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TITLE PAGE:**Full Title:**

The Self-perception of Dyspnoea threshold during the six minute walk test: a good alternative to estimate the ventilatory threshold in Chronic Obstructive Pulmonary Disease.

Short Title:

The Self-perception of Dyspnoea threshold during the six minute walk test:

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ABSTRACT:

In order to determine and/or adjust exercise training intensity for patients when cardiopulmonary exercise test is not accessible, the determination of dyspnoea threshold (defined as the onset of self-perceived breathing discomfort) during the 6-minute walk test could be a good alternative. The objective of this study was to evaluate the feasibility and reproducibility of Self-perceived Dyspnoea Threshold and to determine if a useful equation to estimate ventilatory threshold from Self-perceived Dyspnoea Threshold could be derived. 82 patients were included and performed two 6-minute walk tests during which they raised a hand to signal Self-perceived Dyspnoea Threshold. The reproducibility in terms of heart rate was analysed. On a subsample of patients (n=27), a stepwise regression analysis was performed to obtain a predictive equation of heart rate at ventilatory threshold measured during cardio pulmonary exercise test estimated from heart rate at Self-perceived Dyspnoea Threshold, age and FEV₁. 80% of patients were able to identify Self-perceived Dyspnoea Threshold during 6-minute walk test. Self-perceived Dyspnoea Threshold was reproducibly expressed in heart rate (CV=2.8%). A stepwise regression analysis allowed to estimate heart rate at ventilatory threshold from heart rate at self-perceived dyspnoea threshold, age and FEV₁ (adjusted r=0.79, r²=0.63, and RSD = 9.8 bpm). This study shows that a majority of patients with chronic obstructive pulmonary disease are able to identify a self-perceived dyspnoea threshold during the 6-minute walk test. This heart rate at the dyspnoea threshold is highly reproducible and allow to estimate heart rate at ventilatory threshold.

KEYWORDS

Chronic Obstructive Pulmonary Disease, Ventilatory threshold, 6MWT, Breathlessness, Exercise heart rate.

INTRODUCTION

Exercise training is an essential component of pulmonary respiratory rehabilitation for chronic obstructive pulmonary disease (COPD) patients. The efficiency of exercise training programs depends on three parameters: the number of sessions, the duration or frequency of sessions and the exercise intensity. According to the recommendations, exercise intensity could be defined as a percentage of the maximal aerobic power (50 to 80%) or the target heart rate (HR) equivalent to the ventilatory threshold (V_{th}) obtained during cardiopulmonary exercise testing (CPET) (American Thoracic & American College of Chest, 2003; Vallet et al, 1997). The interest of individualization of exercise training at ventilatory threshold is to allow for patients to increase effort tolerance while ensuring better ventilatory comfort (Vallet et al, 1997). CPET is defined as the gold standard to determine ventilatory threshold. However, when CPET is not accessible or feasible, it is difficult to individualised exercise training for all patients and/or follow their evolution when they came back to home.

An alternative to the prescription of V_{th} might be the use of a subjective parameter. Indeed, Nelson *et al.* 2007 offers an original approach of prescribing exercise intensity useable by all subjects. The interest of this approach is to replace the intensity defined by V_{th} during CPET by a self-assessment of the difficulty of exercise (Nelson et al, 2007). In COPD, given that dyspnoea is the major criterion of limiting effort and that is defined as a subjective breathing discomfort felt by patients, the use of dyspnoea threshold could be an alternative to V_{th} . Indeed, V_{th} correspond to the highest exercise intensity before an exponential increase of ventilation. On the other hand, dyspnoea correspond to a disharmony between pulmonary effectors and control of respiratory centres, constrain patient to increase their ventilatory level. In that case, it can be quite simple to say that the perception of that moment by the patient should be fairly spontaneous and precise.

Furthermore, it would be interesting to rely on this subjective criterion to a field test close to daily life activity. Currently, the six-minute walk test (6MWT) is recommended

in COPD to assess exercise tolerance, diagnose exercise-induced desaturation, prescribe oxygen therapy for ambulation, and quantify therapeutic effects (Spruit et al, 2013). It is a simple and reliable field test. In addition, it gives a more accurate vision of the individual's functional capacity to carry out daily living activities.

We hypothesized that patients with COPD would be able to identify during 6MWT the critical threshold when breathing becomes uncomfortable and that the HR corresponding to this self-perceived dyspnoea threshold (SDT6) could be used to estimate ventilatory threshold.

The objective of this study was therefore to determine the feasibility and reproducibility of SDT6 and to determine if a useful equation to estimate ventilatory threshold from SDT6 could be derived.

METHODS

Subjects

Eighty-two patients with COPD admitted to a pulmonary rehabilitation centre (Clinique du Souffle® La Vallonie, Lodève, France) were included in this study (Figure 1). COPD was diagnosed according to standard criteria, and post-bronchodilator forced expiratory volume in one second (FEV₁) was used to distinguish the stage of bronchial obstruction severity (Vestbo et al, 2012).

We excluded unstable patients (exacerbation < 4 weeks) and/or those with restrictive or mixed respiratory syndrome, angina, recent heart attack (< 1 month) or progressive coronary pathology, and cognitive or motor problems that would significantly limit comprehension or SDT6 evaluation; patients taking beta-blockers were also excluded. This project received the approval of the Internal Ethics Committee (Research Committee, Fontalvie Group, France).

Study design

In order to screen COPD patients, anthropometric and clinical measures were collected. Respiratory function was evaluated by plethysmography (Body Box 5550, Medisoft, Belgium). Vital capacity (VC) and FEV₁ were collected and the Tiffenau ratio (FEV₁/VC) was calculated. The normal European values were the references values (Laszlo, 1993). The BODE index, a grading system predicting the risk of death and, was calculated (Celli et al, 2004). Once the inclusion criteria validated, patients performed a 6MWTs familiarization in order to avoid learning effect. 24h after, they performed a CPET and 24h after that they performed two experimental 6MWTs and the HR_{SDT6} was collected.

Evaluations:

The 6MWTs were performed indoors along an unobstructed corridor. Patients were instructed to cover as much distance as possible in six minutes. Standardized encouragement was given during the test. In order to minimize methodological bias related to the experimenter, the same clinician trained in this evaluation monitored the two 6MWTs for each patient and followed the current international recommendations (Brooks et al, 2003). At least one hour separated the two 6MWTs. We ensured that HR values and dyspnoea at rest were identical for both 6MWTfor all patients. For each test, oxygen saturation and HR values were recorded every minute through a digital pulse oximeter (Nonin Onyx, Nonin Medical, Inc.Minneapolis, MN, USA).

CPET was conducted by an investigator blinded to the 6MWT. CPET was performed on an electronic ergocycle using an individualized and validated protocol. After a 3 min warm-up period pedalling corresponding to 20% of estimated power, the work rate was increased by 8% of estimated power every minute. The exercise were stopped when patients was unable to maintain the imposed pedalling rhythm. A 12 lead electrocardiogram was continuously monitored. Gas exchange and O₂ saturation were measured continuously. Two blinded and independent evaluators determined the first

V_{th} from the changes in the O_2 and CO_2 curves using the V-Slope method of Sue *et al.* (Sue & Wasserman, 1991). HR values corresponding to the first V_{th} was noted. If $HR_{V_{th}}$ differed between the two evaluators (± 5 bpm), the mean of these two values determined V_{th} .

Self-perceived Dyspnoea threshold during 6MWT (SDT6)

Before 6MWT, each patient was interviewed and the evaluator systematically asked three questions. *Question 1:* In your opinion, which daily physical activities typically leave you feeling breathless? *Question 2:* When you perform these activities do you recognize a critical moment where your breathlessness becomes uncomfortable? *Question 3:* In your own words, could you describe your sensations when this critical moment appears? As recommended by Williams *et al.* 2008 (Williams et al, 2008), the evaluator did not propose or prompt responses, but simply noted the patient's words and clarified when it was deemed necessary. In addition to the standard instructions relative to 6MWT, the evaluators gave all patients the following instructions: "You have described your sensation when breathing becomes uncomfortable in carrying out daily activities. This is a critical moment that you are able to identify. During the 6MWT, we ask you to simply raise your hand as soon as you feel that this critical moment is reached. All you have to do is raise your hand as you continue walking." During each 6MWT, the evaluator noted the corresponding HR. This moment, indicated by the patient's raised hand, was called the "self-perceived dyspnoea threshold of the 6-minute walking test" or "SDT6."

Statistics

Statistical analysis was performed using STATISTICA Version 10.0.

Data were expressed as mean (\pm SD). Normal Gaussian distributions of the data were verified by the Shapiro-Wilk test. In case of violation of normality hypothesis, nonparametric tests were used. The feasibility was analysed by descriptive statistics.

The reproducibility of HR_{SDT6} was analysed by a means comparison with a paired Student t test (or Wilcoxon signed rank test if normality was not verified), by calculating the variation coefficient and an intraclass correlation coefficient (ICC) for repeated measurements. In addition, Spearman's correlation and Bland & Altman plots were performed between the first and the second walk test.

The relationship between HR_{SDT6} and HR_{Vth} was analysed by a means comparison with a paired Student t test.

A stepwise regression analysis was performed to obtain a predictive equation of HR_{Vth} estimated from HR_{SDT6} . The HR_{Vth} was used as variable to explain and a set of potential explanatory variables was used (age, height, weight, BMI, FEV_1 and HR_{SDT6}) after verification of absence of collinearity between these variables.

The results were considered as statistically significant when p values were ≤ 0.05 .

RESULTS

Baseline

Baseline subject characteristics are shown in Table 1. FEV_1 was $37.4\% \pm 16.4$ with 5% at stage I of the GOLD standard, 18% at stage II, 42.5% at stage III and 34.5% at stage IV. On average, the BODE index was 4 ± 2 , with 20% patients in quartile 1, 42% in quartile 2, 27% in quartile 3 and 11% in quartile 4.

Feasibility

Language of dyspnoea: All patients were able to describe their sensations when breathing became uncomfortable during activities of daily living. Three word categories were distinguished: 44% of patients described a feeling of "suffocation," 19% a feeling of "chest tightness," and 16% a feeling of "increased respiratory rate." In addition, 11% described at least two of these three feelings ("mixed") and 10% confused dyspnoea with general fatigue or discomfort due to phlegm ("other").

Identification of SDT6: In the whole study population, 80% (n=66/82) of patients were able to recognize SDT6 during 6MWT and raised their hand when it occurred. Of these 66 patients, 91% (n=60) signalled a SDT6 during both 6MWTs and 9% (n=6) during one of the two 6MWT (Figure 1). For patients who did not identify a dyspnoea threshold, the results reveal a lesser increase of heart rate compared to patients with SDT6 (Table 1).

Reproducibility of SDT6

Reproducibility was assessed in 60 patients (Figure 1).

On average, the absolute HR_{SDT6} during the first and second tests were statistically similar: 110 ± 15 bpm and 110 ± 14 bpm ($p=0.84$) (Table 2). The means of paired differences were 0.15 ± 6.08 bpm. The coefficient of variation was 2.8% and the ICC (ICC=0.96) indicated very good reproducibility and concordance (Table 2). Furthermore, a strong correlation between HR_{SDT6-1} and HR_{SDT6-2} was observed ($r=0.90$, $r^2=0.81$; $p<0.0001$) (Figure 2). Bland & Altman plots between HR_{SDT6-1} and HR_{SDT6-2} showing a bias at 0.06 bpm and confidence interval at 12.43 bpm (Figure 3).

Relationship between HR_{Vth} and HR_{SDT6}

The relationship between HR_{Vth} and HR_{SDT6} was evaluated in a sample of 27 patients (Figure 1). The HR revealed a significant difference (107 ± 16 and 115 ± 16 bpm respectively between ventilatory and dyspnoea thresholds respectively; $p<0.01$). Mean of differences between HR_{SDT6} and HR_{Vth} was 8 ± 11 bpm.

Estimation of ventilatory threshold from SDT6

Multiple linear regression analysis was performed to estimate HR_{Vth} from HR_{SDT6} in a sample of 27 patients (Figure 1). The stepwise regression analysis selected the following explanatory variables: HR_{SDT6} (bpm), FEV_1 (L) and age (years). The equation obtained was the following:

$$\text{Estimated HR}_{V_{th}} = 46.21 + (0.607 \times \text{HR}_{SDT6}) + (8.93 \times \text{FEV}_1) - (0.3 \times \text{age})$$

Its predictive value was 63% (adjusted $r=0.79$; $r^2=0.63$) and the standard error of estimated was 9.8 bpm.

DISCUSSION

The aims of this study were to test the ability of patients to identify a dyspnoea threshold during 6MWT, evaluate its reproducibility and determine a useful generalized equation allowing to estimate a ventilatory threshold. Our principal results show that: 1) A large majority of patients (80%) were able to identify SDT6 during the 6MWT, 2) the heart rate at SDT6 was highly reproducible. In addition, we defined a linear equation integrating HR_{SDT6} , FEV_1 and age allowing to estimate closely $\text{HR}_{V_{th}}$.

As a first step, our aim was to appreciate the feasibility. As recommended in literature, we based our approach on the self-description of dyspnoea (Mahler et al, 1996; Nosedá, 2003; O'Donnell et al, 1997; Williams et al, 2008). We identified the words that each patient had associated with breathing discomfort and have provided them with guidelines for identifying the SDT6. This procedure allowed the patients to freely express their sensations without prior orientation or influence from the standardized words of dyspnoea categorization (predefined list of words or sentences). In this context, we obtained three main lexical fields: "increased respiratory rate," "chest tightness" and "suffocation," with the highest prevalence of responses for this last ("suffocation"). These results were comparable to those reported in previous studies, in which the authors used different interview strategies and multivariate statistical analyses (Mahler et al, 1996; Nosedá, 2003; O'Donnell et al, 1997; Williams et al, 2008). We therefore concluded that the ability of patients to define a SDT6 is easily detectable when the good procedure were applied.

The 6MWT is described in the literature as an easy and reproducible field test, and it was therefore important in this study to ensure that the definition of SDT6 during this

test met these same criteria (Troosters et al, 1999; Troosters et al, 2002). Concerning feasibility, our results showed that 80% of the patients raised a hand during the 6MWT to signal SDT6. The prevalence is comparable to the highest results reported in literature for V_{th} (66 to 79% in cardiac disease (Marzolini et al, 2012) and 77% in pulmonary disease (Ong et al, 2004)).

Concerning the 20% of patients who did not identify a SDT6 during 6MWT, we could note that, for comparable distances and a maximal theoretical heart rate similar between groups, maximum heart rate was significantly less than for patients having a SDT6. These results, associated with a higher FEV1, highlight either a smaller relative intensity of effort or either a better cardiorespiratory adaptation during exercise in this group and could explain why they have not reached their dyspnoea threshold.

Concerning reproducibility, our results showed that SDT6 occurred at comparable HR in the two experimental tests. Indeed, all statistical results were consistent and support the good reproducibility of the measurements. Moreover, they were consistent to the results obtained with different tests (6MWT, CPET) and study populations (pulmonary, cardiac and healthy subjects) (Meyer et al, 1996; Poulain et al, 2003). It means that COPD patients can detect in a highly reproducible way their dyspnoea threshold, when it is explained with their own words.

In a subgroup of patients, we tested the relationship between HRSDT6 and HRV_{th}. Our results revealed that the mean HR for these thresholds exhibited a bias of 8 bpm between both thresholds. This could be explained by the difference between these tests (nature and modalities). Indeed, CPET is an incremental test and were administrated on ergocycle rather than 6MWT is auto-calibrated test and were realized by walking. On COPD population, it has been shown that V_{th} occurred at a lower VO_2 during cycling than walking (Mahler et al, 2011). This confirms that V_{th} determine during cycling test appears before walking test. In the same vein, Cunha et al. (2014) showed that maximal HR obtained during walking was higher than maximal HR during cycling and with a difference of 7 bpm (Cunha et al, 2014). This supports the idea that

HR_{SDT6} (determined by auto-calibrated walking test) was consistent with HR_{Vth} (determined during incremental exercise test on ergocycle) and with to a fluctuation of HR between both tests close to previous studies (Cunha et al, 2014; Mahler et al, 2011).

Another interest of this study was to determine a useful equation allowing to estimate the heart rate at ventilatory threshold. Using Stepwise linear regression, we were able to account for 63% of the variance in HR_{Vth} using the HR_{SDT6} when combined with patients FEV₁ and age according to the following equation: *Estimated* HR_{Vth} = 46.21 + (0.607 × HR_{SDT6}) + (8.93 × FEV₁) - (0.3 × age). From clinical point of view, this equation allows also to estimate a heart rate close to HR_{Vth} in order to individualized exercise training when CPET is not accessible. The difference of 9.8 bpm between estimated HR_{Vth} and HR_{Vth} from CPET is in the same amplitude that the difference observed between HR SD6 and HR_{Vth} from CPET (8 bpm). The hypothesis described in the above paragraph and the related nature and modalities both tests could explain this difference.

To the best of our knowledge, this study is the first to demonstrate that dyspnoea threshold determined during 6MWT is a relevant alternative to predict exercise intensity close to ventilatory threshold. Contrary to ventilatory threshold determined by CPET which needs cost materials and specific staff, SDT6 could be evaluated by the patient himself, and consequently encourage patients in his self-management, which is one of the most important aim to reach in respiratory rehabilitation.

Study limitations

The determination of SDT6 is based on a subjective approach (a hand signal of the critical breathing discomfort during the 6MWT) and is therefore closely linked to the health status and psychological state of the patients. For this reason, patients in exacerbation or an unstable state were not included in our study, and SDT6

determination by our methods is relevant only for patients in steady state. Similarly, even though the 6MWT and HR_{SDT6} are reproducible, using HR_{SDT6} to evaluate therapeutic regimens cannot be considered at this point. From a clinical point of view, the positive effect of a therapeutic is expressed either by a decreased HR for a given intensity or a delay in the threshold. However, as the 6MWT is a self-calibrated test (i.e., patients automatically adjust their effort to their sensations), this type of interpretation cannot be made. The SDT6 cannot replace the determination of ventilatory threshold to evaluate the effects of exercise training, but it remains an interesting alternative tool for predicted this threshold in order to individualizing the exercise training intensity.

Conclusion

This study shows that a large majority of patients with COPD are able to identify a self-perceived dyspnoea threshold during the 6MWT. This heart rate associated to this dyspnoea threshold is highly reproducible and allow to estimate heart rate at ventilatory threshold. These findings suggest that SDT6 may be used as a new clinical tool for predicting heart rate at ventilatory threshold in COPD patients in order to individualizing exercise training intensity when CPET is not accessible and/or to follow in ambulatory rehabilitation.

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FIGURE CAPTION

Figure 1: Study flowchart. SDT6: Dyspnoea threshold in 6MWT; 6MWT: 6 minute walk test; V_{th} : Ventilatory threshold; CPET: Cardiopulmonary Exercise test.

Figure 2: Relationship between heart rate of Self-perceived Dyspnoea Threshold (SDT6) during the first and the second 6 minute walk test (SDT6-1 and SDT6-2). Significant and positive correlations of heart rate of SDT6 between both tests.

Figure 3: Bland & Altman Plots of inter-reproducibility of HR of SDT6 measurement between both 6MWT.

1 **Table 1: Characteristics of the study population.**

	All patients (n=82)	Patients without SDT6 (n=16)	Patients with SDT6 (n=66)	p
	Mean ± SD	Mean ± SD	Mean ± SD	
Age	63,7 ± 10,3	63,7 ± 8,7	63,7 ± 10,7	ns
Gender	26 ♀ 56 ♂	5 ♀ 11 ♂	21 ♀ 45 ♂	ns
BMI (Kg/m ²)	24,3 ± 4,5	24,2 ± 3,6	24,3 ± 4,7	ns
PaO ₂ (mmHg)	72,3 ± 11,9	73,4 ± 10,4	71,9 ± 12,3	ns
FEV ₁ (%pred.)	38,3 ± 17,2	48,0 ± 20,8	35,9 ± 15,4	<0.05
BODE Index	3,9 ± 2,0	3,0 ± 2,4	4,1 ± 1,9	ns
6MWT distance (m)	396,7 ± 97,5	403,8 ± 77,1	395,0 ± 102,3	ns
Heart rate at rest (bpm)	90,2 ± 14,3	89,1 ± 19,4	90,4 ± 13,0	ns
Heart rate max (bpm)	119,5 ± 17,9	111,8 ± 16,8	121,4 ± 17,7	<0.05

2 *Data presented as mean ± standard deviation, except gender (absolute number). BMI: Body mass*
3 *index; FEV₁: Force Expiratory Volume in 1 s expressed in percentage of predicted value; 6MWT: 6*
4 *minute walk test; p values between patients with and without SDT6; bpm: beats per minute; ns: no*
5 *significant (p>0.05)*

6

7

Table 2: Comparison of heart rate of SDT6 during both 6MWTs

	6MWT-1	6MWT-2	p	CV (%)	ICC
Heart rate SDT6 (bpm)	110 ± 15	110 ± 14	0.84	2.8 %	0.96

Data presented as mean ± standard deviation; SDT6: dyspnoea threshold during 6 minute walk test;

bpm: beats per minute; CV: coefficient of variation and ICC: IntraClass Coefficient

Figure 3:

