

Twenty-Four-Hour Ambulatory Oximetry Monitoring in COPD Patients With Moderate Hypoxemia

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BACKGROUND: The relationship of diurnal desaturations (oximetry-measured blood oxygen saturation [S_{pO_2}] < 90%) during activities of daily living and clinical aspects in patients with chronic obstructive pulmonary disease (COPD) and moderate hypoxemia has not been systematically evaluated. **METHODS:** We prospectively studied 88 patients with stable COPD (forced expiratory volume in the first second [FEV_1] < 80% of predicted, ratio of FEV_1 to forced vital capacity < 70% of predicted, and P_{aO_2} 60–70 mm Hg) with 24 hours of ambulatory oximetry. Desaturators were defined as those who spent $\geq 30\%$ of the time with S_{pO_2} < 90%. Patients engaged in their usual activities of daily living. We correlated these desaturations with the following variables, measured immediately before the 24 hours of oximetry: body mass index, dyspnea (measured with the modified Medical Research Council dyspnea scale), gas exchange, pulmonary function, quality of life (measured with the Saint George's respiratory questionnaire), and comorbidity (measured with the Charlson index). **RESULTS:** Thirty-three (38%) of the patients were desaturators: 50% nocturnal and 22% diurnal. We also measured daytime arterial blood gas values from arterial blood samples and found that the desaturators had higher P_{aCO_2} ($p = 0.001$) and lower P_{aO_2} ($p = 0.007$) than the nondesaturators. There were no differences in the other variables. The correlation between nocturnal and diurnal time with S_{pO_2} < 90% was $r^2 = 0.67$, and the concordance was low (Cohen's kappa 0.43, $p < 0.001$). **CONCLUSIONS:** Patients with stable COPD and moderate hypoxemia have frequent and potentially important desaturations during activities of daily living and at night. In addition, there is a big difference in the profile and degree of nocturnal and diurnal desaturations. Twenty-four hours of oximetry provides valuable information for comprehensive evaluation of patients with COPD. *Key words:* chronic obstructive pulmonary disease, COPD, ambulatory, oximetry, hypoxemia. [Respir Care 2006;51(12):1416–1423. © 2006 Daedalus Enterprises]

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of death worldwide.¹ Long-term oxygen therapy

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(LTOT) is an important treatment for patients with severe hypoxemia.^{2,3} However, LTOT does not appear to be effective in patients with moderate hypoxemia, because it does not improve survival.^{4,5} Nevertheless, there have been no studies of the possible prognostic value of LTOT for selected clinical variables and quality of life of patients with COPD.⁶ In addition, the only large longitudinal study of nonseverely hypoxemic COPD patients did not analyze the differences between awake and asleep oxygen desaturations and the presence or absence of comorbidities.⁴

Currently, the standard assessment to prescribe LTOT includes arterial blood gas measurement, with the blood sample drawn while the patient is at rest, sitting.^{1,7} However, the dynamic and temporal saturation profile obtained via oximetry may offer important information in patients with similar P_{aO_2} at rest.⁸⁻¹⁷ In COPD patients with moderate hypoxemia it is unknown whether or how often they develop clinically important hypoxemia during normal activities of daily living. The overall profile might influence outcomes in the natural course of COPD.¹⁸

There is a large body of evidence that describes the changes in oxygen levels during sleep in patients with COPD. Patients become more hypoxemic due to a variable combination of alveolar hypoventilation and ventilation-perfusion mismatch,¹⁹⁻²¹ but, interestingly, we lack information regarding diurnal variation in oxygenation. Moreover, COPD patients with moderate hypoxemia might be more physically active than those with severe hypoxemia, which has been considered, for example, in patients referred for pulmonary rehabilitation.^{1,7} Whether the physical activity in these patients results in different clinical expressions of the disease remains unexplored.

In COPD patients with moderate hypoxemia, we prospectively conducted 24 hours of ambulatory oximetry (24-hour oximetry) to determine their 24-hour oxygen saturation profiles, and we explored the impact of desaturations on several clinical variables that help predict outcome.

Methods

A total of 88 patients with COPD, diagnosed in 4 Spanish tertiary-care hospitals (Hospital Universitario Nuestra Señora de Candelaria, Tenerife; Hospital Universitario de Canarias, Tenerife; Hospital Insular de Canarias, Gran Canaria; and Hospital Doctor Negrin, Gran Canaria, participated in the study, which was approved by the human studies review board at each center. Patients were enrolled from June 2001 to September 2004. The patients were recruited from the wards before discharge, from the pulmonary department, or from the out-patient clinic. COPD was defined by smoking history of > 20 pack-years, post-bronchodilator forced expiratory volume in the first second $< 80\%$ of predicted, ratio of forced expiratory volume in the first second to forced vital capacity $< 70\%$, and total

lung capacity $\geq 80\%$ of predicted. Moderate daytime hypoxemia was defined as a daytime P_{aO_2} of 60–70 mm Hg on 2 measurements separated by 2–4 weeks. Patients were clinically stable for at least 6 weeks and received optimal medical therapy. Exclusion criteria were diagnosis of sleep apnea syndrome and history of asthma.

The patients were evaluated within 4 weeks of enrollment. P_{aO_2} was measured at rest while breathing room air in the sitting position.^{1,7} Pulmonary function tests, spirometry, lung volumes, and diffusing capacity of the lung for carbon monoxide were measured according to American Thoracic Society guidelines.²² Maximum inspiratory pressure was measured at residual volume. The inspiratory capacity was measured using the protocol described by O'Donnell and Webb.²³ Because there are no current equations for normal spirometric inspiratory capacity values, we used inspiratory fraction or the ratio of inspiratory capacity to total lung capacity as a measure of resting hyperinflation.²⁴ We also used the best of two 6-min-walk tests, separated by at least 30 min.²⁵ Dyspnea was measured with the modified Medical Research Council dyspnea scale.²⁶ Quality of life was measured with the Saint George's Respiratory Questionnaire.²⁷ We used the combined Charlson index to determine the degree of comorbidity.²⁸ The BODE index (which uses the body mass index, degree of airflow obstruction, dyspnea, and exercise capacity, measured by the 6-min walk test) was calculated in the standard fashion.¹⁸ COPD exacerbations were registered during the previous 12 months as out-patient treated exacerbations or hospitalization. We used a portable pulse oximeter (Pulsox 3iA, Minolta, Japan) to obtain 24-hour oximetry data. To minimize artifact and optimize signal quality, special attention was paid to attaching the finger probe per the manufacturer's instructions and to avoid changing the probe position on the finger. Oximetry-measured blood oxygen saturation (S_{pO_2}) and pulse was recorded every 2 s. For the analysis we excluded every period during which the heart rate fell abruptly (≥ 25 beat/min).

With right-handed patients the oximetry probe was attached to the left hand, and vice versa. The probe was attached to the finger and the oximeter was secured to the wrist. All the oximetry data were downloaded to a computer for analysis. A calibration check was run according to the manufacturer's instructions and checked before and after use. With a group of 4 patients we validated the oximeter's registration during the 6-min-walk test, by also obtaining the oxygen saturation via CO-oximetry.²⁹

We defined as desaturators those patients who spent $\geq 30\%$ of the continuous 24 hours of oximetry with $S_{pO_2} < 90\%$, because 90% is the most frequently used threshold.³⁰ We also evaluated other possible thresholds: $\geq 20\%$ of the diurnal period, $\geq 30\%$ of the diurnal period, $\geq 40\%$ of the nocturnal period, $\geq 50\%$ of the nocturnal period,

≥ 40% of the 24-hour period, and ≥ 50% of the 24-hour period.

We evaluated the correlation between health status score and clinical variables with different expressions of oxygen desaturation: time with $S_{pO_2} < 90\%$, mean S_{pO_2} , and lowest S_{pO_2} .

During the 24-hour oximetry, the patients engaged in normal activities of daily living and recorded the period of sleep. Following the patient's description, those periods were defined as the nocturnal period, and the rest of the time was defined as the daytime period. The patients did not record any nap times during the 24-hour oximetry. The shortest recording period comprised 18 hours with a 6-hour nocturnal period.

In addition to recording all S_{pO_2} values < 90%, we also measured the number of desaturation episodes per hour, where S_{pO_2} fell by > 4%.

In a group of 11 patients, the 24-hour oximetry was repeated 1–3 weeks after the first 24-hour oximetry, to determine the consistency of the results.

Statistics

The data for categorical variables are expressed as relative frequency. The data for normally distributed variables are expressed as mean ± 1.96 standard error of the mean. The data for non-normally distributed variables are expressed as median and 5th–95th percentiles. The differences in relative frequencies between groups were tested with the chi-square Pearson test. Student's *t* test was used for normal variables. The Mann-Whitney U test was used for non-normal variables. The percents of nocturnal and diurnal time with $S_{pO_2} < 90\%$ were compared with the Pearson linear coefficient, and the concordance was estimated with the Cohen's kappa index. A 2-tailed *p* < 0.05 was considered significant. The calculations were made with statistics software (SPSS 11.5.1, SPSS, Chicago, Illinois).

Results

The cohort of 88 patients was geographically distributed as follows: 49 (56%) at Hospital Universitario Nuestra Señora de Candelaria, 22 (25%) at Hospital Universitario de Canarias, 14 (16%) at Hospital Insular de Canarias, and 3 (3%) at Hospital Doctor Negrin. The patients' age was 65 ± 10 years, and 86% were men. Table 1 shows the baseline characteristics of the cohort.

Thirty-eight percent of the patients were desaturators: 50% were nighttime desaturators; 22% were daytime desaturators. Table 2 shows the oximetry characteristics of the desaturators and nondesaturators. The recording time, including nocturnal period, was similar in both groups: 8.1 h (6.2–9.9 h) among the nondesaturators, versus 8.2 h (7–10.3 h) among the desaturators (*p* = 0.715). As ex-

Table 1. Baseline Characteristics of the Cohort*

Characteristic	Value Mean ± 1.96 SEM or median (5 th –95 th percentile)
Sex (male/female)	76/12
Age (y)	65 ± 10
BMI (m ² /kg)	27 ± 4
P _{aO₂} (mmHg)	64.7 ± 2.8
P _{aCO₂} (mmHg)	45 ± 5.7
FEV ₁ (% of predicted)	38 ± 13
FVC (% of predicted)	67 ± 18
FRC (% of predicted)	145 ± 35
IC/TLC	0.30 ± 0.07
D _{LCO} (% of predicted)	78 ± 32
P _{imax} (% of predicted)	56 ± 24
6 MWD (m)	444 ± 86
MMRC dyspnea	1 (0–4)
BODE Index	3 (1–6)
SGRQ	44 ± 21
Exacerbations	1 (0–5)
Charlson Comorbidity Index	4 (2–7)

**n* = 88 patients
 BMI = body mass index
 FEV₁ = forced expiratory volume in the first second
 FVC = forced vital capacity
 FRC = functional residual capacity
 IC = inspiratory capacity
 TLC = total lung capacity
 D_{LCO} = diffusing capacity of the lung for carbon monoxide
 P_{imax} = maximum inspiratory pressure
 6MWD = 6-min walk distance
 MMRC = modified Medical Research Council dyspnea scale
 BODE index = 4-factor index of (B) body mass index, (O) airflow obstruction, (D) dyspnea, and (E) exercise capacity, measured by the 6-min walk test
 SGRQ = Saint George's Respiratory Questionnaire

pected, the desaturators showed larger desaturation dips and lower mean and lowest S_{pO_2} (*p* < 0.001). The percent of desaturators was similar at 3 of the hospitals: 37% at La Candelaria Hospital, 41% at Universitario de Canarias Hospital, and 43% at Insular Hospital (*p* = 0.46). The small number of patients recruited at Hospital Doctor Negrin precluded this analysis for that data.

Table 3 shows the participants' clinical characteristics. During the daytime, the desaturators were more hypercapnic (P_{aCO₂} 47.6 ± 5.6 mm Hg vs 43.4 ± 5.3 mm Hg, *p* = 0.001) and slightly more hypoxemic (P_{aO₂} 63.6 ± 2.6 mm Hg vs 65.3 ± 2.8 mm Hg, *p* = 0.007). There were no significant differences in the pulmonary function test values, dyspnea, quality of life, or exacerbations. These results did not significantly change when we used more severe desaturation thresholds (≥ 40% or ≥ 50% of the 24-hour period with $S_{pO_2} ≤ 90\%$). We obtained the same results when we used different thresholds in the partial analysis (20% and 30% for the diurnal period; 30%, 40%, and 50% for the nocturnal period), and when we used lowest S_{pO_2} , mean S_{pO_2} , and time with $S_{pO_2} < 90\%$.

Table 2. Oximetry Characteristics

Characteristics	Desaturators (n = 33)	Nondesaturators (n = 55)	p
Duration of registration (h)	23 (19–24)	23 (19–24)	0.91
Mean O ₂ saturation (%)	88.8 ± 1.4	92 ± 1.1	< 0.001
Lowest O ₂ saturation (%)	70 ± 6.4	76.9 ± 5.4	< 0.001
Desaturation/4 h (mean ± SD %)	5.4 ± 3.2	2.6 ± 1.9	< 0.001
TS _{pO₂} < 90% 24 h (mean ± SD %)	55.1 ± 16.2	12.2 ± 8	< 0.001
TS _{pO₂} < 90% Nocturnal (mean ± SD %)	77.3 ± 15.4	18.8 ± 16	< 0.001
TS _{pO₂} < 90% Diurnal (mean ± SD %)	42.3 ± 24.5	8.9 ± 8.2	< 0.001

TS_{pO₂} < 90% = percent of time with S_{pO₂} < 90%.

The correlation between nocturnal and diurnal ambulatory oximetry was $r^2 = 0.67$, and the concordance was low (Cohen’s kappa 0.43, $p < 0.001$, Fig. 1). When we used the 30% threshold, 28% of patients with nocturnal desaturation were not captured during the diurnal oximetry, and 21% of patients were desaturators in both periods (see Fig. 1). The concordance was stronger between nocturnal and 24 hours than diurnal and 24 hours (Cohen’s kappa 0.76 vs 0.64, $p < 0.001$, Figs. 2 and 3). Twelve percent of patients with nocturnal desaturation were not captured by the 24-hour oximetry, and, conversely, 15% percent of patients with the 24-hour oximetry were missed with the diurnal oximetry values alone (see Figs. 2 and 3).

In 11 patients we conducted a second 24-hour oximetry, 1–3 weeks after the first 24-hour oximetry. In 2 of these patients there was a difference $\geq 15\%$ in the percent of time with S_{pO₂} < 90%. In none of these patients was there a difference large enough to justify reclassifying the patient into the other group (desaturator vs nondesaturator).

Discussion

To our knowledge, this is the first systematic study of the temporal profile of S_{pO₂} and its relation to clinical variables in patients with COPD and moderate hypoxemia during 24 hours of normal daily activities. One third of the patients had important desaturation, as defined by Levis-Valensi and co-workers²⁹ (S_{pO₂} < 90% for $\geq 30\%$ of the oximetry period). Most of them were nocturnal desaturators, and there was a low concordance between the nocturnal and diurnal oxygen saturation profiles. The desaturators were more hypercapnic and hypoxemic during the

Table 3. Characteristic According to Oxygen Saturation Status

Characteristic	Desaturators (n = 33)	Nondesaturators (n = 55)	p
Sex (male/female)	31:2	45:10	0.20
Age (y)	67 ± 10	65 ± 10	0.31
BMI (m ² /kg)	28 ± 5	27 ± 4	0.43
P _{aO₂} (mmHg)	63.6 ± 2.6	65.3 ± 2.8	0.007
P _{aCO₂} (mmHg)	47.6 ± 5.6	43.4 ± 5.3	0.001
FEV ₁ (% of predicted)	38 ± 11	38 ± 13	0.89
FVC (% of predicted)	65 ± 18	69 ± 18	0.36
FRC (% of predicted)	138 ± 37	149 ± 35	0.21
IC/TLC	0.31 ± 0.06	0.29 ± 0.08	0.34
D _{LCO} (% of predicted)	84 ± 34	75 ± 30	0.27
P _I max (% of predicted)	52 ± 21	59 ± 25	0.20
6MWD (m)	464 ± 92	433 ± 82	0.14
MMRC dyspnea	1 (0–4)	1 (0–4)	0.96
BODE Index	3 (1–6)	3 (0–6)	0.85
SGRQ score	43 ± 22	44 ± 20	0.84
Exacerbations	1 (0–5)	1 (0–5)	0.44
Charlson comorbidity Index	4 (2–8)	4 (2–7)	0.81

*n = 88 patients
 BMI = body mass index
 FEV₁ = forced expiratory volume in the first second
 FVC = forced vital capacity
 FRC = functional residual capacity
 IC = inspiratory capacity
 TLC = total lung capacity
 D_{LCO} = diffusing capacity of the lung for carbon monoxide
 P_Imax = maximum inspiratory pressure
 6MWD = 6-min walk distance
 MMRC = modified Medical Research Council dyspnea scale
 BODE index = 4-factor index of (B) body mass index, (O) airflow obstruction, (D) dyspnea, and (E) exercise capacity, measured by the 6-min walk test
 SGRQ = Saint George’s Respiratory Questionnaire

daytime, but they had similar pulmonary function, similar health-related quality-of-life scores, and they reported the same number of exacerbations as the nondesaturators.

Only one study has evaluated the S_{pO₂} profile in COPD patients with moderate hypoxemia (P_{aO₂} 60–70 mm Hg).²⁹ In that study, only nocturnal S_{pO₂} was evaluated. They reported that 45% of the patients could be classified as desaturators, using the same threshold that we used in our study. However, they did not measure the daytime S_{pO₂} profile, during which most of the physical activities are performed. In addition, they did not study the clinical repercussions of the desaturation episodes. In contrast to our study, the daytime arterial blood gas values could not discriminate between desaturators and nondesaturators. This discrepancy may be explained because the studied sample size was smaller.²⁹

Two other prospective and longitudinal studies have assessed COPD patients with less severe hypoxemia (P_{aO₂} 56–69 mm Hg). In the first study, Gorecka et al⁴ randomized 135 patients: 68 to LTOT (15 h/d) and the rest to the control group. After 3 years, the survival was similar in

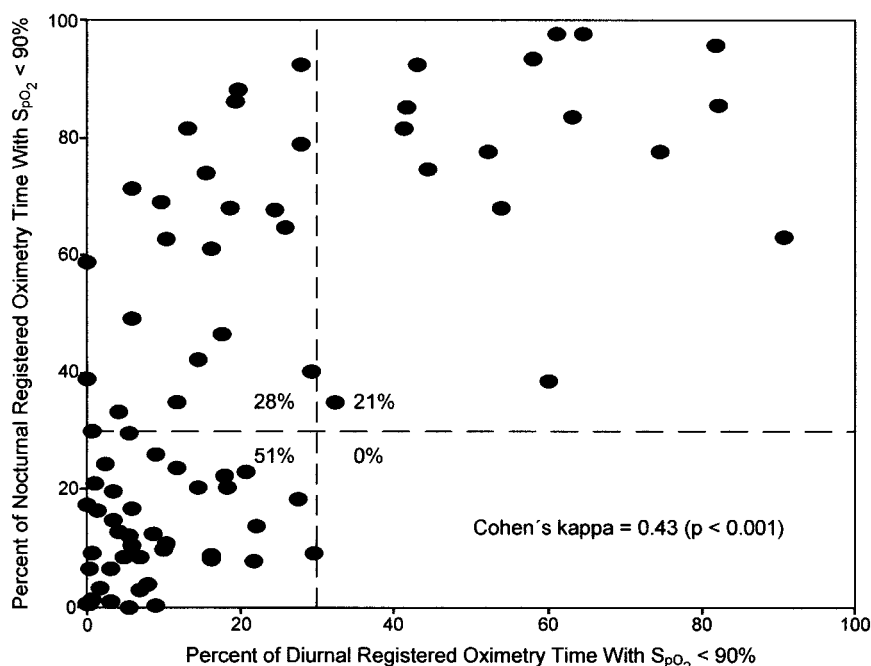


Fig. 1. Relationship between percentages of nocturnal oximetry time and diurnal oximetry time during which oximetry-measured blood oxygen saturation (S_{pO_2}) was < 90%.

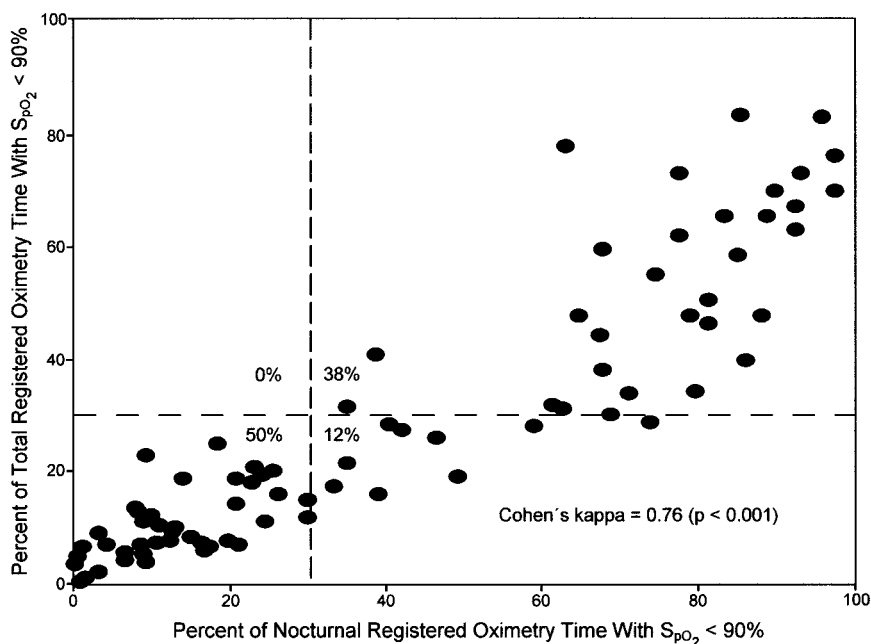


Fig. 2. Relationship between percentages of total oximetry time (24 h) and nocturnal oximetry time during which oximetry-measured blood oxygen saturation (S_{pO_2}) was < 90%.

both groups. However, they did not separate the patients by the presence or absence of nocturnal or diurnal desaturation, and they did not describe the degree of comorbidity in their mortality analyses. In addition, other important outcomes, such as pulmonary symptoms, exacerbations,

and quality of life, were not measured. In the second study, Chaouat et al⁶ studied nocturnal desaturation in 64 COPD patients and they found, as we did, that during the daytime the desaturators were more hypercapnic. After 2 years follow-up they did not observe any significant changes in

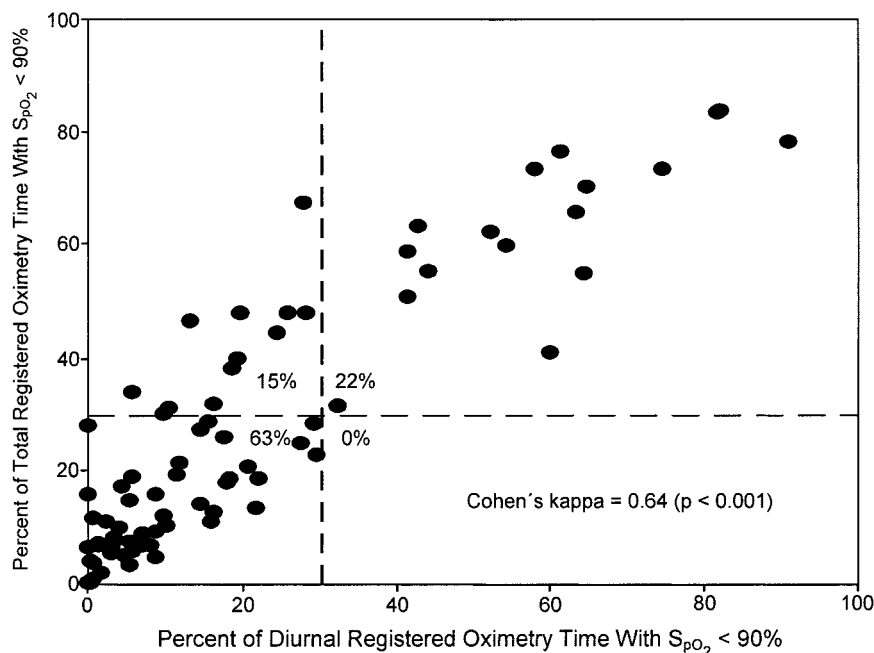


Fig. 3. Relationship between percentages of total oximetry time (24 h) and diurnal oximetry time during which oximetry-measured blood oxygen saturation (S_{pO_2}) was $< 90\%$.

gas exchange, pulmonary arterial pressure, or mortality between the oxygen-treated patients and the controls. However, the survival analyses lacked the power to detect a difference because of the relatively small number of deaths. Chaouat et al⁶ also did not report the effect of oxygen desaturation or therapy on pulmonary symptoms, quality of life, or exacerbations.

One large cohort study analyzed the prognostic implications of nocturnal desaturation.³⁰ Unfortunately, that study was retrospective, which is an important limitation. The same group reported a double-blind randomized 3-year trial using nasal oxygen versus room air in 2 groups of nocturnal desaturators with COPD. Although they found a trend toward a decrease in pulmonary arterial pressure with oxygen therapy, there was no significant survival benefit.³¹ This might be explained by a type 2 error, resulting from the small number of patients in the study.

In the last decade, 8 studies have evaluated the utility of 24-hour oximetry in COPD patients.^{10–17} These studies described clinically important desaturations in most of the patients during activities of daily living, despite good oxygenation at rest. However, the populations in those studies were not comparable with ours, because seven of those series included patients with severe hypoxemia and who were receiving LTOT, and such patients are likely to desaturate during sleep while breathing oxygen. A study by Soguel et al¹² included patients with severe hypoxemia and patients with normal P_{aO_2} values.

We believe that 24-hour oximetry could assist clinicians in making treatment decisions, especially with borderline

patients. In addition, ambulatory oximetry could be added to similar tools used in managing other important prevalent diseases, such as arterial hypertension and arrhythmic cardiopathy.³² Ambulatory 24-hour oximetry provides a more accurate picture of the temporal profile of oxygen saturation while patients are engaged in activities of daily living. We observed important diurnal desaturations and important variability among the patients. There was better concordance between the nocturnal desaturations and the 24-hour oximetry evaluation, but the diurnal period was at least twice as long as the nocturnal period, and the consequences of desaturation time may be different. These data support that nocturnal oximetry may be useful as a screening tool for COPD desaturators. Twenty-four-hour oximetry would be indicated in COPD patients who have nocturnal desaturations. In patients with less severe hypoxemia, the long-term effect of temporary oxygen desaturations on clinical outcomes needs to be studied, and the advent of 24-hour oximetry may help implement those studies.

One important finding of our study was the lack of association between the intensity of oxygen desaturation and clinical expressions of the disease. The explanation is not clear, but it could be that the body adjusts to this degree of hypoxemia, as long as it is transitory. It could also be that the clinical variables we evaluated are not sensitive to the effects of hypoxemia; however, they are all predictive of important outcomes. New studies using other variables of disease expression may be needed. Finally, it may very well be that we need much longer follow-up

time to detect changes in the clinical variables we evaluated. Future studies are needed to explore this possibility.

The present study had some limitations. First, few women were included. This was not by design, because we offered the opportunity to join the study independent of sex. The low number of women probably reflects the problem of underdiagnosis of COPD in women and in Spain.

Second, it could be argued that our sample size did not allow the detection of more differences in lung function between desaturators and nondesaturators (type 2 error). However, our study is the largest to date and the only one that has evaluated 24-hour oximetry in COPD patients within a narrow P_{aO_2} range.

Third, it could be argued that we did not register our patients' physical activity during the oximetry monitoring time. Nevertheless, patients were encouraged to engage in their usual activities of daily living, and they showed high 6-min-walk-test values that correlate well with the degree of activity (registered by pedometer) performed by COPD patients.³³

Fourth, it is possible but unlikely that we may have included previously undiagnosed and asymptomatic patients with sleep apnea, but the low desaturation index and the oximetry profiles suggest that in the unlikely event that this occurred, the sleep apnea would have been mild and therefore unlikely to change our conclusions.

Fifth, there were important differences between the numbers of study patients recruited by the 4 hospitals. However, all the hospitals are from the same zone, they assist people with similar anthropometric and cultural characteristics, they followed the same methods, and the percent of desaturators was similar among the hospitals.

Conclusions

COPD patients with moderate hypoxemia (P_{aO_2} 60–70 mm Hg) have important oxygen desaturations. Although these desaturations are mostly nocturnal, we also observed important diurnal desaturations, with low concordance between the nocturnal and diurnal periods. Twenty-four-hour ambulatory oximetry gives a more precise picture of the saturation profile in patients with moderate hypoxemia. However, nocturnal oximetry could be the first step in evaluating desaturations in these patients, and long-term follow-up studies are needed to fully evaluate the impact of oxygen desaturation on outcomes.

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