every single patient.

Table 4. Determinants of exercise capacity

	6MWD			VO _{2SS}		
	estimate	SE	p value	estimate	SE	p value
Age, years	-0.75	1.25	0.5485	2.64	3.06	0.391629
BMI	2.63	2.47	0.2911	27.32	4.97	$6.43 \times 10^{-7***}$
FEV ₁ , l/s	61.31	30.88	0.05099	266.13	69.00	0.00026***
FEV ₁ , % predicted	1.99	0.84	0.02153*	6.42	1.99	0.00195**
FVC, liters	20.78	15.28	0.1781	101.88	35.31	0.005277**
HR max, bpm	0.72	0.61	0.24638	3.49	1.44	0.01831**
HR reserve, bpm	-0.50	0.60	0.4044	-3.81	1.37	0.007029**
HR rest, bpm	-1.76	0.83	0.03811*	-2.50	2.18	0.2565
SpO ₂ max, %	11.45	3.65	0.00249**	11.93	9.21	0.1997
SpO ₂ min, %	2.14	1.74	0.2241	2.22	4.20	0.5993
VE reserve, l/min	0.29	1.01	0.7718	0.52	2.46	0.8327
wMRT, min ² /ml	-9,913.28	2,395.73	$9.74 \times 10^{-5***}$	-117,278.42	16,146.35	$5.5 \times 10^{-10*}$
VE rest, l/min	-1.81	2.97	0.5450	13.28	7.010	0.06557
VO ₂ rest	0.024	0.12	0.8434	0.86	0.28	0.003091**
Dyspnea (Borg scale)	-7.385	14.250	0.606	-16.375	5.570	0.004**

SE = Standard error; SpO₂ max = SpO₂ at rest; SpO₂ min = SpO₂ at the end of 6MWT; VE = mean ventilation.
 * $0.01 \leq p < 0.05$. ** $0.001 \leq p < 0.01$. *** $p < 0.001$.

Table 5. Predictors of exercise capacity

6MWD

	Estimate	SE	t value	p value
Intercept	-490.82	348.66	-1.41	0.163904
SpO ₂ max, %	8.87	3.57	2.48	0.015586*
HR reserve, bpm	-0.12	0.85	-0.14	0.887210
FEV ₁ , % predicted	0.65	0.86	0.75	0.457409
wMRT, min ² /ml	-8,563.08	2,453.14	-3.49	0.000864***

VO_{2SS}

	Estimate	SE	t value	p value
Intercept	8.17×10^2	1.16×10	7.028	$1.79 \times 10^{-9***}$
HR reserve, bpm	-1.69	1.03	-1.65	0.1040
VO ₂ rest	4.69×10^{-1}	2.14×10^{-1}	2.19	0.0321*
FEV ₁ , liters	1.744×10^2	5.41×10^1	3.23	0.0020**
wMRT, min ² /ml	-8.68×10^4	1.64×10^4	-5.31	$1.53 \times 10^{-6***}$
Dyspnea (Borg scale)	5.141	13.447	0.382	0.704

SE = Standard error; SpO₂ max = oxygen saturation at rest.

* $0.01 \leq p < 0.05$. ** $0.001 \leq p < 0.01$. *** $p < 0.001$.

There is growing interest in submaximal exercise parameters capable of objectively evaluating the functional capacity of patients with COPD. As VO₂ on-kinetics provide information about oxygen delivery and muscle me-

tabolism, they have proved to be very successful in reflecting functional capacity in several studies [23, 24]. In addition, assessing VO₂ on-kinetics is clinically relevant because they are influenced only by the underlying disease, not by the patient's motivation or the criteria used to terminate the test [25]. It has been recently demonstrated that VO₂ on-kinetics of patients with COPD are slowed when compared to healthy age-matched controls [26, 27]. In this study, VO₂ on-kinetics (wMRT) and exercise capacity as assessed by VO_{2SS} were significantly reduced across the stages of COPD.

Furthermore, we found that VO₂ on-kinetics (wMRT) were independently associated with exercise capacity. At the onset of exercise, oxygen kinetics mostly depend on the rate of increase of pulmonary blood flow [28]. The increase in cardiac output at the onset of exercise predominantly depends on the increase in stroke volume. As patients with COPD exhibit impairment in the distensibility and vasodilatory capacity and a reduction in size of the pulmonary vascular bed, the capacity for stroke volume to augment cardiac output is limited [29, 30]. In accordance with our results, Watz et al. [29] demonstrated that impaired left ventricular diastolic filling was independently associated with reduced exercise tolerance. Although it has been postulated that exercise capacity in patients with COPD is predominantly associated with the combination

of increased ventilatory requirements (mainly secondary to increased ventilation/perfusion mismatching) and acute derangements in dynamic ventilatory mechanics [31], the results of our study underline the role of diminished stroke volume on exercise intolerance.

Our findings suggest that modification of cardiocirculatory function may be beneficial in the treatment of COPD patients and improve their outcome more than previously anticipated.

Study Limitations

It should be stressed that a causal relationship cannot be established from a cross-sectional study. In addition, the number of subjects was low, given the variance in data. Future data from controlled trials are needed to assess the impact of cardiocirculatory function on exercise capacity in patients with COPD. Another limiting factor

was the fact that MRT could not be calculated in all patients. Some patients were unable to perform the 6MWT with a constant walking speed or without interruptions, which could explain the marked variability in VO_2 in patients in whom curve fitting failed. Those patients whose VO_2 did not reach a plateau probably increased their walking speed during the 6MWT, thereby increasing work rate.

Conclusions

The cardiopulmonary and gas exchange responses of patients with COPD during the 6MWT demonstrate an alteration in VO_2 on-kinetics and a reduced exercise capacity across the GOLD stages. Most patients with COPD fulfilled the criteria for maximal effort during the 6MWT. After adjustment for covariates, wMRT was independently associated with 6MWD and $\text{VO}_{2\text{SS}}$.

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