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Time to desaturation in the 6-min walking distance test predicts 24-hour oximetry in COPD patients with a PO_2 between 60 and 70 mmHg

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KEYWORDS
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Summary
Background: The 6-min walking distance (6MWD) test is a useful tool for assessing patients with chronic obstructive pulmonary disease (COPD), but little is known about the changes in oxygen saturation that occur during the test.
Objective: To predict the oximetry profile during daily living activities by the time to desaturation in the 6MWD test in COPD-affected patients.
Patients and methods: We studied 67 COPD patients with moderate hypoxemia performing a 6MWD test and a 24-hour ambulatory pulse oximetry (24-hr PO). We determined the time to desaturation ($SatO_2 \leqslant 90\%$) in the 6MWD test, in the daytime, nighttime and 24-hr PO. We then estimated the time to desaturation that better predicts desaturation in diurnal, nocturnal and 24-hour oximetries using the ROC type II analysis.
Results: The patients who desaturated after 3′30 min have a 100% probability not to desaturate during diurnal, nocturnal and 24-hr PO. Those patients who desaturated during the first minute of the 6MWD test have a 74% probability to desaturate in these oximetries.
Conclusions: The time to desaturation in the 6MWD test can discriminate early desaturators who desaturate during their daily living activities and late desaturators

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who do not desaturate. Ambulatory oximetry would thus only be necessary in patients with a time to desaturation that ranges between 1 and 3′30″.

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent disease with a high morbidity and mortality.[1,2] In order to adequately evaluate the disease, pulmonary function tests and the 6-min walking distance test (6MWD) are necessary. The 6MWD test has become a common tool for assessing the disease.[3] Decker et al.[4] were the first to perform oximetric monitorization with old and uncomfortable devices that evaluated the changes in haemoglobin desaturation observed during the test. Small and comfortable portable pulse oximetry devices which can monitor data up to 24 h (24-hour pulse oximetry, 24-hr PO) are now available. Most of the published work in this field has been performed during the nighttime period,[5–7] whereas few studies have been conducted during the daytime when patients perform most of their daily living activities.[8,9] When the desaturation time is equal to or greater than 30% of the total sleeping time, it is considered to be significant.[6,10]

Even though a 24-hr PO evaluation provides useful clinical information, it is somewhat cumbersome for the patients because they are required to collaborate while performing their activities of daily living.

The 6MWD test is simple and well tolerated. Moreover, it does not need complex devices, and it has been shown to correlate well with peak VO_2[11] and health-related quality of life.[12] Pulse oximetry during the test can provide useful information regarding the time when the oxygen saturation ($SatO_2$) falls under 90% in those patients at risk to desaturate.

Our hypothesis is that the time it takes for a patient to desaturate under 90% in a 6MWD test can predict the amount of time it takes this patient to spend $SatO_2$ under 90% during his daily living activities, including the daytime period. We believe that if this hypothesis is confirmed by experimental data, a 6MWD test could substitute a 24-hr PO to evaluate COPD patients at risk to develop hypoxemia.

Methods

Patients

We prospectively included patients who attended the Candelaria University Hospital and the Canarian University Hospital from February 2002 to December 2005 who fullfilled the following criteria: smoker or former smoker with a COPD diagnosis according to the ATS criteria,[13] i.e. $FEV_1/FVC < 70\%$ with a resting PaO_2 that ranges between 60 and 70 mmHg. Patients were excluded if they had a history of asthma, bronchiectasis, pulmonary hypertension, obstructive sleep apnea, central apnea, cardiovascular or renal disease that may predispose to the development of hypoxemia. All the patients were in a stable condition, free of exacerbation for at least 2 months. Sixty-one patients (51 patients with 50/500, 10 patients with 50/250) were administered tiotropium and a combination of salmeterol/fluticasone, and 6 patients were administered tiotropium only. All the patients had to be able to perform a 6MWD test and a 24-hr PO. They were all informed about the study and they all signed a written informed consent that had been approved by the Ethical Committee of both hospitals.

Patients were evaluated within 4 weeks of enrollment. PaO_2 was measured while the patients were at rest, breathing room air and in the sitting position. The arterial blood gas sample was obtained from the radial artery and analysed by a blood gas analysis machine (Gem Premier 3000-mod 5700, Gem Systems Instrumentation Laboratory, Lexington, MA, USA). Pulmonary function tests, including spirometry, lung volumes and CO diffusion were measured according to ATS guidelines[14] by a pulmonary function laboratory (Master Lab Jaegger, GMBH, Wuerzburg, Germany). Because there is no equation to assess the normal spirometric inspiratory capacity (IC) values, the ratio between IC and total lung capacity (IC/TLC) was used as a measure of resting hyperinflation. The best of two 6MWD tests, separated one from the other by at least 30 min, was selected following ATS recommendations.[15] The body mass index (BMI) was calculated in kg/m^2. The BODE index (BMI, Obstruction, Dyspnea, Effort) was calculated following Celli et al.[16]

Oximetry was performed with a portable pulse oximeter (pulsio3ia; Minolta; Japan) with computer software to record ambulatory oximetry data (AOM). Each parameter (O_2Sat and pulse rate) was recorded every 2 s. The digital probe was attached to the left hand for right-handed patients and to the right hand for left-handed ones. The probe was attached to the finger and secured to the wrist. All data obtained during the AOM monitoring period were downloaded from the oximeter to a computer for final analysis. A calibration check was run following the manufacturer instruction and checked before and after use by the patients. The time to desaturation was validated in a group of 15 patients and was the same for two consecutive tests.

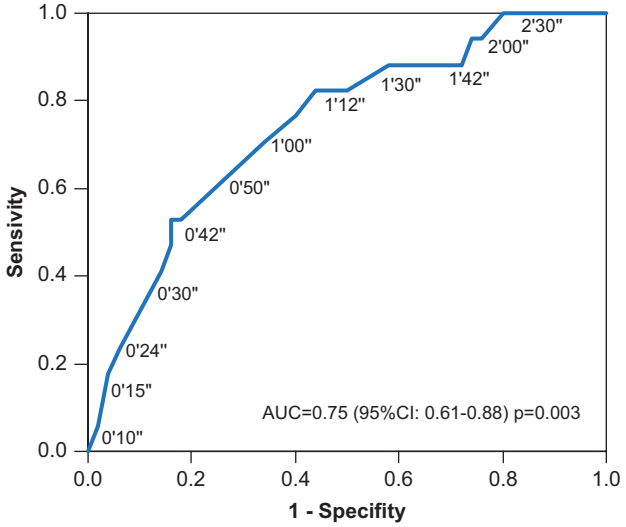
Pulse oximetry profile

Fletcher et al.[5] considered a desaturation time of more than 30% under 90% O_2Sat to define a desaturator in the nighttime oximetry. We used that same definition of desaturation time for 24 h and daytime periods. Because of lack of consensus in the literature, we also evaluated 3 different cut-off points to define a ''desaturator'', viz., we considered 20%, 30% and 40% or more spent under a $O_2Sat < 90\%$. Daytime oximetry was defined as the time when the patient was awake, and nighttime oximetry as the time when the patient was sleeping, including the naptime. The sleeping time analysed was the one mentioned by the patient on the following

morning. Ambulatory oximetry analysis was performed without knowing the 6MWD test results.

Early and late desaturators during the 6MWD

"Early" and "late" desaturator thresholds were defined. The early desaturator value was defined as the time a patient desaturates in the walking test that highly predicts the time spent $<90\%$ O_2Sat in the 24-hr PO. We selected the time to desaturation as the one with the highest sensitivity in order to select all the patients who desaturate during the 24-hr PO. The late desaturator value was defined as the time a patient desaturates in the walking test that highly predicts the possibility not to desaturate in the 24-hr PO. We then selected again the time to desaturation with the highest sensitivity and specificity in order to avoid including in this group any patient who may desaturate during the 24-hr PO, as was previously explained. We performed each calculation for the 3 different cut-off values of time spent $<90\%$ in the 24-hr PO (20%, 30% and 40%).



Time to desaturation in 6MWD Test with Pulsioximeter Validity Parameters for 30% or more of Time under SatO2<90% in Diurnal Oxymetry Pronostic*

Time to Desaturation in 6MWD Test Cut-Off (minutes)	Se (%)	Sp (%)	PRPV (%)	NRPV (%)	DY
0'30"	40	86	69	81	2.85
1'00"	71	66	67	87	2.05
1'30"	88	34	29	89	1.33
2'00	91	26	28	94	1.23
2'30"	100	20	27	100	1.21
3'00''	100	12	24	100	1.13
3'30''	100	9	22	100	1.09

AUC=Area Under Curve.
*Prevalence for 30% or more of time with $SatO_2<90\%$ in diurnal oximetry is 25%.
Se-Sensivity, Sp-Specifity, PRPV-Positive Result Predictive Value, NRPV-Negative Result Predictive Value, DV-Diagnostic Yield.

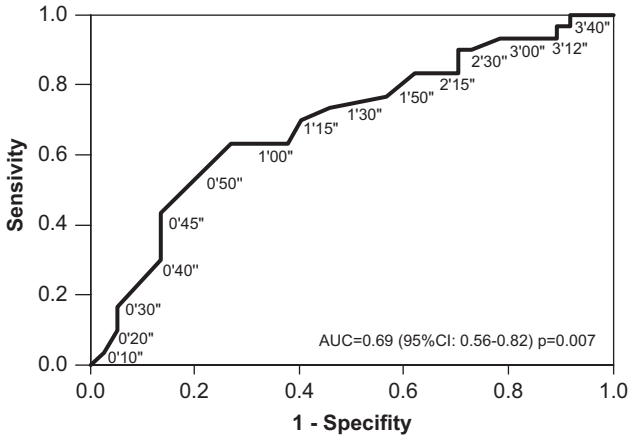
Figure 1 Receiver-operating characteristic curve for time to desaturation in 6MWD test with pulsioximeter as predictor of 30% or more of time with $SatO_2<90\%$ in diurnal oximetry.

Data processing

Because of the variable skewness, their median and range values were used. Range was used instead of percentiles in order to obtain more information about the variable extreme values. Spearman's coefficients were used to assess the correlation between the time to desaturation in the 6MWD tests and the time of desaturation in the daytime, nighttime and 24-hr PO. Taking into consideration the desaturators and non-desaturators in each period of the ambulatory oximetry evaluation (daytime, nighttime and 24-hour period), a ROC type II analysis was applied to evaluate the sensitivity, specificity, positive and negative predictive values of the time to desaturation to predict the pulse oximetry desaturation. All the calculations were performed by means of the statistical software package SPSS 12.0™ Inc.© Chicago, IL, USA.

Results

The cut-off point of 30% of time with $SatO_2$ $<90\%$ included 20 patients (30%) in the 24-hour period, 17 (25%) in the daytime and 30 (45%) in the nighttime periods. The correlation between the time to desaturation in the 6MWD tests and more than 30% of time desaturating $<90\%$ for the different cut-off values were: -0.576 ($p<0.001$) for

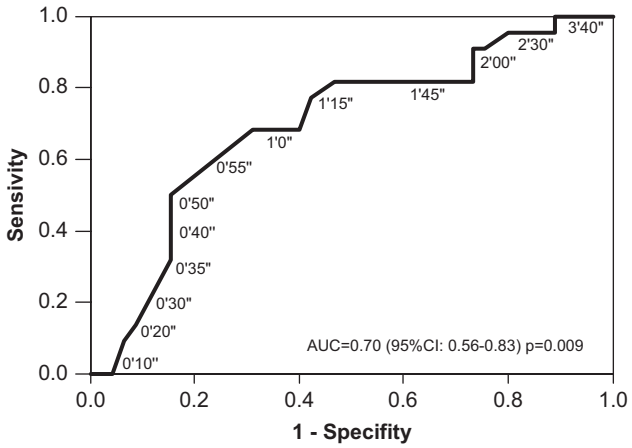


Time to desaturation in 6MWD Test with Pulsioximeter Validity Parameters for 30% or more of Time under SatO2<90% in Nocturnal Oxymetry Pronostic*

Time to Desaturation in 6MWD Test Cut-Off (minutes)	Se (%)	Sp (%)	PRPV (%)	NRPV (%)	DY
0'30"	17	94	78	58	2.83
1'00"	63	73	74	68	2.33
1'30	79	42	53	71	1.36
2'00	90	30	51	76	1.28
2'30"	92	22	49	77	1.17
3'00	93	11	48	80	1.04
3'30"	100	8	47	100	1.02

AUC= Area Under Curve.
*Prevalence for 30% or more of time with $SatO_2<90\%$ in nocturnal oximetry is 45%.
Se-Sensivity, Sp-Specifity, PRPV-Positive Result Predictive Value, NRPV-Negative Result Predictive Value, DV-Diagnostic Yield.

Figure 2 Receiver-operating characteristic curve for time to desaturation in 6MWD test with pulsioximeter as predictor of 30% or more of time with $SatO_2<90\%$ in nocturnal oximetry.



Time to desaturation in 6MWD Test with Pulsioximeter Validity Parameters for 30% or more of Time under SatO2<90% in 24-hours Oxymetry Pronostic*

Time to Desaturation in 6MWD Test Cut-Off (minutes)	Se (%)	Sp (%)	PRPV (%)	NRPV (%)	DY
0'30"	20	92	62	70	2.5
1'00	68	69	61	77	3.12
1'30"	82	38	36	81	1.32
2'00	91	27	36	85	1.24
2'30"	91	25	34	85	1.21
3'00	96	11	34	85	1.07
3'30"	100	8	32	100	1.08

AUC= Area Under Curve.
*Prevalence for 30% or more of time with $SatO_2$<90% in 24-hours oximetry is 33%.
Se-Sensivity, Sp-Specifity, PRPV-Positive Result Predictive Value, NRPV-Negative Result Predictive Value, DV-Diagnostic Yield.

Figure 3 Receiver-operating characteristic curve for time to desaturation in 6MWD test with pulsioximeter as predictor of 30% or more of time with $SatO_2 < 90\%$ in 24-hour oximetry.

daytime, −0.464 ($p < 0.001$) for nighttime and −0.417 ($p < 0.001$) for the 24-hour period.

Figure 1 shows the ROC type II curve for the values of the time to desaturation in the 6MWD tests that predicts a desaturation time >30% for the daytime period. Figure 2 shows the ROC type II curve for the values of the time to desaturation in the 6MWD tests that predicts a desaturation time >30% for the nighttime period.

Figure 3 shows the ROC type II curve for the values of the time to desaturation in the 6MWD tests that predicts a desaturation time >30% for the 24-hour period.

An early desaturator was defined as one who desaturated within 1 min of the 6MWD test, because this was the amount of time with the best sensitivity to predict ambulatory oximetry desaturation. By contrast, a late desaturator was defined as one who desaturated 3′30″ (or more) after beginning the 6MWD test because this was the amount of time with the best sensitivity to predict the absence of desaturation during ambulatory oximetry.

Discussion

We analysed the desaturation profile of COPD patients with a PaO_2 between 60 and 70 mmHg during 2 different tests: the 6MWD test on one hand, and the 24-hr PO on the other. The main and most important finding of our study lie in the fact that many patients who desaturated within the first minute of the 6MWD test also desaturated in the 24-hr PO, and those that only desaturated after 3′30″ of the 6MWD test did not desaturate in the 24-hr PO.

Previous research described functional parameters that predict desaturations during the 6MWD test, such as Hadeli et al.[17] who studied 8000 patients. They concluded that a diffusion capacity for CO (DLCO) < 62% of the reference value was a good predictor of desaturation during a submaximal exercise. Other researchers studied the predictive parameters of nocturnal desaturation. Plywaczewski et al., for example, studied 82 patients with COPD who received long-term oxygen therapy (LTOT). They observed that an increased basal daytime $PaCO_2$ was a good predictor of nocturnal desaturation.[18] Our objective was not to analyse basal parameters as CO diffusion or PCO_2 with desaturation during exercise or nocturnal time. As Table 1 indicates, the mean basal PaO_2 media was 66 mmHg, the mean $PaCO_2$ 45 mmHg, and the mean DLCO was 64% of predicted (Table 2).

Few studies compared desaturation profiles while the patients perform an exercise test and during their nighttime period. Mulloy et al. did not find any relationship between the treadmill exercise desaturation and sleep desaturation in 25 COPD patients,[19] while Fletcher et al.'s findings showed that exercise desaturation was not predictive of nocturnal desaturation.[20] The aim of our research was not

Table 1 Patients' sample characteristics and results of 6MWD tests with pulse oximeter and 24-hour oximetry.

Characteristic/parameter/measure	Value*
General characteristics	
Gender (M/F)	61/6
Age (years old)	65 (50–79)
FEV_1 predicted (%)	37 (16–64)
FVC (liters)	64 (28–129)
PO_2 (mmHg)	66 (60–70)
PCO_2 (mmHg)	45 (32–57)
TLCO (mmHg)	64 (21–105)
BODE (points)	4 (1–8)
IC/TLC (%)	28 (25–33)
6MWD test with pulse oximeter results	
Distance walked (m)	417 (125–625)
Time to $SatO_2 < 90\%$ (min)	1′12″ (0′06″–5′30″)
Distance to $SatO_2 < 90\%$ (m)	75 (15–384)
Start saturation (%)	93 (91–96)
Ending saturation (%)	84 (70–88)
24-hour oximetry results	
$SatO_2 < 90\%$ 24-h time (min)	242′ (5′–1080′)
$SatO_2 < 90\%$ 24-h time (%)	17 (0.3–75)
$SatO_2 < 90\%$ diurnal time (min)	98′ (2′–590′)
$SatO_2 < 90\%$ diurnal Holter time (%)	15 (0.2–82)
$SatO_2 < 90\%$ nocturnal time (min)	98′ (3′–618′)
$SatO_2 < 90\%$ nocturnal time (%)	23 (0.7–92)

*Frequency, percentage or median (range).

Table 2 Cut-off points of time to desaturation in the 6MWD test to predict a $O_2Sat < 90\%$ time greater than 20%, 30% and 40% in the diurnal, nocturnal and 24-hour oximetry.

Oximetry reference			Cut-off point for time to desaturation in 6MWD test with pulsioximeter and their prognostic characteristics						No early nor later desaturators remained with indication to ambulatory oximetry (%)
			Early desaturator*			Later desaturator†			
Desaturation threshold (% time with $O_2Sat < 90\%$)	Oximetry day period type	Desaturators over threshold (%)	Time to fall in $O_2Sat < 90\%$ (min)	Desaturators according ambulatory oximetry (%)‡	No desaturators according ambulatory oximetry (%)§	Time to fall in $O_2Sat < 90\%$ (min)	No desaturators according ambulatory oximetry (%)¶	Desaturators according ambulatory oximetry (%)‖	
20	Diurnal	42	1:00	72	13	3:30	100	0	51
	Nocturnal	52	1:00	72	16	3:30	100	0	51
	24 h	43	1:00	67	16	3:30	100	0	52
30	Diurnal	25	1:00	67	18	3:30	100	0	51
	Nocturnal	48	1:00	74	14	3:30	100	0	52
	24 h	33	1:00	61	16	3:30	100	0	52
40	Diurnal	19	1:00	50	19	3:30	100	0	52
	Nocturnal	38	1:00	51	17	3:30	100	0	52
	24 h	18	1:00	50	20	3:30	100	0	52

*Early desaturator: patient with a $O_2Sat < 90\%$ time over threshold in respective oximetry and then candidate for LTOT administration.
†Later desaturator: patient with a $O_2Sat < 90\%$ time under threshold in respective oximetry and then candidate for not LTOT administration.
‡Cut-off time to desaturation in 6MWD test positive predictive value relative to reference oximetry over threshold as gold standard.
§Cut-off time to desaturation in 6MWD test false positive proportion relative to reference oximetry over threshold as gold standard.
¶Cut-off time to desaturation in 6MWD test positive predictive value relative to reference oximetry under threshold as gold standard.
‖Cut-off time to desaturation in 6MWD test false negative proportion relative to reference oximetry under threshold as gold standard.

only to analyse parameters that could predict nocturnal desaturation, but also to find parameters that could predict ambulatory oximetry.

In a prospective study using ambulatory oximetry, Fussell et al. did not find any relationship between desaturations during the 6MWD test and those occurring during daily living activities.[21] They studied ambulatory oximetry during 24 h and desaturation during a 6MWD test with the aim of assessing the need for LTOT. They analysed 20 patients only and the lowest oxygen saturation, but they did not measure the time to desaturation in a 6MWD test. Their conclusion that ambulatory oximetry monitoring is better to prescribe oxygen therapy is quite convincing, but we did find a way to predict desaturation during ambulatory oximetry by using the time to desaturation during the 6MWD test.

We were particularly interested in the group of COPD patients (PaO_2 between 60 and 70 mmHg) who do not formally qualify for oxygen therapy but who are at high risk of developing oxygen desaturations during their activities of daily living. We therefore designed this study to describe these patients' 24-hr-PO profile and then determine whether their 6MWD test pulse oximetry desaturation profile could predict what happened during the 24-hour period. Twenty five percent of the patients were found to be daytime desaturators, 45% nocturnal desaturators and 30% 24-hour desaturators. Our findings agree with previous research and reflect a predominance of nocturnal desaturators in COPD patients. We chose 1 min as the time to desaturation that best predicted daytime, nocturnal and 24-hr-PO desaturations as shown in Figures 1–3. We also chose 3′30″ as the time to desaturate in the 6MWD test that better predicts the event of no desaturation during the daytime, nighttime and 24-hr PO. Our results also indicate that there is a relationship between the time to desaturation during a submaximal effort and desaturation during daily living activities in these patients, although we acknowledge that these are two different efforts. During the 6MWD test, many COPD patients may desaturate, but during their daily activities they may not desaturate because they do not usually perform a submaximal effort. We did find a relation, though, between the desaturation observed during the 6MWD test and that observed during the sleeping time, but we do not know how to explain these findings from a physiological standpoint. Some patients' desaturate during diurnal activity, others during their sleeping time, and some others do so in both periods. However, our results suggest that there is a relationship between the desaturation observed during the 6MWD test and those recorded during the daytime and nighttime periods.

An important implication of our findings is that they could affect the decision to administer LTOT in patients with COPD. Resting oxygen saturation and lowest exercise saturation during a 6MWD test is the standard method of determining LTOT requirement.[13] We agree with Fussell et al.[21] and Pilling and Cutaia[22] that it is with a 24 h ambulatory oximetry that the real life oxygen saturation is best reflected. Furthermore, Turner et al. and Poulain et al. have demonstrated that the 6MWD test is a very sensitive test to detect desaturations in patients with COPD.[23,24] Another recent study has also demonstrated that the 6MWD test is useful for adjusting LTOT.[25] We thus believe that our findings support the idea that the 6MWD test in patients with COPD can also be used for other purposes, as suggested by Pinto-Plata et al.[26] These patients' saturation profile during the test can be used to predict their desaturation profile while performing their daily living activities.

A possible limitation of our study is that the 24-hr PO monitorization was performed without determining the patients' concommitant physical activity by means of a questionnaire or an accelerometer, as recommended by Pitta et al.[27] and Cohen et al.[28] Another limitation is that we do not know the importance these 24-hour oximetry desaturations have over these patients' overall morbidity and mortality. Follow-up studies are required to find an answer to this question.

In conclusion, the time to desaturation $<90\%SatO_2$ less than 1 min in the 6MWD test in COPD patients with PO_2 between 60 and 70 mmHg predicts a high possibility of desaturation during the 24-hr PO. Moreover, a time to desaturation greater than 3′30″ predicts a high possibility not to desaturate in the 24-hr-PO period. The ambulatory oximetry would thus be necessary only in patients with a time to desaturation that ranges between 1 and 3′30″ min. This information can be used to better diagnose and treat this desaturation, the importance of which is still unknown. Further studies are required to apply these results in the administration of oxygen therapy during efforts in early desaturators.

Conflict of interest statement

The authors do not have any conflict of interest.

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