Residual subjective daytime sleepiness under CPAP treatment in initially somnolent apnea patients: A pilot study using data mining methods

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Abstract

Background and purpose: Despite correct treatment with positive airway pressure (PAP), obstructive sleep apnea (OSA) patients sometimes remain subjectively somnolent. The reliability of the Epworth Sleepiness Scale (ESS) has been established for healthy subjects and patients under stable conditions; the ESS may eventually vary among treated OSA patients, biasing the results of a cross-sectional analysis of persisting sleepiness. The objective of this study was to depict the evolution of subjective vigilance under treatment using an index of ESS variability (ΔESS).

Methods: In 80 OSA patients (apnea–hypopnea index [AHI] = 54 ± 26/h), initially somnolent (ESS = 15 ± 3) and treated with auto-titrating PAP (APAP) (oxyhaemoglobin desaturation index 3% [ODIAPAP] = 3.4 ± 2.2/h; daily APAP use = 5.3 ± 1.5 h) during 434 ± 73 days, ESS scores were regularly collected four times every 109 ± 36 days. ΔESS was calculated and data mining methods (Segmentation and Decision Tree) were used to determine homogeneous groups according to the evolution of ESS scores.

Results: When assessed cross-sectionally, 14–25% of the subjects were recognized as somnolent, depending on the moment when ESS was administered. Using data mining methods, three groups were clearly identifiable: two without residual somnolence – group 1, n = 38 (47%), with high ΔESS = −2.9 ± 0.8, baseline ESS = 16.3 ± 3.3, AHI = 58.5 ± 26.1/h, mean ESSAPAP = 5.1 ± 2.4 and group 2, n = 31 (39%), with low ΔESS = −1.1 ± 0.5, baseline ESS = 13.2 ± 1.4, AHI = 53 ± 27.3/h, mean ESSAPAP = 8.8 ± 1.9; and one with persisting sleepiness; group 3, n = 11 (14%), with low ΔESS = −0.3 ± 0.8, baseline ESS = 16.3 ± 3, AHI = 38.7 ± 10.8/h, mean ESSAPAP = 14.1 ± 1.9. Compliance to PAP was high and comparable in the three groups. Age and body mass index (BMI) did not differ.

Conclusion: Data mining methods helped to identify 14% of subjects with persisting sleepiness. Validation needs to be done on a larger population in order to determine predictive rules.

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1. Introduction

Intermittent obstruction of the upper airways during sleep associated with excessive daytime sleepiness
(EDS) is a common pathology affecting approximately 2% of the middle-aged population who require a treatment with nasal continuous positive airway pressure (CPAP) [1]. Nasal CPAP is a well established and evidence-based therapy for these patients, usually leading to rapid improvement of diurnal symptoms [2,3]. Therefore, there is an increasing demand for access to effective treatment. To deal with the difference between demand and capacity [4], new strategies have been proposed for diagnosis and treatment using a simplified procedure based on an index derived from overnight oximetry [5] and auto-CPAP [6–8].

Despite an efficient and effectively used positive airway pressure therapy, some obstructive sleep apnea (OSA) patients, initially sleepy, remain somnolent under treatment. EDS is a major issue which needs to be recognised because of its harmful consequences, in particular with regard to risk for traffic accidents [9,10]. However, given the dramatically increasing number of CPAP prescriptions – up to 30,000 new prescriptions every year in France – the standard practice of systematically making objective measurements (multiple sleep latency test [MSLT] or maintenance of wakefulness test [MWT]) [11] to assess changes in vigilance under treatment conditions has clear limitations. To screen for residual EDS, the use of the Epworth Sleepiness Scale (ESS) [12] has been proposed. Due to its ease of administration, the ESS is used in the majority of sleep clinic studies [13,14] to evaluate the clinical benefit of CPAP therapy and as a baseline in validation studies for molecules stimulating wakefulness [15,16]. Studies of residual EDS with CPAP have typically used only a single ESS value to define patients’ somnolence status [15,16], but the stability of ESS scores has only been validated with healthy subjects or with subjects with a sleep disorder under circumstances when daytime sleepiness is expected to remain constant. In the case of apnea patients whose vigilance is expected to improve under CPAP, the subjective evaluation of their state of vigilance “in the usual way of life in recent times” [17] is potentially influenced by their general health status, sleep hygiene or treatment compliance during the days and weeks preceding assessment [18]. ESS scores can consequently vary transiently around the threshold of 11, which is most commonly used to define the limit of normality [19]. Moreover, a significant improvement in vigilance has already been described in the long-term on CPAP-treated patients [20]. Using a simple cross-sectional analysis could lead to a misclassification of somnolent patients. We, therefore, made the assumption that several consecutive measurements of the ESS are necessary to define the evolution of vigilance under treatment and allow an optimal recognition of authentically somnolent patients. The objective of the present study was to assess in the conditions of everyday clinical practice the evolution of subjective vigilance on OSA patients from initially sleepy to correctly treated with auto-titrating PAP (APAP). Repeated ESS scores were used to monitor subjective vigilance over a period of time.

2. Materials and methods

2.1. Patients

The study was conducted on a prospective patient cohort of OSA patients, diagnosed during a full-night polysomnography in a hospital (apnea–hypopnea index [AHI] ≥ 10/h). Patients were eligible for evaluation of vigilance under treatment if they were initially somnolent (ESS score > 11) and accepted APAP treatment. A minimum follow-up of 12 months and mean daily APAP use above or equal to three hours per night through the period of follow-up were required, as it has been shown that cognitive performance and daytime function could be improved even at this low level of CPAP use [3].

According to the recommendations of the American Academy of Sleep Medicine concerning the initiation of APAP treatment, patients did not have any of the following pathologies: congestive heart failure, significant lung disease (e.g., chronic obstructive pulmonary disease), daytime hypoxemia and respiratory failure from any cause, or prominent nocturnal desaturation other than from OSA (e.g., obesity hypoventilation syndrome) [21].

The study was approved by the Local Medical Ethics Committee.

2.2. Procedures

Patients were fitted with the CPAP masks on the day following the polysomnography diagnosis; the procedure was identical for all patients. After a training session in the hospital, consisting of an explanation of the pathology and the treatment, the mask was selected, and patients were given a 30-min practice session with the CPAP device.

The positive airway pressure device in each case was an auto-titrating positive airway pressure device, Bora Adapt™ (Taema, Antony, France). Variations in pressure levels were based on the detection of apneas, hypopneas, airflow limitations and episodes of rebreathing considered to be micro-arousals. Initially, minimum and maximum pressures were empirically set at 6 and 12 cm H2O, respectively.

Home treatment was carried out by a technician specializing in home-care medical appliances contracted from the service provider. Following a routine procedure, patients were systematically visited by a technician on days 8, 15 and 21. On each visit, CPAP memory readings (compliance, leaks) were collected. The mask was changed in cases of leakage or discom-
fort, and a heated humidifier was provided in cases of nasobuccal dryness.

Overnight oximetry recording (PalmSAT® 2500, NONIN Medical, Inc. Plymouth, MN, USA) was performed on two consecutive nights during the first three months of treatment after verifying that the patient was sufficiently comfortable. Mechanical efficacy was defined by an oxyhaemoglobin desaturation index (ODI) < 10/h; in case of an ODI ≥ 10/h, the range of positive pressures was modified and additional visits were made in order to control treatment efficacy [22,23].

ESS and effective APAP use, determined from the device memory readings, were systematically collected during scheduled visits: visit 1 on the third, visit 2 on the sixth, visit 3 on the ninth, and visit 4 on the 12th month.

Subjective residual EDS was defined by ESS > 11.

Compliance with APAP treatment was expressed by the number of hours of mean daily effective APAP use and by the percentage of effective APAP use per week.

2.3. Data analysis

The analysis was retrospective on data collected prospectively.

The main outcome variable was the mean ESS score variation (ΔESS) across the full study period, defined as follows:

\[
\Delta_{\text{ESS}} = \frac{1}{4} \sum_{i=1}^{4} [(\text{EPW})_i - (\text{EPW})_{i-1}]
\]

Two groups were defined, according to the median value of ΔESS: one group with “low ΔESS” (ΔESS ≤ median (ΔESS)) and one group defined by complementarity, with “high ΔESS” (ΔESS > median (ΔESS)).

Data mining is an activity of information extraction, whose goal is to discover hidden or a priori unknown facts contained in databases. Using a combination of machine learning, statistical analysis, modeling techniques and database technology, data mining finds patterns and subtle relationships in data and infers rules that allow the prediction of future results. We applied the data mining Segmentation method that uses Decision Tree learning [24] (Clementine Software, SPSS Inc., USA) to our database to identify homogeneous patterns of ESS evolution inside the two groups previously cited (“low ΔESS” and “high ΔESS”). The main particular explicative variables were age, gender, body mass index (BMI), AHI, baseline ESS, the four ESS values collected during the follow-up visits and APAP use measured at each visit. Descriptive statistical analysis of the homogeneous groups was performed using the Student’s t-test and the \( \chi^2 \) test. A \( p \) value < 0.05 was considered significant.

3. Results

3.1. Patient selection: the study sample

Eighty patients who met the criteria for recruiting out of a population of 199 consecutive patients diagnosed as having obstructive sleep apnea syndrome (OSAS) were finally selected. Details of the enrollment procedure are shown in Fig. 1.

The study sample was comprised of 69 men and 11 women, of mean age 55 ± 12 years, BMI 30 ± 5 kg/m², AHI 54 ± 26 events per hour, and baseline ESS score 15 ± 3. Under APAP treatment, mean ODI (ODIAPAP) recorded over two nights was 3.4 ± 2.2/h, mean ESSAPAP was 8 ± 4, and mean average daily compliance over the follow-up period was 5.3 ± 1.5 h/night.

From the third month until the end of the follow-up, four ESS measurements were collected with a mean interval of 109 ± 36 days. Mean follow-up time was 434 ± 73 days.

On visit 1, 20/80 (25%) of subjects had an ESS > 11 (14 ± 2) with a mean daily CPAP use of 5.12 ± 1.44 h/night.

On visit 2, 14/80 (18%) subjects had an ESS > 11 (14 ± 3) with a mean daily CPAP use of 5.12 ± 1.25 h/night.

On visit 3, 11/80 (14%) subjects had an ESS > 11 (14 ± 2) with a mean daily CPAP use of 5.37 ± 1.79 h/night.

Fig. 1. Details of the enrollment procedure.
Finally, on visit 4, 15/80 (19%) subjects had an ESS > 11 (15 ± 2) with a mean daily CPAP use of 5.32 ± 1.77 h/night.

3.2. Applying the data mining method to the database

The Segmentation method using Decision Tree learning led to the identification of three homogeneous subgroups: two groups of “no longer somnolent” subjects (groups 1 and 2) and one group of subjects “with persisting sleepiness” (group 3).

Group 1 \((n = 38)\). No residual EDS (mean ESS\text{APAP} = 5.1 ± 2.4). Subjects were characterized by a high ESS variability (high \(\Delta ESS = 2.9 ± 0.8\)). Mean ESS at baseline was 16.3 ± 3.3, mean ESS on visit 1 was 5.9 ± 3.6, mean ESS on visit 2 was 4.9 ± 2.7, mean ESS on visit 3 was 4.8 ± 2.7, and mean ESS on visit 4 was 4.7 ± 2.5.

Group 2 \((n = 31)\). No residual EDS (mean ESS\text{APAP} = 8.8 ± 1.9). Subjects were characterized by a low \(\Delta ESS\) (1.1 ± 0.5). Mean ESS at baseline was 13.2 ± 1.4, mean ESS on visit 1 was 9.4 ± 3.1, mean ESS on visit 2 was 8.2 ± 2.7, mean ESS on visit 3 was 8.9 ± 2.9, and mean ESS on visit 4 was 8.8 ± 2.3.

Group 3 \((n = 11)\). With residual EDS (mean ESS\text{APAP} = 14.1 ± 1.9). Subjects were characterized by a low \(\Delta ESS\) (0.3 ± 0.8). Mean ESS at baseline was 16.3 ± 3, mean ESS on visit 1 was 14 ± 2, mean ESS on visit 2 was 13.8 ± 1.9, mean ESS on visit 3 was 13.6 ± 2.4, and mean ESS on visit 4 was 15 ± 2.6.

3.3. Characteristics of patients in the 3 groups (see Table 1)

Subjects in the three groups did not differ in terms of age, BMI, treatment efficacy and compliance to CPAP. In group 1, despite high baseline ESS, all subjects had recovered normal vigilance after three months of CPAP treatment. Subjects in group 2 were significantly less somnolent at baseline; eventually one individual ESS value could be found higher than or equal to 11 during follow-up, but on the whole, mean ESS on CPAP were clearly under 11 and showed little variation throughout follow-up. Despite high ESS at baseline, subjects in group 3 had significantly less severe OSAS according to AHI; all ESS values remained higher than 11 for all subjects throughout follow-up.

4. Discussion

In a population of 80 initially sleepy patients, correctly treated with APAP with an acceptable compliance, data mining methods allowed us to identify 14% of authentically somnolent subjects, who had remained sleepy from the end of the third month of treatment and throughout their follow-up. Between 14% and 25% of subjects were somnolent, on the basis of cross-sectional analysis carried out at different times. Thus, apart from the “always somnolent” individuals, there were some subjects who may have shown one ESS value above 11 once during their follow-up and who consequently contributed to inflating the number of somnolent subjects under a cross-sectional analysis.

We chose to assess vigilance in OSAS subjects who were initially somnolent, as it is in patients with daytime symptoms that CPAP treatment has proven to be the most effective [25] on daytime functioning and on cardiovascular risk [26]. In our study, sleepy patients were recruited on one initial value of the ESS, as the reliability of the ESS score has been confirmed in a population of sleep-disordered breathing patients [27].

We chose to evaluate somnolence after three months of CPAP treatment. We estimated that the efficacy, regularity and stability of CPAP treatment might have become firmly established at the end of the first three months for most of the patients [20,28].

It needs to be emphasized that these results were obtained for patients who used an auto-CPAP, without initially fixing the pressure level in the laboratory. This unconventional treatment is nevertheless largely used in common practice [6]. The effectiveness of auto-CPAP as an alternative method of CPAP titration or for continual routine use has already been reported in the research literature [7,29–31]. In a recent study by Masa

<p>| Mean characteristics of subjects in the 3 groups |
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<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>BMI (kg/m²)</th>
<th>AHI (per hour)</th>
<th>Baseline ESS</th>
<th>(\Delta ESS)</th>
<th>ODI APAP (per hour)</th>
<th>Daily APAP use (h/night)</th>
<th>Weekly APAP use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 ((n = 38))</td>
<td>54.1 ± 12.9</td>
<td>30.2 ± 5.1</td>
<td>58.5 ± 26.1</td>
<td>16.3 ± 3.3</td>
<td>2.9 ± 0.8</td>
<td>2.9 ± 1.7</td>
<td>5.6 ± 1.6</td>
</tr>
<tr>
<td>Group 2 ((n = 31))</td>
<td>55.2 ± 10.2</td>
<td>29.4 ± 4.2</td>
<td>53 ± 27.3</td>
<td>13.2 ± 1.4</td>
<td>1.1 ± 0.5</td>
<td>3.1 ± 2.1</td>
<td>5.5 ± 1.5</td>
</tr>
<tr>
<td>Group 3 ((n = 11))</td>
<td>59 ± 13.5</td>
<td>30.1 ± 4.1</td>
<td>38.7 ± 10.8</td>
<td>16.3 ± 3</td>
<td>0.3 ± 0.8</td>
<td>2.8 ± 1.6</td>
<td>5.4 ± 1.9</td>
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<td>(&lt;0.05)</td>
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\(\text{ns}\) Group 1 compared to group 3.
\(\dagger\) Group 2 compared to group 3.
\(*\) Group 1 compared to group 2.

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et al. [8], no difference was found in the mechanical effectiveness of nasal CPAP, the objective compliance to treatment or the improvement of vigilance as measured by the ESS, when comparing fixed pressure to auto-adjusted CPAP. In our patients, the effectiveness of APAP treatment was clearly confirmed by the data from repetitive nocturnal oximetry recordings under ventilation, with an average ODI = 3.4 ± 2.2/h. Oximetry has indeed proven to be a convenient and accurate means of detecting clinically relevant upper airway obstructions [22,23,32,33]. One could reasonably think that this ODIAPAP implies a satisfying correction of the nocturnal abnormal oxyhaemoglobin desaturations thought to be responsible for cardiovascular risk. We are nevertheless conscious that some inspiratory flow limitations resulting in micro-arousals may have been underestimated [34], which could lead to persisting sleepiness and justify a full-night polysomnography reevaluation.

Because the results of a cross-sectional analysis, between 14% and 25% of somnolent subjects, could seem simplistic, we found it more interesting to use data mining methods for a retrospective assessment. An important use of the data mining method is to be able to place categorical variables into classes, and eventually to predict the category of categorical data by building a model based on some predictive variables. Thanks to data mining methods, three different kinds of patterns in the evolution of vigilance could be described. Subjects who would remain somnolent (group 3) were typically highly somnolent at baseline and had less severe OSAS, and their ESS under treatment did not vary much; they remained somnolent despite compliance to CPAP which was quite compelling (5.4 ± 1.9 hours per night, 81.4 ± 19.4% of days per week). On the contrary, there was another group of subjects (group 1) also highly somnolent at baseline but with severe OSAS, whose ESS decreased rapidly under treatment; this group could be considered to be no longer somnolent after three months of CPAP. Finally, a third subgroup was identified (group 2), comprised of subjects with severe OSAS, moderately somnolent at baseline, whose ESS decreased also but in less significantly. Compliance with CPAP was equally satisfactory in the three groups (indeed mean CPAP use exceeded five hours per night in groups 1, 2 and 3 [18] and could not, therefore, be an explanation for such differences in the evolution of subjective vigilance).

The data mining approach seemed to us to be more informative than a single cross-sectional study of vigilance at a particular moment of the follow-up; we are nevertheless conscious that the number of subjects is relatively small and that studies on larger populations are needed in order to establish predictive rules. Knowing that a patient will remain somnolent can help to anticipate and can lead to a complete reevaluation, looking for an associated and before unrecognised diagnosis; a polysomnography looking for respiratory effort-related arousals and eventually objective vigilance tests should be programmed without delay. Inversely, any further exam should be considered dispensable in the case of a rapid normalization of ESS scores. Patients of group 2 (tending less rapidly towards improvement) may be compatible with those subjects who need time to improve [20] and need not be urgently reevaluated.

In conclusion, a merely cross-sectional analysis of the ESS in a population of treated patients without taking into account the evolution of ESS would only imperfectly reflect the impact of treatment on subjective daytime vigilance. Several values of the ESS, over an extended interval of time associated altogether with a measurement of the trend (ΔESS) could give a better insight into the patients’ results, and certainly predict the long-term evolution of vigilance. This method needs nevertheless to be validated prospectively on a larger number of patients, in order to determine a predictive equation, based on the values of baseline and third month ESS, the strongest predictive variables, and the initial severity of the sleep apnea syndrome having been taken into account.

References


