Clinical characteristics of COPD patients with early-onset desaturation in the 6-minute walk test

I. García-Talavera a,*, J.M. Figueira-Gonçalves a, N. Gurbani a, L. Pérez-Méndez b, c, A. Pedrero-García b

a Pneumology Service and Thoracic Surgery, University Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain
b Division of Clinical Epidemiology and Biostatistics, Research Unit, University Hospital Nuestra Señora de Candelaria, and Primary Care Management, Santa Cruz de Tenerife, Spain
c Networked Biomedical Research Centre (CIBER) of Respiratory Diseases, Carlos III Health Institute, Madrid, Spain

Received 15 September 2017; accepted 7 April 2018
Available online 15 June 2018

Abstract

Background: Exercise-induced desaturation in chronic obstructive pulmonary disease (COPD) frequently has prognostic implications. Desaturation within the first minute of the walk 6-minute walk test will probably also occur in daily life activities and translate into hypoxaemic respiratory failure at rest in later years. This study aimed at comparing these patients with those who desaturate after the first minute and determine potential markers.

Methods: We conducted a cross-sectional, retrospective study collecting data on respiratory function tests, cardiovascular comorbidity, body mass index, pack-year index, 6-minute walk test outcomes, BODE index, and Charlson comorbidity index. Patients who desaturated during the first minute of the test were referred to as early desaturators compared to the non-early ones.

Results: We observed a higher mean body mass index in early desaturating patients, and an inverse relation as to the body mass index categories <25, 25-29, and ≥30. Early desaturators had a lower FEV1/FVC index. The mean distance walked in the test was shorter in early than in non-early desaturators, and they desaturated more deeply.

Conclusion: Overweight and obesity, as determined by body mass index, seem to behave like markers for early desaturation. This simple anthropometric measure might indicate point to potential early desaturation in COPD patients.

© 2018 Sociedade Portuguesa de Pneumologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

* Corresponding author.
E-mail address: igarmark@gmail.com (I. Garcia-Talavera).

https://doi.org/10.1016/j.pulmoe.2018.04.007
2531-0437/© 2018 Sociedade Portuguesa de Pneumologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

Exercise-induced oxygen desaturation (EID) occurs in up to 20% of the patients with chronic obstructive pulmonary disease (COPD). However, despite being a relatively frequent condition, its definition has not yet been agreed upon. The most widely accepted criterion in common practice comprises a drop in oxygen saturation (SatO2) of more than 4% with a nadir of at least 88%. Although the pathophysiology of EID is a matter of debate, aspects such as the severity of airflow obstruction, a low CO diffusion capacity (DLCO), a high degree of emphysema, obesity, and a SatO2 at rest ≤93% have been related to it.

Studies carried out by our group show that the decrease in the SatO2 curve during the 6-minute walk test (6MWT) has prognostic implications. Patients with such an event before the end of the first minute of the test, termed ‘early desaturators’ (EDs), had a high probability of also experiencing them during their daily life activities and of additionally developing hypoxaemic respiratory failure at rest within the subsequent 5 years compared to subjects who desaturated after 3 min. Given the occurrence of the two desaturation profiles in patients with the same disease, the assessment of possible differential factors associated with this behaviour is imperative.

The purpose of this study was to characterise COPD patients with early desaturation versus non-early desaturation as well as determine potential markers that point to events of EID before the end of the first minute.

Methods

Patients

From a pool of 163 patients with COPD and exercise desaturation on the 6 min walking test registered on our laboratory database, 57 were not selected because they had interstitial disease, severe cardiac disease, domiciliary oxygentherapy. Then we conducted a cross-sectional study in 106 COPD (Table 1) patients, normoxaemic at rest but experiencing EID. The inclusion criteria were: aged over 40 years, active or former smoker with a pack-year index (PYI) >10 and a post-bronchodilator ratio of forced expiratory volume in one second (FEV1/FVC) <70%, in addition to a basal SatO2 >90%. Patients with SatO2 at rest ≤90% or who were not able to correctly perform the 6MWT were excluded.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of patients with exercise-induced desaturation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables, units</td>
<td></td>
</tr>
<tr>
<td>Gender male (%)</td>
<td>79%</td>
</tr>
<tr>
<td>Age, in years median (P25-P75)</td>
<td>68 (61-76)</td>
</tr>
<tr>
<td>Charlson index, median (P25-P75)</td>
<td>5 (3-7)</td>
</tr>
<tr>
<td>BODE index, median (P25-P75)</td>
<td>4 (2-5)</td>
</tr>
<tr>
<td>FEV1 (% predicted), mean ± SD</td>
<td>46 ± 18</td>
</tr>
<tr>
<td>Initial SpO2 (%)</td>
<td>94 ± 2</td>
</tr>
<tr>
<td>6-min walk distance (m), mean ± SD</td>
<td>415 ± 117</td>
</tr>
<tr>
<td>Nadir SpO2 (%)</td>
<td>85 ± 4</td>
</tr>
<tr>
<td>Time to SpO2 &lt;90%, median (P25-P75)</td>
<td>1:34 (0:49-2:18)</td>
</tr>
</tbody>
</table>

Data are given as median (25th, 75th percentile) or mean ± SD (mean ± standard deviation); FEV1: forced expiratory volume in 1 s.

Statistical analysis

Data were summarised as frequencies for categorical variables, as mean±SD for normally distributed data, and median (25th–75th percentile) for non-normally distributed outcome data. Comparisons between the groups ED and NED were explored using Pearson Chi-squared test, the Mann–Whitney U-test, and Student t-test as appropriate.

Differential patient characteristics before performing the 6MWT test were BMI and initial pulse oximetre saturation (SpO2) (Table 1). We applied multivariate logistic regression analysis, adjusted by initial SpO2, to determine
Table 2: Characteristic of early and non early desaturators patients.

<table>
<thead>
<tr>
<th>Variables, units</th>
<th>Early (n=32)</th>
<th>Non early (n=74)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years, median (P25–P75)</td>
<td>68 (63-76)</td>
<td>68 (60-75)</td>
<td>0.620</td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td>29 ± 5</td>
<td>25 ± 6</td>
<td>0.002</td>
</tr>
<tr>
<td>Haemoglobin g/dl, mean ± SD</td>
<td>14.2 ± 2.0</td>
<td>14.4 ± 1.7</td>
<td>0.667</td>
</tr>
<tr>
<td>Smoking pack-year index, median (P25–P75)</td>
<td>40 (10-68)</td>
<td>40 (14-53)</td>
<td>0.939</td>
</tr>
<tr>
<td>Dyspnoea, mMRC scale, median (P25–P75)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>0.997</td>
</tr>
<tr>
<td><strong>GOLD 2009</strong></td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>Stage I (%)</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Stage II (%)</td>
<td>44</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Stage III (%)</td>
<td>37</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Stage IV (%)</td>
<td>13</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td><strong>GOLD 2017</strong></td>
<td></td>
<td></td>
<td>0.986</td>
</tr>
<tr>
<td>Stage A (%)</td>
<td>22</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Stage B (%)</td>
<td>41</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Stage C (%)</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Stage D (%)</td>
<td>31</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td><strong>Charlson index, median (P25–P75)</strong></td>
<td>5 (4-7)</td>
<td>5 (3-6)</td>
<td>0.129</td>
</tr>
<tr>
<td><strong>BODE index, median (P25–P75)</strong></td>
<td>4 (2-5)</td>
<td>4 (2-5)</td>
<td>0.913</td>
</tr>
<tr>
<td><strong>Pulmonary function parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-min walk distance (m), mean ± SD</td>
<td>371 ± 105</td>
<td>435 ± 117</td>
<td>0.011</td>
</tr>
<tr>
<td>Time to SpO2 (%) &lt;90%, median (P25–P75)</td>
<td>40 (35-46)</td>
<td>110 (90-150)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Initial SpO2 (%)</td>
<td>93 ± 1</td>
<td>94 ± 2</td>
<td>0.002</td>
</tr>
<tr>
<td>Nadir SpO2 (%)</td>
<td>83 ± 5</td>
<td>86 ± 3</td>
<td>0.001</td>
</tr>
<tr>
<td>Initial to nadir SpO2 (%)</td>
<td>11 ± 5</td>
<td>8 ± 4</td>
<td>0.023</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>47 ± 12</td>
<td>41 ± 11</td>
<td>0.007</td>
</tr>
<tr>
<td>FEV₁ litres (%) predicted, mean ± SD</td>
<td>1.2 ± 0.577 (48 ± 17)</td>
<td>1.2 ± 0.654 (45 ± 19)</td>
<td>0.421</td>
</tr>
<tr>
<td>FVC litres (%)</td>
<td>2.5 ± 0.673 (76 ± 19)</td>
<td>2.8 ± 0.795 (81 ± 19)</td>
<td>0.196</td>
</tr>
<tr>
<td>IC litres (%)</td>
<td>2.2 ± 0.703 (88 ± 22)</td>
<td>2.3 ± 0.695 (87 ± 23)</td>
<td>0.913</td>
</tr>
<tr>
<td>RV/TLC, mean ± SD</td>
<td>142 ± 35</td>
<td>142 ± 32</td>
<td>0.979</td>
</tr>
<tr>
<td>DLCO (% predicted), mean ± SD</td>
<td>51 ± 18</td>
<td>55 ± 21</td>
<td>0.346</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>59%</td>
<td>49%</td>
<td>0.310</td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>59%</td>
<td>49%</td>
<td>0.310</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>28%</td>
<td>15%</td>
<td>0.109</td>
</tr>
<tr>
<td>Ischaemic heart disease (%)</td>
<td>9%</td>
<td>15%</td>
<td>0.443</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>16%</td>
<td>9%</td>
<td>0.358</td>
</tr>
<tr>
<td>Arrhythmia (%)</td>
<td>16%</td>
<td>15%</td>
<td>0.920</td>
</tr>
</tbody>
</table>

Data are given as median (25th, 75th percentile) or mean ± SD (mean ± standard deviation). Pearson Chi-squared, Mann–Whitney U, or Student t-test were applied. BMI: body mass index; FEV₁: forced expiratory volume in 1 s; FVC forced vital capacity; FEV₁/FVC index; IC: inspiratory capacity; RV: residual volume; TLC: total lung capacity; DLCO: carbon monoxide diffusion capacity. mMRC: modified Medical Research Council scale.

the association between BMI and ED. Finally, to evaluate the discriminative capacity of the continuous BMI scale as a possible marker of ED, a receiver operator characteristic (ROC) curve was generated and the area underneath the curve (AUC) calculated.

The sample size (n=106) was estimated based on a frequency-of-outcomes factor of at least 20% of ED in the population with a confidence interval of 95% and a beta error of 20%. The significance level was established as p < 0.05. All analyses were performed with the SPSS/PC statistical programme (version 21.0 for Windows; SPSS, Inc., Chicago, IL, USA). The study was approved by the ethics committee of the University Hospital Nuestra Señora de Candelaria (Tenerife, Spain).

Results

Subject characteristics

A total of 106 patients were included in this study, all of them had COPD diagnosed and were staged as per GOLD guidelines. All patients desaturated either before or after the first minute of the 6MWT. The patients’ characteristics are reflected in Table 1. Most of them were men (ratio 4/1) with a median age of 68 years and a predicted FEV₁ of 46%. The baseline oxygen saturation was above 90%. 93% of patients had moderate to severe airflow limitation and a high risk measured by BODE scale. Thirty two subjects (30%) were classified as EDs.
Differences between ED and NED

Table 2 compares the baseline characteristics of the ED versus the NED group, which resembled each other in age, GOLD stages with most of the subjects suffering from moderate to severe obstruction, as well as BODE and Charlson index. Hypertension and dyslipidaemia were the most frequent comorbidities in general; no differences were observed in mortality. When performing the 6MWT, differential BMI values became evident. The mean BMI was higher in ED than in NED patients with an inverse relation as to the categorical BMI levels <25, 25–29, and ≥30 (p for trends = 0.011; Fig. 1).

Although we observed a significantly lower mean initial SpO2, this was clinically not relevant. Therefore its influence was adjusted in the multivariate analysis using the quartil of initial SpO2. The probability of ED during exercise increased by 1.79 (ORadjusted) in overweight and obese patients (95% CI 1.12–2.86; p = 0.015).

Finally, the area under the curves showed the discriminative capacity of the continuous scale for BMI analysis: AUC = 70% (95% CI, 60–81%; p = 0.001; Fig. 2).

Table 2 also reflects the distribution of clinical, functional parameters and lung function. We did not detect any differences in static functional respiratory parameters except that EDs had a lower FEV1/FVC index than NEDs. ED patients also walked 64 m less (mean) in the 6MWT (p = 0.011), and they desaturated more deeply (10.7 ± 4.6% versus 8.6 ± 3.5%; p = 0.025).

Discussion

ED is the result of a mismatch between ventilation and perfusion during physical effort. Airflow limitation and loss of lung elasticity lead to increased air trapping and dynamic hyperinflation, increasing patient inspiratory work and thereby increasing oxygen consumption in COPD patients.3,11,12 Until a few years ago, this phenomenon observed during the 6MWT, did not provide any further information than that of the change in SatO2. It was considered a mere curiosity, which appeared in a group of COPD patients but did not translate into a change in medical attitude, perception of poor prognosis or treatment modification. Takigawa et al.9,15 demonstrated that, in addition to the distance walked in the 6MWT, the variation in SatO2 also had prognostic implications. Later, the phenomenon came to be no longer regarded as an unimportant fact, but one to be taken into account together with parameters such as the metres covered in the 6MWT, the FEV1, and the oxygen partial pressure in blood. A few years later, these findings were corroborated by the ECLIPSE group, who demonstrated that both desaturation and the frequency of stops during the walk test were prognostic factors. However, the possible different types of desaturation have not yet been well characterised, neither in terms of their definition, which remains ambiguous, nor addressing the different forms as to the distinction between basal and minimal desaturation, its quality and nature. We defined a category, termed ED, to differentiate it from late and intermediate desaturation. This was the result of a study where we compared desaturation in two different settings, the 6MWT and daily life activities. Only the patients who desaturated within the first minute of the test also did so outside the hospital in their daily activities, something that was not true of those who desaturated only after 3.5 min.9 Therefore, early desaturation in the 6MWT is a relevant aspect, because it implies desaturation during everyday activities and under low levels of physical strain. In addition to this aspect, the ED patient group is more likely to develop respiratory insufficiency over time than the NEDs. Hence, the elapsed time to desaturation in the 6MWT is a useful variable, which provides information of clinical interest. Additional potential markers to consider are the depth and persistence of desaturation. Of note, early desaturation also tends to be deep; according to our observations in this study, the nadir is very low. We were interested in defining a profile of patients who desaturate early and analyse clinical and functional characteristics to identify potential differential parameters between EDs and patients who desaturate after the first minute of the 6MWT. Like other authors,2,6 we
found that desaturation is typical of patients with low FEV1
and relatively low baseline DLCO and SatO2 values. But it
remained to be determined whether there was a defined
profile for ED patients. We did not observe differences in
either age or FEV1 values, and although DLCO was some-
what lower in EDs, this was not statistically significant. From
a functional point of view, basal SatO2 and the distance
walked in the 6MWT were significantly lower in EDs com-
pared to the NED group, and it should be emphasised that the
desaturation in the ED group was more profound, which may
be considered as another feature of severity. However, BMI
was the most outstanding parameter in the ED group. These
patients were more obese, although this was not associated
with comorbidities such as ischaemic heart disease, cardiac
arrhythmia, or AHT. Recently, Andrianopoulos et al.9 ana-
ysed patients from the ECLIPSE cohort and described obesity
as a factor involved in EID (OR 1.57, 95% CI 1.15–2.14) along
with additional parameters, such as a high degree of airflow
obstruction and low DLCO values. While obesity has been
linked to low baseline SatO2 and EID, we think
this feature appears to be limited to ED COPD patients.
COPD patients may exhibit very diverse characteristics,
which depend on the association with other conditions such
as bronchial asthma, sleep apnoea, and fibrosis. EID
occurs preferentially in severe patients with low DLCO val-
ues; although, unexpectedly, it is not observed in lean
but in obese patients. Early desaturation, which we think
is of great importance because it translates to increased
severity, is preferentially observed in subjects with a BMI
≥30. Alterations in respiratory mechanics or higher levels
of proinflammatory cytokines such as leptin may possibly
explain this phenomenon.17

There are some limitations; the study is retrospective,
the number of patients is not very high, the proportion
of women is very low, we did not select non-smoker patients
and the study only took place in hospital.

In summary, we would like to draw special attention to
COPD patients with severe to very severe obstruction, low
DLCO, and overt obesity, because they may experience early
and profound desaturation during exercise and, together
with the obesity, suffer from very harmful long-term effects.

Funding

Menarini SA Corp Foundation.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

K, Aerts JG, Rohde G, Lacoma A, Rakic J, Boeck L, Castel-
lotti P, Scherr A, Marin A, Hertel S, Giersdorf S, Torres A,
Welte T, Tamm M. Exertional hypoxemia in stable COPD is com-
mon and predicted by circulating proadrenomedullin. Chest.
2014;146:328–38.
2. Van Gestel AJ, Clarenbach CF, Stowhas AC, Teschler S, Russi EW,
oxygen desaturation in patients with chronic obstructive pul-
hyperinflation correlates with exertional oxygen desaturation
in patients with chronic obstructive pulmonary disease. Lung.
2013;191:177–82.
4. Kelley MA, Panettieri RA Jr, Krupinski AV. Resting single-breath
diffusing capacity as a screening test for exercise-induced
5. Owens GR, Rogers RM, Pennock BE, Levin D. The diffusing capac-
ity as a predictor of arterial oxygen desaturation during exercise
in patients with chronic obstructive pulmonary disease. N Engl
6. Cri safeguard E, Lattoni A, Venturelli E, Siscaro G, Beneventi C,
Cesario A, et al. Predicting walking-induced oxygen desatu-
ratings in COPD patients: a statistical model. Respir Care.
7. Taguchi O, Gabazza EC, Yoshida M, Yasui H, Kobayashi T, Yuda H,
et al. CT scores of emphysema and oxygen desaturation during
8. Andrianopoulos V, Celli BR, Franssen FM, Pinto-Plata VM, Calver-
ley PM, Vanfleteren LE, et al. Determinants of exercise-induced
oxygen desaturation including pulmonary emphysema in COPD:
9. Garcia-Talavera I, Garcia CH, Macario CC, de Torres JP, Celli
BR, Aguirre-Jaime A. Time to desaturation in the 6-min walking
distance test predicts 24-hour oximetry in COPD with a PO2
between 60 and 70 mmHg. Respir Med. 2008;102:1026–32.
Jame A, et al. Time to desaturation less than one minute
predicts the need for long-term home oxygen therapy. Respir
11. Rubio MA, Salas-Salvadó J, Barbany M, Moreno B, Aranceta J,
sobrepeso y la obesidad y el establecimiento de criterios de
12. Global strategy for the diagnosis, management and prevention
of COPD, global initiative for chronic obstructive lung disease
(GOLD); 2009. http://www.goldcopd.org
14. Cooper CB. The connection between chronic obstructive pul-
monary disease symptoms and hyperinflation and its impact on
15. Loring SH, Garcia-Jacques M, Malhotra A. Pulmonary character-
istics in COPD and mechanisms of increased work of breathing.
16. Takigawa N, Tada A, Soda R, Date H, Yamashita M, Endo S, Taka-
hashi S, Kawata N, Shibayama T, Hamada N, Sakaguchi M, Hirano
A, Kimura G, Okada C, Takahashi K. Distance and oxygen desat-
uration in 6-min walk test predict prognosis in COPD patients.
17. Poulin M, Doucet M, Drapeau V, Fournier G, Tremblay A,
Poirier P, Maltais F. Metabolic and inflammatory profile in obese
patients with chronic obstructive pulmonary disease. Chron