Physiological responses to the 6-min walk test in patients with chronic obstructive pulmonary disease

T. Troosters*, J. Vilaro[#], R. Rabinovich[¶], A. Casas[¶], J.A. Barberà[¶], R. Rodriguez-Roisin[¶], J. Roca[¶]

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ABSTRACT: The 6-min walking test (6MWT) is frequently used to assess functional capacity in chronic cardiopulmonary disorders because of its simplicity. The study examines the physiological responses during encouraged 6MWT in patients with chronic obstructive pulmonary disease.

Pulmonary oxygen (O_2) uptake ($V'O_2$) was measured in 20 male patients (age 66 ± 6 yrs, forced expiratory volume in one second $45\pm14\%$ predicted) during 6MWT and incremental cycling, in random order. O_2 tension in arterial blood, carbon dioxide tension in arterial blood and arterial lactate concentration ($[La]_{art}$) were obtained in the last 10 patients. During the 6MWT, $V'O_2$ showed a plateau after the 3rd min (1.39 ± 0.28, 1.42 ± 0.31, and 1.40 ± 0.30 L·min^{-1}, 4th, 5th and 6th min, respectively), and minute ventilation ($V'E$) (42 ± 8 L·min^{-1}) was 91% maximal voluntary ventilation.

No differences were shown between 6MWT (6th min) and peak cycling exercise in $V'O_2$ (1.40 ± 0.30 *versus* 1.41 ± 0.28 L·min^{-1}, respectively), cardiac frequency (126 ± 13 *versus* 130 ± 12 beats·min^{-1}), or arterial respiratory blood gases. The two tests were significantly different in $V'E$ (42 ± 8 *versus* 47 ± 8 L·min^{-1}, 6MWT *versus* cycling, respectively), carbon dioxide production (1.30 ± 0.31 *versus* 1.45 ± 0.18 L·min^{-1}) and $[La]_{art}$ (2.9 ± 1.99 *versus* 5.9 ± 1.51 M).

The study demonstrates that an encouraged 6-min walking test generates a high but sustainable oxygen uptake. Since the oxygen uptake plateau reflects the integrated response of the system, it may explain the high prognostic value of the 6-min walking test.
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*Faculty of Physical Education and Physiotherapy, and Laboratory of Pneumology, Respiratory Muscle Unit, Katholieke Universiteit Leuven, Leuven, Belgium. [#]Escola Universitària d′Infermeria i Fisioteràpia (EUIF) Blanquerna, Universitat Ramon Llull, and [¶]Pneumology Department (Institut Clinic de Pneumología i Cirugía Torácica (ICPCT)), Hospital Clínic, Faculty of Medicine, Instituto de Investigaciones Biomédicas Agustí Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain.

Correspondence: J. Roca, Servei de Pneumologia, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain.
Fax: 34 932275455
E-mail: jroca@clinic.ub.es

Timed walking tests [1] have been extensively used in the clinical evaluation of patients with chronic cardiopulmonary disorders, mainly because of their simplicity. At present, it is recognised that these tests add prognostic information useful to the staging of patients with chronic obstructive pulmonary disease (COPD) [2, 3], primary pulmonary hypertension [4] and heart failure [5]. Timed walking tests have been shown to be sensitive to changes after interventions such as inhaled bronchodilators [6], volume reduction surgery [7, 8] and pulmonary rehabilitation [9, 10]. The 6-min walking test (6MWT), for example, is currently used in ~80% of rehabilitation programmes in the USA [11]. Despite the increasing acceptance of its usefulness, only limited data are available on the physiological load imposed on patients during the test. It is accepted that cardiopulmonary responses during constant speed treadmill walking [12] cannot be extrapolated to a patient′s performance during corridor walking tests [13–15].

The aim of the present study was to investigate pulmonary and cardiovascular responses during encouraged 6MWT in 20 patients with moderate-to-severe COPD. The authors speculate that the 6MWT is a submaximal test with oxygen (O_2) requirements clearly below measured peak O_2 uptake ($V'O_2$). Consequently, it generates ventilatory and cardiocirculatory responses below peak exercise. Despite the differences between the 6MWT and incremental exercise testing in terms of amount of exercising muscle mass and

ergonomics, the study uses incremental cycling for comparison because it is recommended as a standard for assessment of exercise tolerance in the lung function laboratory [16].

Methods

Study design

Twenty clinically-stable COPD patients (table 1) capable of performing a 6MWT were included in the study. Patients with overt comorbidity preventing them from safely performing an exercise test could not participate in this trial. One patient was refused due to an inability to support the face mask. As part of the characterisation procedures, resting pulmonary function testing and a practice walking test were carried out in all patients. Patients who required O_2 during the 6MWT were excluded from the study. On day 2, two exercise protocols were carried out in random order: 6MWT and incremental cycling exercise. Sufficient rest was assured between tests ($\geqslant$30 min and until the first test's baseline measurements of $V'O_2$, minute ventilation ($V'E$) and cardiac frequency (fC) were reproduced). In the last 10 patients, arterial respiratory blood gases (O_2 tension in arterial blood (Pa,O_2) and carbon dioxide tension in arterial blood (Pa,CO_2)) and arterial lactate concentration ($[La]art$) were also measured. All participants were informed of any risks and discomfort associated with the experiment, and written informed consent was obtained in accordance with the Committee on Investigations Involving Human Subjects at the Hospital Clínic, Universitat de Barcelona (Barcelona, Spain), which approved the study.

Pulmonary function testing

Forced spirometry, static lung volumes (MasterScreen; Jaeger, Wüerzburg, Germany), and arterial blood gas analysis at rest (Ciba Corning 800, Medfield, MA, USA) were performed in all patients [17, 18]. In

Table 1. – Characteristics of the study group

Subjects n	20
Age yrs	66±6
Height cm	165±6
Weight kg	76±15
BMI kg·m^{-2}	28±6
FEV1 L	1.36±0.46
FEV1 % pred	45±14
FEV1/FVC %	46±11
RV/TLC %	60±7
FRC % pred	131±26
Pa,O_2 mmHg	74±11
Pa,CO_2 mmHg	41±6

Data are presented as mean±SD. BMI: body mass index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; FRC: functional residual capacity; Pa,O_2: oxygen tension in arterial blood; Pa,CO_2: carbon dioxide tension in arterial blood; % pred: % predicted.

the last 10 patients in whom arterial blood gases and lactate were assessed during exercise, an arterial catheter (Seldicath; Plastimed, Saint-Leu-La-Foret, France) was put in place in the radial artery before the exercise tests.

Exercise testing

During all exercise tests, the patients breathed through a face mask with a dead space of <30 mL (series 8900; Hans Rudolph, Kansas City, MO, USA), which was carefully adjusted to the patient's face and checked for air leaks. On-line calculations of breath-by-breath $V'O_2$, carbon dioxide production ($V'CO_2$), $V'E$, respiratory exchange ratio (RER), and fC were obtained (K4b2; Cosmed, Pavona di Albano, Italy). The gas analysers and turbine were calibrated before each test. Because the device used to measure gas exchange was light weight (800 g), patients were able to move freely without discomfort. Data could be checked for quality on-line through radio transmission. The device has been used previously in COPD patients [12].

The incremental cycling exercise was carried out on an electro-magnetically braked cycle ergometer (CardiO$_2$ cycle; Medical Graphics Corporation, St Paul, MN, USA). After 3 min of unload pedalling, work rate was increased by 5 or 10 W·min^{-1}. Arterial blood samples were taken every 3 min throughout the test for analysis of blood gases and lactate.

In the 6MWT, performed in a 90-m long quiet corridor, the patients were asked to cover as much ground as possible within 6 min. Every 30 s they were encouraged by an experienced physiotherapist to continue walking as fast as possible [19]. In the last 10 patients, arterial blood samples were taken at rest and at the end of the 6MWT (<15 s). To avoid interference with the patients' exercise performance, blood samples were drawn immediately at the test termination (within 10–15 s in all subjects) from the indwelling arterial catheter. Reproducibility of the test was evident from the small difference between the practice walk and the final walk (15±29 m or 2.6±5.4%). All patients involved in the present trial had performed 6MWT previously as part of their routine follow-up.

Statistical analysis

Results are expressed as mean±SD. Paired t-tests were used to compare the two testing conditions (cycling and walking). One-way analysis of variance (repeated measures) was used to analyse the $V'O_2$ profile throughout the 6MWT. A multiple stepwise analysis was used to analyse the variability in the $V'O_2$ during walking.

Results

The study group (table 1) showed moderate-to-severe airflow obstruction (mean forced expiratory volume in one second 45% predicted, range 21–71%

pred) with mild arterial hypoxemia at rest (mean Pa,O_2 10 kPa (75 mmHg), range 8–11 kPa (60–97 mmHg)). Four patients presented hypercapnia at rest (mean Pa,CO_2 5.5 kPa (41 mmHg), range 3.5–7.3 kPa (26–55 mmHg)). Peak cycling $V'O_2$ was 19±3.2 mL·min^{-1}·kg^{-1} (range 12.3–25.6 mL·min^{-1}·kg^{-1}). Ventilation at peak cycling exercise was 99±34% of the maximal voluntary ventilation (MVV). The 6-min walking distance was 539 m (range 428–620 m). Peak incremental exercise and 6MWT (6th min) responses are compared in table 2.

Physiological responses during walking

Figure 1 summarises $V'O_2$ (individual data), $V'E$ and fC (mean group data) responses during 6MWT. $V'O_2$ showed a steady-state profile from min 3 to 6 of the test (1.37±0.27, 1.39±0.28, 1.42±0.31 and 1.40±0.29 L·min^{-1} at 3, 4, 5 and 6 min, respectively) in all but two patients. In these two patients, in whom a slow phase of O_2 uptake was identified, the increases in $V'O_2$ over the 3–6-min period were 6.8 and 14%, respectively, whereas the remaining 18 patients showed a $\Delta V'O_2$ of <4% over the last 3 min of the 6MWT. It is worth noting that $V'E$ also reached a plateau after the 4th min of walking ($V'E$ was 42.3±7.6 and 42.4±8 L·min^{-1} at the 5th and 6th min, respectively). This represented 91±37 and 91±34% of MVV.

Walking speed, which was monitored throughout the test, was shown to be constant. Figure 2 illustrates the fluctuations of the walking speed in relation to the average value, confirming that the walking speed hardly varied by >0.5 km·h^{-1} during the test. The $V'O_2$ during the walking test was, as expected, closely correlated to body weight (r=0.69, p<0.01) and $V'O_2$·kg^{-1} during walking was related to walking

Table 2. – Physiological responses at peak cycling exercise and during the last minute of the 6-min walking test (6MWT)

	Peak cycling	6MWT (6th min)	p-value
Work rate w	82±21		
6MWT m		539±56	
$V'O_2$ L·min^{-1}	1.41±0.18	1.40±0.29	
$V'CO_2$ L·min^{-1}	1.45±0.18	1.30±0.31	0.02
RER	1.04±0.08	0.92±0.07	0.001
$V'E$ L·min^{-1}	47±8	42±8	0.01
$V'E$ %MVV	99±35	91±34	
fC beat·min^{-1}	130±13	126±13	
fC % pred	85±9	82±9	
Pa,O_2[#] mmHg	73±13	77±15	
Pa,CO_2[#] mmHg	47±8	46±8	
[La]art[#] mmol·L^{-1}	5.91±1.51	2.92±1.99	0.003

$V'O_2$: oxygen untake; $V'CO_2$: carbon dioxide production; RER: respiratory exchange ratio; $V'E$: minute ventilation; fC: cardiac frequency; Pa,O_2: oxygen tension in arterial blood; Pa,CO_2: carbon dioxide tension in arterial blood; [LA]art: arterial lactate concentration; % pred: % predicted. n=20 patients. [#]: n=10 patients, in whom these measurements were performed.
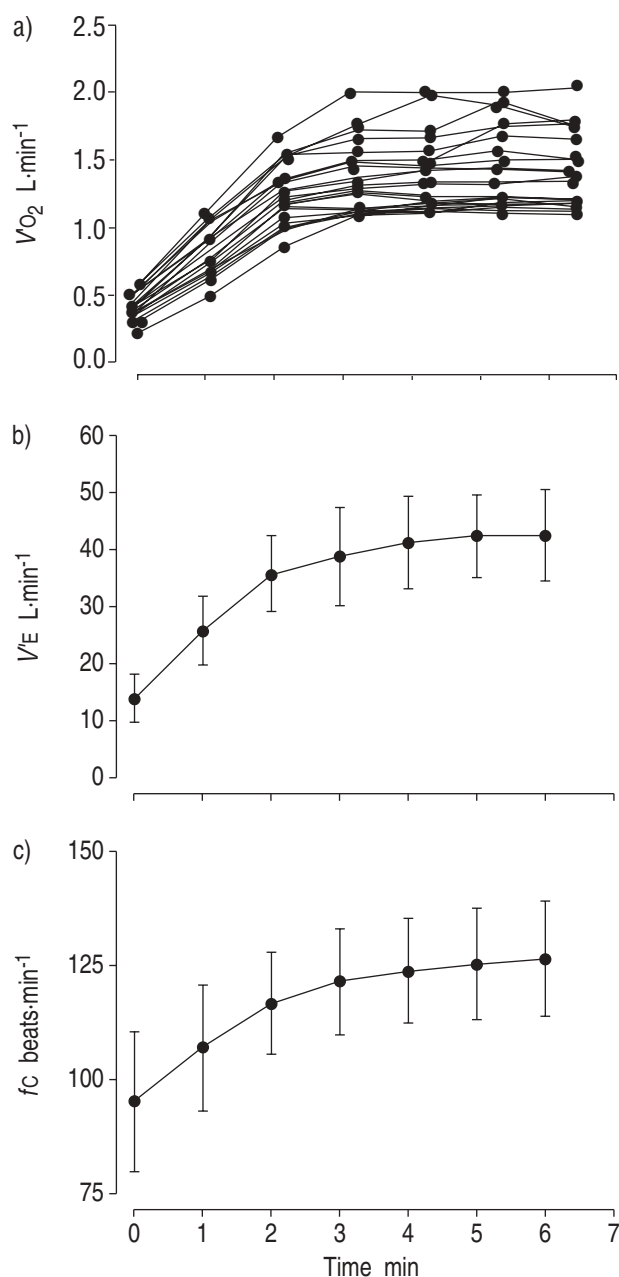

Fig. 1. – Cardiopulmonary responses during the 6-min walking test. a) Individual data for oxygen uptake ($V'O_2$); b) mean±SD group data for minute ventilation ($V'E$); and c) mean±SD group results for cardiac frequency (fC).

speed (r=0.48, p<0.05). Together, body weight and walking speed explained 56% of the variance in $V'O_2$ during the walking test.

Comparison between 6-min walking test and incremental cycling

Although O_2 uptake was similar between peak cycling exercise and the 6MWT (4th–6th min) and was shown to be significantly correlated between both tests (r=0.51, p<0.05), both $V'E$ and $V'CO_2$ were significantly lower (p<0.05 each) during walking than
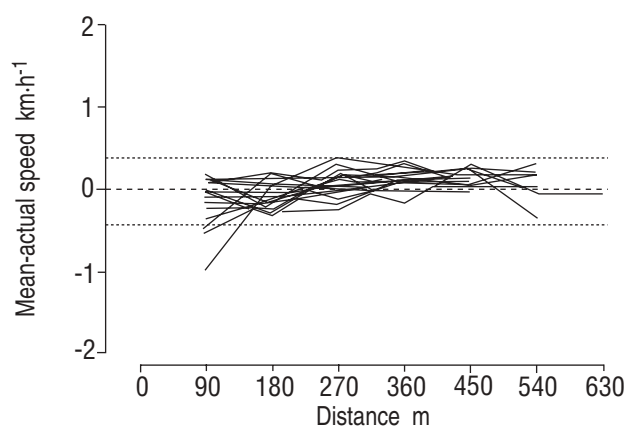
Fig. 2. – Individual data of walking speed during the 6-min walking test. Data are displayed as the difference in walking speed relative to the average walking speed. ---: ± 0.5 km·h^{-1}.

at peak cycling (table 2). The RER and [La]art were also lower during walking than at peak cycling. As expected, exercise-induced increase in $V'\text{E}$ was related to $\Delta V'\text{CO}_2$ during exercise ($\Delta V'\text{E}$ *versus* $\Delta V'\text{CO}_2$, r=0.78, p<0.001). Similarly, the increase in the RER and $V'\text{E}$ showed a significant correlation with the rise in [La]art (ΔRER *versus* Δ[La]art, r=0.71, p<0.01; and $\Delta V'\text{E}$ *versus* Δ[La]art, r=0.65, p=0.04). No statistically significant differences in $P\text{a},\text{O}_2$ and $P\text{a},\text{CO}_2$ were observed between 6MWT and peak cycling (table 2).

Discussion

The study showed a clear $V'\text{O}_2$ plateau after the 3rd min of the 6MWT, indicating that steady state $V'\text{O}_2$ is a distinct feature of this test in most (90%) moderate-to-severe COPD patients capable of performing a 6MWT without interruption. The comparison between encouraged 6MWT (4th–6th min) and peak cycling showed identical $V'\text{O}_2$ and similar fC responses, indicating that this timed walking test generates high, albeit submaximal, metabolic and cardio-vascular requirements. It is worth noting, however, that the physiological burden imposed on the system, in terms of $V'\text{CO}_2$ and ventilatory response, is lower during walking (6MWT) than at peak cycling. The $V'\text{O}_2$ during walking is caused by a larger amount of muscle mass at work, compared with cycling [20]. Hence, the $V'\text{O}_2$ relative to the amount of working muscle was lower during walking. In addition, walking may be a more efficient movement, especially in the elderly who are not used to cycling [21]. Incremental cycling protocols [16] are recommended to assess exercise tolerance in the laboratory, partly because they allow an appropriate analysis of the relationships between $V'\text{O}_2$ and work rate for a given patient throughout the test. Unfortunately, the work load during 6MWT can only be roughly estimated. Both body weight and walking speed are pivotal factors determining the energy requirements during this test, which is illustrated by the relatively high proportion in variance of the $V'\text{O}_2$ during walking, explained by these two variables (56%).

Since the walking speed chosen by the patients is almost constant throughout an encouraged 6MWT, as indicated by the current results (fig. 2) and earlier data [22], it seems reasonable to assume that the work rate is constant throughout a 6MWT. It can be speculated that walking speed is set by the patient to achieve a sustainable work rate (and $V'\text{O}_2$) throughout the test. In these circumstances, the physiological data from the test is highly relevant, since it may reflect the integrated response of the organ systems involved in O_2 transport/O_2 utilisation, which allows a high but sustainable level of whole-body exercise.

The lower $V'\text{O}_2$ per unit of exercising muscle mass during walking compared with cycling may partly explain why steady state $V'\text{O}_2$ can be maintained at a $V'\text{O}_2$ equivalent to peak $V'\text{O}_2$ during incremental cycling. This hypothesis is supported by the low [La]art found in the present study during walking. PALANGE *et al.* [12], who studied COPD patients during cycling and treadmill walking, also reported lower lactate levels during walking. Similarly, BAARENDS *et al.* [23] found a similar phenomenon during a self-paced 12-min treadmill test. It is reasonable to speculate that low $V'\text{CO}_2$, RER and $V'\text{E}$ during walking can be partly explained by low blood lactate levels during 6MWT. The physiological relationships between these variables, and the correlations among them described in the Results section, further support this interpretation. It is well accepted that peak $V'\text{O}_2$ during incremental walking or running protocols may exceed the peak $V'\text{O}_2$ obtained during cycling by 10–15% because of the larger exercising muscle mass in the former protocols. The current study indicates that high levels of ventilation are sustainable during the 6MWT. Ventilation reached 88 ± 30, 91 ± 37 and $91\pm34\%$ of the predicted MVV during the last 3 min of the walking test. These results are in line with recent findings of NEDER *et al.* [24], who demonstrated that patients with COPD, with a similar degree of airflow obstruction, were able to endure exercise for a similar period with $V'\text{E}$ slightly >90% pred MVV.

A possible limitation of the present study is that patients who were unable to perform a 6MWT without supplemental O_2 were excluded. This was due to the inability of the equipment to measure $V'\text{O}_2$ while breathing high inspiratory O_2 fractions, which would have been necessary to prevent exercise-induced oxyhaemoglobin desaturations in these patients [25]. The physiological response to corridor walking in these patients with severe gas exchange impairment remains unclear. Interestingly, the $\Delta P\text{a},\text{O}_2$ during incremental cycling was not significantly related to the $\Delta P\text{a},\text{O}_2$ during walking (r=0.43, NS) and 20% of the patients showed a greater decrease in $P\text{a},\text{O}_2$ during walking than during the incremental cycling exercise. This observation supports the use of the 6MWT as a valuable test in the assessment of exercise-induced oxyhaemoglobin desaturation.

The current findings provide original information on the physiological responses during 6MWT, which in turn sheds light on the usefulness of this test in the clinical evaluation of patients with COPD. These results suggest that when it is properly standardised, and provided that adequate encouragement is given,

the 6MWT might reflect "maximal" sustainable exercise capacity in the patients studied. The data provided by GOSSELINK et al. [26], which showed that the 6-min walking distance is more related to skeletal muscle dysfunction, whereas the peak $V'O_2$ relates more to pulmonary function, further supports the idea that both tests measure different aspects of exercise performance. Given the clear plateau in $V'O_2$ and the lower $V'E$, $V'CO_2$ and $[La]art$, the 6MWT should be referred to as submaximal, but strenuous. The data provided support the need for appropriate monitoring of O_2 saturation and symptoms by a trained technician during the 6MWT. It should be noted, however, that the present study was not designed to investigate the impact of different imposed walking speeds (work rates) on patients, so it remains uncertain whether the speed during the 6MWT matches critical walking speed.

In conclusion, the results of the present study have identified the 6-min walking test as a strenuous protocol that imposes a significant, but sustainable, load to the exercising body. The 6-min walking test differs from incremental cycling exercise protocols in that it evaluates steady state exercise performance. The two tests clearly measure different aspects of exercise tolerance and should be considered complementary.

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