

# Metabolic Requirements during Six Minutes Walking Tests in Patients Affected by Chronic Obstructive Pulmonary Disease in Different Stages

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## ABSTRACT

**Backgrounds:** In Chronic Obstructive Pulmonary Disease (COPD) a multi factorial effort limitation becomes progressively relevant as the disease progresses in the consecutive stages. It is measured by both six minutes walking test (6MWT) and maximal cardiopulmonary incremental test (CPET). **Aim:** It is important to assess in each stage of disease the metabolic load during 6MWT referring to the outcome of CPET and to ascertain whether there is a significant relationship between the measures obtained by CPET and 6MWT. **Methods:** Four group of fifteen patients affected by COPD in stage I to IV underwent 6MWT and maximal CPET in the same day and results were compared to a group of healthy people. Airflow obstruction was measured by whole body plethysmography, blood gases by gas analysis, maximal oxygen consumption and metabolic parameters by ergometer, lactic acid levels by analyzer. **Results:** Maximal oxygen consumption ( $V'O_2\text{max}$ ) and 6MWT are progressively impaired and related ( $V'O_2\text{max} = 1.25 \pm 0.26, 1.152 \pm 0.4, 1.03 \pm 0.44, .85 \pm 0.2$  l/m; 6MWD =  $452 \pm 84, 446 \pm 82, 381 \pm 165, 200 \pm 100$  respectively in GOLD I to IV stage). Oxygen consumption ( $V'O_2$ ) during 6MWT becomes stable after 3 - 4 minutes and reached at the end of the test close to those measured at de-compensated metabolic acidosis anaerobic threshold (TDMA) ( $85 \pm 0.4$  l/m vs.  $9 \pm 0.4$  l/m) in stage I to III, while in COPD there is no difference between  $V'O_2\text{max}$  and  $V'O_2$  during 6MWT ( $0.85 \pm 0.2$  vs.  $0.8 \pm 0.23$  l/m). 6MWT is more suitable to determine oxygen desaturation than CPET ( $d\text{SaO}_2 -4 \pm 2\%$  vs.  $-2 \pm 1\%$ ). 6MWD, the workload performed in 6MWT and  $V'O_2\text{max}$  are significantly related. **Conclusion:** 6MWT looks as a suitable sub maximal test related CPET. Metabolic requirements under 6MWT are close to TDMA and are obtained in a suitable, self paced, usual exercise, close to everyday experience and thus related to activity daily levels. As the disease worsens the differences between  $V'O_2$  during 6MWT and  $V'O_2\text{max}$  wane.

**Keywords:** COPD; 6MWT; CPET; AT; TDMA

## 1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an invalidating disease characterized by a progressive airways obstruction [1]. During the natural history of the disease there is a progressive worsening of airways obstruction, diffusing capacity, functional geometry of respiratory muscle, cardiovascular performance and peripheral muscles function leading to a multi factorial exercise limitation. The degree of exercise limitation is evaluated by the cardiopulmonary exercise test (CPET), assumed as the "gold standard" since it allows an insight into the mechanisms determining effort limitation and the measure of the maximal oxygen consumption ( $V'O_2\text{max}$ ), the maximal workload (Watt max or W peak), the anaerobic Threshold (AT) and the decompensated metabolic

acidosis threshold (TDMA) [2,3]. CPET has several limitations since it is expensive, time consuming and potentially harmful [2,3]. In the clinical practice the Six-Minute Walk Test (6MWT) has replaced CPET because of the lesser requirements of time, technology and facilities and because walking is a normal activity for patients and better reflects the capacity for performing the activities of daily life than the standard exercises tests [3-6]. Lastly, the 6MWT has acquired clinical relevance since its relationship with survivability and it became one of the four domain determining the comprehensive BODE index [7-8]. Nevertheless the correct performance of 6MWT requires careful operative standards, such as the verbal motivation and the supervision by a skilled operator [3,4]. Despite its importance and widespread use, the

6MWT outcome is just a measure of the distance covered in the allowed time (Six Minutes Walking Distance or 6MWD), and the operator is unaware of the physiological characteristics and of the metabolic requirements during the test whether the severity of the disease affects these features. Experimental evidences indicates that 6MWT behaves as a constant load sub-maximal exercise where the patients assumes a constant walking speed at the maximal sustainable load [6], closely related to daily activity, reaching a plateau of oxygen consumption ( $\dot{V}O_2$ ) after three minutes [9]. The comparison of the outcomes of CPET as compared to 6MWT [5,10] shows several discrepancies: during the 6MWT the  $\dot{V}O_2$  may be similar to [11,12] or less than [6,13] that measured during the CPET, while the ventilation per minute ( $\dot{V}e$ ), the carbon dioxide production ( $\dot{V}CO_2$ ), the respiratory quotient (RQ) and the arterial lactate were lower [9-13] and the dyspnoea similar to or less than during CPET [6,12]. The inconsistencies identified may be determined by the differences in the stages of the disease, by the small number of patients included in these studies, by the methodological issues associated with the standardisation of the 6MWT, by the different types of effort (cycling versus walking) [14].

The aim of this study was to investigate the level of the metabolic requirements under 6MWT, as compared to CPET outcomes, and if they change in the progressive stages of the disease.

## 2. Methods

### 2.1. Experimental Design

The goal to compare the metabolic requirements during incremental CPET and 6MWT was achieved by the performance of both tests in both healthy people and COPD patients. During the effort and under recovery, oxygen consumption, carbon dioxide production, ventilation ( $\dot{V}e$ ), dyspnoea (D), leg fatigue (LF), cardiac frequency (CF), blood pressure (BP) were continuously measured. Lactic acid serum levels were measured under the maximum workload under CPET and at the end of 6MWT. On the same day, patients executed pulmonary function tests and effort tests. 6MWT and CPET were performed in random order, allowing a suitable time between the tests to obtain a complete recovery to baseline. The relationship between CPET and 6MWT was studied by comparing the performances and the outcomes.

### 2.2. Selection of Patients

We examined five sets, each one was composed by fifteen subjects: the former one consisted of fifteen healthy compliant non-smoking subjects used as control group, while the following ones by four groups of patients affected by COPD, diagnosed according to ATS and

GOLD statement [1], belonging to stage I to IV (according to GOLD statements). Patients were consecutively recruited as they come to observation. The biometric variables were similar between the groups (**Table 1**). Criteria for inclusion were: a) diagnosis of COPD, according to ATS and GOLD statements [1]; b) presence of airways obstruction (according to ATS statement and GOLD rules) with a FEV1/FVC (forced vital capacity) less than 70% after receiving 200 mg of salbutamol; c) presence of a stable phase, checking clinical and functional parameters along one month lasting period; d) signed written informed consent; e) not smoking since at least one month; f) absence of comorbidities that would prevent the patient from performing an exercise test such as, obstructive arteriopathy, neurological or orthopaedic problems, respiratory failure requiring oxygen therapy or determining the need of sudden stops during performance of 6MWT. Patients belonging to GOLD 1 stage used salbutamol twice a day, in GOLD II stage inhaled salmeterol twice a day, while in GOLD stage III and IV all patients used association of salmeterol and fluticasone and 7/15 in GOLD III inhaled tiotropium as well; In stage IV 10/15 in stage IV used oral theophylline, that was not assumed in the day of testing.

**Table 1.** Biometric and functional patterns.

	Healthy	I	II	III	IV	Units
Age	62 ± 9	62 ± 14	65 ± 8	69 ± 7	69 ± 5	years
Height	170 ± 13	168 ± 8	164 ± 5	165 ± 8	160 ± 6	cm
Weight	82 ± 10	87 ± 13	77 ± 8	78 ± 13	70 ± 5	kgs
Sex	9 : 6	10 : 5	9 : 6	10 : 5	10 : 5	M:F
VC	96 ± 11	86 ± 11	68 ± 7*	60 ± 13*	31 ± 8**	%
FEV1	97 ± 11	87 ± 7	64 ± 8*	44 ± 4**	27 ± 4**	%
RV	96 ± 14	117 ± 22	123 ± 20*	143 ± 13*	215 ± 46**	%
TICO	95 ± 10	83 ± 7	64 ± 14*	58 ± 15**	40 ± 14**	%
PaO <sub>2</sub>	84 ± 10	78 ± 13	78 ± 10	64 ± 8*	60 ± 13*	mmHg
SaO <sub>2</sub>	97 ± 1	95 ± 3	95 ± 2	93 ± 2*	90 ± 7*	%
PaCO <sub>2</sub>	40 ± 4	41 ± 8	39 ± 5	46 ± 13*	49 ± 7*	mmHg
AWR	2.2 ± 0.3	3 ± 1	4 ± 2	8 ± 3**	10 ± 3**	cmH <sub>2</sub> O/l/s
ArtHyp	4/15	5/15	4/15	6/15	6/15	n
Diabet.	3/15	4/15	4/15	5/15	4/15	n
n	15	15	15	15	15	

VC = Vital capacity; FEV1 = forced expired volume in one sec.; RV = residual volume; TICO = diffusion capacity for CO; VC, FEV1, RV, TICO are expressed as % of ERS normal standards; PaO<sub>2</sub> = arterial oxygen tension, PaCO<sub>2</sub> = carbon dioxide arterial tension AWR = airways resistances; mean ± s. d.; \* = difference from healthy people (p < 0.05); \*\* = p < 0.001; M:F = male:female ratio.

### 2.3. Functional Testing

Lung volumes, expiratory flows and airways resistances were measured by whole body barometric pletismograph (Pulmolab Autobox 2000, Sensormedics, Yorba Linda, California, USA). The BODE index was computed, according to Celli [8], by measuring effort tolerance (evaluated by the MRC scale), the degree of airways obstruction (by FEV1), 6MWD and the body mass index (BMI). Gas analysis of the arterial blood obtained from the brachial artery was analysed by an automated blood gas analyser (Rapidlab 405 Bayer Health Care, FRG). Lactic acid was measured by a portable analyzer (Lactate Pro test strip, Arkray, JPN) using venous blood samples drawn at the beginning and at the end of CPET and 6MWT.

### 2.4. Effort Testing

The CPET consisted of a progressive exercise test limited by symptoms performed, according to ERS standards [3], by means of incremental test (10 Watt/min) (electromagnetic braked cycloergometer Siemens, FRG) up to the maximal tolerable workload sustained for more than 30 seconds under verbal encouragement for the duration of the test.  $\dot{V}^e$ ,  $\dot{V}^{\text{O}_2}$  and  $\dot{V}^{\text{CO}_2}$  were obtained by a portable ergometer (Metasoft Cortex, FRG equipped with turbine spirometer,  $\text{CO}_2$  infrared analyser and polarographic Oxygen analyser). Dyspnoea and muscle fatigue were checked by Borg scale. Oxygen saturation ( $\text{SaO}_2$ ) was measured by pulseoxymeter (Nonin 8500, USA). Anaerobic threshold (AT) and the threshold of decompensated metabolic acidosis (TDMA) were identified by the "V" slope method and analysing the relationship between the ventilatory equivalents plotted versus  $\dot{V}^{\text{O}_2}$  [3]. 6MWT was conducted, according to ATS statement [4], under careful supervision and verbal encouragement of therapist, monitoring of dyspnoea,  $\text{SaO}_2$  and muscle fatigue. The gas exchange was measured with the same instrument used under CPET. Workload performed under 6MWT was computed, according

to the literature [15], by the product of the weight and 6MWD. Experimental values were referred to ERS normal standards for CPET [3] and to Enright's [16] for 6MWT.

### 2.5. Statistical Analysis, Ethical Advice

The data are expressed as means with  $\pm$  1SD in the text and tables. Statistical analysis was obtained by computer aided software (Epistat, USA) by means of unpaired T Student tests, comparing each group of patients to the control group. Differences between groups have been assessed by two tail Anova test. T student test and two tail Anova test allowed the comparison of the outcome between baseline and values observed during CPET at the maximal workload, the AT, the TDMA and during 6MWT. The relationship between variables was assessed by least square method analysis applied to linear fitting procedures. Differences are referred as highly significant for a "p" value less than 0.001 and significant for a "p" of less than 0.05. The Ethics Committee of our institution gave a formal authorization to the performance of the protocol before the beginning of the study. Each patient signed an informed consent. There was no conflict of interest.

### 3. Results

Biometric values were not significantly different between COPD and healthy subjects, and between COPD stages ( $p < 0.5$ ) (**Table 1**). Lung volumes showed progressive hyperinflation associated with a decrease in FEV1,  $\text{PaO}_2$  and  $\text{SaO}_2$  and increase of  $\text{PaCO}_2$ . Borg index and BODE score increased significantly under stage IV, according to T test for unpaired values.

During CPET (**Table 2**), patients showed a progressive diminution of  $\dot{V}^{\text{O}_2\text{max}}$ , maximal ventilation ( $\dot{V}^{\text{emax}}$ ), maximal workload (Watt max), threshold (AT) in the successive stages, according to T test for unpaired observation.  $\dot{V}^{\text{emax}}$  and ventilatory reserve (MVV-

**Table 2. Ergometric performance assessed by maximal incremental test (CPET) in COPD.**

	Healthy	Whole Serie	I	II	III	IV	Units
$\dot{V}^{\text{O}_2}$	1.5 $\pm$ 0.15	1.08 $\pm$ 0.6	1.25 $\pm$ 0.26	1.152 $\pm$ 0.4	1.03 $\pm$ 0.44*	0.8 $\pm$ 0.2*	l/m
CF	130 $\pm$ 12	119 $\pm$ 12	123 $\pm$ 18	121 $\pm$ 12	117 $\pm$ 14*	116 $\pm$ 8*	bpm
$\dot{V}^e$	47 $\pm$ 7	36 $\pm$ 12	40 $\pm$ 9	38 $\pm$ 11	36 $\pm$ 11*	32 $\pm$ 13*	l/m
Watt	152 $\pm$ 21	103 $\pm$	140 $\pm$ 48	101 $\pm$ 32*	88 $\pm$ 30*	85 $\pm$ 10*	Watt
Borg d.	4 $\pm$ 3	7.2 $\pm$ 7	5.4 $\pm$ 3	6.2 $\pm$ 4	7.5 $\pm$ 5*	9.6 $\pm$ 6*	u
Borg l. f.	3 $\pm$ 3	7 $\pm$ 6	5 $\pm$ 3	7.2 $\pm$ 4*	7.8 $\pm$ 5*	7.8 $\pm$ 4*	u
$\text{SaO}_2$	96 $\pm$ 2	94 $\pm$ 10	97 $\pm$ 1	95 $\pm$ 3	92 $\pm$ 3	87 $\pm$ 4*	%

$\dot{V}^{\text{O}_2}$  = maximal oxygen consumption; Watt max = maximal load; CF max = maximal cardiac frequency; Borg d = Borg dyspnoea index; Borg l. f. = Borg muscular leg fatigue index;  $\text{SaO}_2\text{6WD}$  = oxygen saturation during 6MWD;  $\text{SaO}_2$  = oxygen saturation; \* level of difference between healthy people and stage of COPD significant (less than 0.05);  $x \pm s. d.$  = mean  $\pm$  standard deviation.

**Table 3. Ergometric performance assessed by six minutes walking distance test (6MWT).**

	Healthy	COPD	I	II	III	IV
6MWD	563 ± 65	370 ± 250	452 ± 84	446 ± 82	381 ± 165*	200 ± 100*
V'e 6MWT	28 ± 11	26 ± 9	26 ± 8	27 ± 10	28 ± 11	24 ± 8
VO <sub>2</sub> 6MWT	1.1 ± 0.3	0.85 ± 0.3	0.95 ± 0.15	0.90 ± 0.3	0.82 ± 0.4*	0.8 ± 0.23*
CFmax	114 ± 15	106 ± 15	113 ± 20	104 ± 12	109 ± 10	116 ± 16
Kgmmax	45 ± 5	30 ± 22	41 ± 10	33 ± 9	31 ± 14*	14 ± 7*
Borg d.	2 ± 2	3.85 ± 3	2.4 ± 2	3 ± 3	4.8 ± 3*	5.2 ± 4*
Borg l. f.	2.5 ± 2	3.35 ± 3	2.2 ± 2	3 ± 3	4.2 ± 3*	4 ± 3*
SaO <sub>2</sub>	96 ± 2	92 ± 10	96 ± 3	94 ± 3	90 ± 4*	87 ± 5*

V'O<sub>2</sub> = maximal oxygen consumption; Watt max = maximal load; CF max = maximal cardiac frequency; Borg d = Borg dyspnoea index; Borg l. f. = Borg muscular leg fatigue index; SaO<sub>2</sub> 6WD = oxygen saturation during 6MWD; SaO<sub>2</sub> = oxygen saturation; \* level of difference between healthy people and stage of COPD significant (less than 0.05); x ± s. d. = mean ± standard deviation; units: & MWD in mt; V'e in l/m; V'O<sub>2</sub> in l/m; CF in bpm; Kgmmax in mt × 1000 Borg dispnea and leg fatigue in units SaO<sub>2</sub> in %.

V'e diminished progressively (V'emax = from 40% of MVV in stage I to 60% in stage IV). Maximal cardiac frequency diminished slightly while oxygen pulse (V'O<sub>2</sub>/CF) decreased in advanced stages together with diminution of SaO<sub>2</sub>. All patients completed the test, although under stage III and IV workload tolerated was low.

During 6MWT (Table 3) patients and healthy people showed increased cardiac rate. 6MWD progressively worsened. Maximal workload tolerated showed a similar trend. Thirty percent of COPD developed also oxygen desaturation; 15% of patients, affected by more advanced airways obstruction (mainly in stage III and IV) showed tachycardia, oxygen desaturation and marked increase of Borg Dyspnea index. Dyspnoea and fatigue were significantly worst in last stages. Both in healthy people and in COPD after about three minutes a stable V'O<sub>2</sub> was achieved during 6MWT. Under 6MWT 9/15 the V'O<sub>2</sub> measured (V'O<sub>2</sub>6MWT) was lower than AT observed during CPET (V'O<sub>2</sub>AT) (Table 4); 4/15 reached AT with requirements overlapping those measured under CPET and only 2/15 of subjects reached a V'O<sub>2</sub>6MWT close or bigger than that measured at TDMA during CPET (V'O<sub>2</sub>TDMA). The comparison of the means by T test for paired values and of two tails variance by Anova test showed that V'O<sub>2</sub>max was statistically different from each other measure (p < 0.001). The V'O<sub>2</sub>6MWT was not statistically different from V'O<sub>2</sub>TDMA or V'O<sub>2</sub>AT (p = 0.844) (no difference between columns, significant difference between rows, p = 0.004 and 0.0012 respectively) and it was significantly related to V'O<sub>2</sub>max, V'O<sub>2</sub> at TDMA and at AT. During COPD under stage I, 8/15 required a V'O<sub>2</sub>6MWT close to V'O<sub>2</sub>AT, 2/15 between V'O<sub>2</sub>AT and V'O<sub>2</sub>TDMA and only 5/15 reached or exceed V'O<sub>2</sub>TDMA. Under stage II, 6/15 V'O<sub>2</sub>6MWT was close to V'O<sub>2</sub>AT, while 3/15 between V'O<sub>2</sub>AT and V'O<sub>2</sub>TDMA and 6/15 close to V'O<sub>2</sub>TDMA. Patients in

stage III showed V'O<sub>2</sub>6MWT lesser or close to V'O<sub>2</sub>AT in 10/15, between V'O<sub>2</sub>AT and V'O<sub>2</sub>TDMA in 3/15 and close to V'O<sub>2</sub>TDMA in 2/15. During stage IV, in 10/15 V'O<sub>2</sub>6MWT was close to V'O<sub>2</sub>AT, 3/15 between V'O<sub>2</sub>AT and V'O<sub>2</sub>TDMA and 2/15 close to V'O<sub>2</sub>TDMA. Under stage IV, V'O<sub>2</sub>6MWT showed no significant difference within V'O<sub>2</sub>AT and V'O<sub>2</sub>TDMA values both within rows (p = 0.94 and 0.18 respectively) and columns (0.18 and 0.36 respectively). The mean V'O<sub>2</sub>6MWT was not statistically different from V'O<sub>2</sub>TDMA and V'O<sub>2</sub>AT during CPET in stages I to III with no significant differences between columns and significant differences between rows. V'O<sub>2</sub>6MWT was significantly related to V'O<sub>2</sub>TDMA. In healthy people the V'e and the CF reached during 6MWT were not statistically different from those measured at TDMA and AT under CPET (Tables 5-7). In COPD patients, V'e and CF during 6MWT were not different than those measured at AT or TDMA (Table 3) in stage I to III; they are not different from maximal values in stage IV. Lactate concentration was higher under walking than cycling. The comparison of values obtained under both effort procedures (Table 5) showed that oxygen desaturation is worst under walking in stage II-III, while dyspnoea and muscle fatigue under cycling. Lactic acid was doubled in 30% of patients under walking. Under both CPET and 6MWT, in stage IV there was an increased resting V'e and a reduced V'emax determining a reduced ventilatory reserve (MVV-V'e), indicating a ventilatory limit, quickly reached under effort.

#### 4. Discussion

Current available data allow for the first time to assess the metabolic requirements and the effort level reached during 6MWT in healthy people and in the each stage of COPD. The most important findings of this study are

**Table 4. Metabolic parameters in basal conditions, CPET and 6MWT.**

		Baseline	Maximal CPET	TDMA CPET	AT CPET	6MWT	Units
COPD	V'O <sub>2</sub>	0.3 ± 0.07	1.08 ± 6	0.9 ± 0.4	0.78 ± 0.4	0.85 ± 0.3	l/m
	CF	80 ± 11	119 ± 12	115 ± 13	111 ± 15	106 ± 15	bpm
	V'e	11 ± 4	36 ± 12	27 ± 11	23 ± 11	26 ± 11	l/m
	LAT	3.16 ± 0.5	10.7 ± 7	n. a.	n. a.	15.68 ± 10	mmol/l
Healthy	V'O <sub>2</sub>	0.27 ± 0.05	1.5 ± 0.15	1.2 ± 0.2	1.08 ± 0.24	1.09 ± 0.3	l/m
	CF	80 ± 11	130 ± 12	117 ± 8	105 ± 9	114 ± 15	bpm
	V'e	9 ± 2	47 ± 7	32 ± 6	26 ± 7	29 ± 11	l/m
	LAT	3 ± 0.3	8.6 ± 9	n. a.	n. a.	12 ± 10	mmol/l

LAT = Lactate level; Maximal = CPET maximal values; AT = anaerobic threshold; TDMA = decompensated metabolic acidosis threshold; 6MWT = 6MWT maximal values; AT 6MWT = anaerobic threshold during 6MWT; n. s. = difference not significant; n. a. = not available; n = 60 for COPD and n = 15 for healthy people (health).

**Table 5. Oxygen consumption during rest, CPET (at maximum, AT and TDMA) and 6MWT.**

	V'O <sub>2</sub> MAX	V'O <sub>2</sub> TDMA	V'O <sub>2</sub> AT	V'O <sub>2</sub> 6MWT	Rest
Healthy	1.5 ± 0.15*	1.2 ± 0.2	1.08 ± 0.24	1.09 ± 0.3	0.29 ± 0.05*
Stage I	1.2 ± 0.26*	1 ± 0.2	0.8 ± 0.2	0.91 ± 0.15	0.3 ± 0.06*
Stage II	1.2 ± 0.4*	0.98 ± 0.3	0.8 ± 0.2	0.90 ± 0.3	0.3 ± 0.06*
Stage III	1.03 ± 0.44*	0.86 ± 0.33	0.78 ± 0.28	0.82 ± 0.38	0.3 ± 0.04*
Stage IV	0.85 ± 0.2	0.8 ± 0.11	0.75 ± 0.10	0.8 ± 0.23	0.3 ± 0.08
Units	l/m	l/m	l/m	l/m	l/m

Maximal = CPET Maximal values; AT = anaerobic threshold; TDMA = decompensated metabolic acidosis threshold; 6MWT = 6MWT maximal values; \* = p level of difference between values during 6MWT and CPET less than 0.05; V'O<sub>2</sub> = oxygen consumption; V'e = minute ventilation; CF = cardiac frequency.

**Table 6. Global ventilation during rest, CPET (at maximum, AT and TDMA) and 6MWT.**

	CPET Max	CPET TDMA	CPET AT	6MWT	Rest
Healthy	47 ± 7*	32 ± 6	26 ± 7	28 ± 11	9 ± 1.6*
Stage I	40 ± 9*	27 ± 7	21 ± 3	26 ± 8	10 ± 2
Stage II	38 ± 11*	29 ± 8	25 ± 7	27 ± 10	10 ± 3*
Stage III	36 ± 11*	28 ± 8	24 ± 7	28 ± 11	11 ± 3*
Stage IV	32 ± 13*	25 ± 8	22 ± 4	24 ± 8	12 ± 4*
Units	l/m	l/m	l/m	l/m	l/m

**Table 7. Cardiac rate during rest, CPET (at maximum, AT and TDMA) and 6MWT.**

	CPET Max	CPET TDMA	CPET AT	6MWT	Rest
Healthy	130 ± 12*	117 ± 8	105 ± 9	114 ± 15	80 ± 11*
Stage I	123 ± 8*	116 ± 16	108 ± 14	113 ± 20	73 ± 7
Stage II	121 ± 12*	110 ± 10	103 ± 9	104 ± 12	80 ± 7
Stage III	117 ± 14*	110 ± 11	104 ± 9	109 ± 10	85 ± 10*
Stage IV	116 ± 8*	111 ± 7	102 ± 7	116 ± 16	82 ± 7*
Units	bpm	bpm	bpm	bpm	bpm

the following: a) the  $\dot{V}O_2$  achieved during the 6MWT was constant after three minutes both in healthy people and in patients with COPD in stage III and IV; b)  $\dot{V}O_2$  max is an independent variable; c) 6MWD was significantly related with the  $\dot{V}O_2$ max of the CPET; d)  $\dot{V}O_2$  at the end of 6MWT is very close to those measured at AT and TDMA in healthy people and in GOLD stage I to III; e) as disease progresses to stage IV the difference between  $\dot{V}O_2$  max and  $\dot{V}O_2$ 6MWT wanes; f) walking and cycling determined differences in dyspnoea, lactic acid, oxygen desaturation.

#### 4.1. Metabolic Load under 6MWT

The performance and the metabolic requirements during 6MWT depend largely on several factors: a) Logistics and execution mode, such as length of corridor, speed adopted or verbal incentivitation; b) subject, such as body weight, gender, lean body mass; c) degree of obstruction; d) co morbidity; e) drugs [9,15,17,18].

Our data fairly agree that in healthy subjects and patients a stable state is achieved after about three minutes and that the test behaves like a constant load sub maximal test [5-15,19] held at average values close to AT or TDMA in healthy people and in the patients with COPD in stage I-III. Other researchers [6] recently confirmed the same results by means of increasing speeds, indicating 6MWT as close to the maximum sustainable exercise. According to literature it is possible to appreciate that during 6MWT patients choose their usual speed walking, performing a self paced, effort limited exercise with energy requirement at the maximal sustainable workloads, close to daily life requirements [20-26]; these features explain the relationship between 6MWD and the activity daily level (ADL) or quality of life (SF36, St George's). The observed relationship between  $\dot{V}O_2$ TDMA and  $\dot{V}O_2$ 6MWT fairly agrees with the cited literature reports since the level reached express the maximal sustainable power (PMS) tolerable only for brief periods. The loss of effort power observed in the consecutive stages of COPD can be explained by the fact that the degree of obstruction mainly determines expiratory flow limitation and hyperinflation leading to: a) reduction of inspiratory capacity; b) altered functional geometry of muscles determining the diaphragmatic excursion; c) the marked arterial oxygen desaturation; d) increase of impedance of right ventricle determining the after load; e) worsening of cardiac output allotment (diminution of the ratio between leg arterial supply versus diaphragmatic arterial supply). In very advanced stages the limitation during both CPET and 6MWT is early and sudden and associated with lactic acidosis and the  $\dot{V}O_2$ 6MWT can be similar or exceed the  $\dot{V}O_2$ max [14]. These findings fairly agree with those observed under advanced stages of cardiac failure, interstitial pulmonary fibrosis and cys-

tic fibrosis[27-29], where there is no difference between  $\dot{V}O_2$ 6MWT and  $\dot{V}O_2$ max. The literature [6,9,11,12] reports the same outcome: the comparison between external paced test (shuttle test) and self paced test (6MWT) shows that the differences become even smaller as the functional capacity become more limited. It is possible to explain the occurrence of  $\dot{V}O_2$ 6MWT exceeding  $\dot{V}O_2$ max assuming that walking involves more muscles of the trunk and upper limbs than cycling or in case of an inappropriate non tolerable external load imposed during cycling, causing high lactate levels and sudden stops or finally by inappropriate shortness of the corridor used leading to a marked increase in  $\dot{V}O_2$  [14]. In very advanced stages, the workload required by 6MWD exceeds the functional reserve of patients and the aerobic supply with frequent stops and recovery phases; the same happens during CPET and both tests behave as the sum of multiple brief maximal aerobic-anaerobic efforts followed by hyperventilation recovery periods, although these patients were excluded from the current study.

#### 4.2. Relationship between CPET and 6MWT

The comparison of  $\dot{V}O_2$ max between CPET and 6MWT must consider the different settings, the heavier workload during cycling in patients with moderate disease, the effect of weight during walking in patients with advanced disease, the different posture and functional geometry of respiratory muscles, the more extensive involvement of muscles during walking [30]. The significant relationship between  $\dot{V}O_2$ max and 6MWD is confirmed by other authors [14,19]: in patients with mild disability ( $\dot{V}O_2$ max > 20 ml/kg/min) a 6MWD higher than 520mt could be expected, while in patients with moderate disease ( $\dot{V}O_2$ max 15 - 20 ml/kg/min) the 6MWD was in the range 250 to 550 mt with a mean of 420 mt. Both measures have prognostic power: a 6MWD lesser than 350mt a 6MWORK lesser than 5000 kgm or a  $\dot{V}O_2$ max lesser than 15 ml/kg/min are associated with poor prognosis and increased mortality [20,24]. The reported differences [6,9,13,14] within metabolic or cardio respiratory outcomes between CPET and 6MWT can be explained taking into account the different levels of metabolic requirements reached in stage I-III and stage IV, the different maximal workload tolerated, the different involvement of muscular groups, the different trend over time of variables, since dyspnoea and the cardiac frequency increase linearly during effort in CPET, while in 6MWT they are constant after the 3<sup>rd</sup> minute. Nevertheless 6MWT, although submaximal, is able to determine a worst oxygen desaturation [31] than the maximal CPET, thus rendering more suitable 6MWT in the study of diseases with effort hypoxemia, like idiopathic pulmonary fibrosis, pulmonary hypertension and COPD. Oxygen desaturation can be due to a lower ventilatory response ( $\dot{V}e/\dot{V}CO_2$ ) dur-

ing the walk test [32]. Both induce worsening end expiratory lung volumes, dynamic hyper-inflation, respiratory work, increase of pulmonary artery pressure and release of oxidants load and Il6 from muscles in exercising wasted patients [33-35].

### 4.3. Conclusion

Literature and current data allow to appreciate that from a physiologic point of view 6MWT and the CPET, although significantly related, are not interchangeable exercise tests. Both CPET and 6MWT allow to measure the progressive effort limitation in different stages of COPD with a useful knowledge as the disease proceeds to advanced stages[13]. CPET allows to ascertain the causes underlying exercise intolerance while 6MWT is self paced and related to daily activity levels and outcomes can be improved, using a multi parametric index, expressing both 6MWD and oxygen desaturation and dyspnoea [36]. As disease worsens, the difference of metabolic requirements between 6MWT and CPET diminish. 6MWT is more suitable in diseases associated with effort-related oxygen desaturation [13,32].

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