Predictors of residual sleepiness in adequately treated obstructive sleep apnoea patients

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Abstract

Some patients with obstructive sleep apnoea syndrome (respiratory distress index >5 events/hour) experience residual excessive daytime subjective sleepiness [Epworth sleepiness scale (ESS) score >10], despite adequate use of continuous positive airway pressure (CPAP) therapy. We aimed to identify clinical and polysomnographic predictors of this sleepiness.

Clinical and polysomnographic variables, and ESS score were evaluated in 208 obstructive sleep apnoea syndrome patients with ESS score >10 before (initial assessment) and after at least 6 months of adequate (≥ 4 hours daily) CPAP use.

After CPAP treatment, 114 patients (55%) presented abnormal ESS score (>10; CPAP non-responders), whereas 94 (45%) patients presented normal ESS score (<11; CPAP responders). Among CPAP responders none had a history of depression, while the contrary was true for 38.8% of CPAP non-responders. In addition, multivariate logistic regression analysis revealed that the independent predictors of residual excessive daytime sleepiness after CPAP therapy were a history of diabetes.
and heart disease, and higher ESS score and lower respiratory distress index at initial assessment.

In conclusion, predictors of residual excessive sleepiness in adequately CPAP-treated obstructive sleep apnoea syndrome were a history of depression, diabetes and heart disease, and higher ESS score and lower respiratory distress index at initial assessment.

**Keywords:** depression, diabetes, heart disease, Epworth sleepiness scale, residual excessive sleepiness, obstructive sleep apnoea syndrome

**Introduction**

Continuous positive airway pressure (CPAP) is considered the standard treatment of obstructive sleep apnoea syndrome (OSAS) [1]. Results of meta-analyses of randomised controlled trials have suggested that CPAP treatment can reduce subjective sleepiness associated with OSAS, with the greatest benefit found in patients with more severe apnoea and sleepiness [2, 3].

However, there are patients who despite the significant reduction in sleep-disordered breathing with CPAP therapy continue to complain of excessive daytime sleepiness [4, 5]. Indeed, GUILLEMINAULT et al reported that tiredness, fatigue and/or sleepiness persisted in 5% of OSAS patients despite appropriate treatment [6]. This issue represents an important clinical problem because residual sleepiness in supposedly treated OSAS patients may still lead to significant socioeconomic hardship including driving and job-related accidents [7] and neurocognitive impairment [8]. That is the reason why several clinical trials have tested the efficacy of wake-promoting agents such as modafinil in the treatment of CPAP-resistant daytime sleepiness of OSAS patients [4].

The etiologic factors leading to persistent excessive sleepiness despite ideal CPAP use remain unclear and only sparse and indirect data have suggested a link with clinical variables such as obesity [9]. The multifactorial pathophysiology of sleepiness in patients with OSAS before treatment has been well documented [10, 11]. Indeed, the present authors have shown that OSAS along with common medical comorbidities, primarily depression and diabetes, contribute to increased subjective sleepiness of patients suspected for OSAS [10]. Additionally, polysomnographic variables such as hypoxaemia or sleep fragmentation are commonly implicated in the aetiology of daytime sleepiness [11]. Consequently, it is plausible to suggest that persistent excessive daytime sleepiness in effectively treated OSAS patients also results from these clinical and nocturnal factors. Knowledge of such factors prior to CPAP implementation would be valuable for patients, their relatives, physicians and insurance organizations.

Therefore, the present study intended to investigate clinical and polysomnographic determinants of residual excessive daytime subjective sleepiness of
CPAP treated OSAS patients. We hypothesized that factors which increase daytime sleepiness of OSAS patients before treatment [10], could also predict the persistence of excessive sleepiness when CPAP therapy adequately abolishes sleep disordered breathing.

Methods

Patients

Patients screened for the current study were subjects who referred to the Centre of Sleep Disorders of Evangelismos General Hospital (Athens, Greece), between November 2004 and January 2008 for suspected sleep-disordered breathing (fig. 1). Participants were eligible if they met the following two inclusion criteria: 1) respiratory distress index (RDI) at baseline diagnostic full-night polysomnography > 5 events/h, and 2) excessive daytime sleepiness at initial assessment manifested by an Epworth sleepiness scale (ESS) score > 10. Exclusion criteria were: 1) not acceptance of CPAP therapy, 2) follow-up < 6 months, 3) poor compliance to CPAP therapy or insufficient CPAP pressure titration, 4) use of antihistamine or hypnotic medication, 5) coexisting sleep disorders (narcolepsy, idiopathic hypersomnia, and periodic limb movement disorder), and 6) shift work. The protocol was approved by the hospital human ethics committee and written informed consent was obtained from all participants.

Study design

All patients underwent three assessments: at baseline, at CPAP titration and at follow-up visit at least 6 months later. The baseline assessment consisted of an overnight polysomnography used to confirm the diagnosis of OSAS, self-administration of ESS, along with clinical screening as previously described [10]. In brief, patients with documented ischemic heart disease, hypertension, heart failure or cardiac arrhythmia were classified as having heart disease and equally, patients with documented history of stroke or chronic obstructive airway disease (COPD) were categorized in patients with stroke or COPD respectively. Additionally, the use of any antidepressant medication prescribed by a psychiatrist and a CES-D (Center for epidemiologic studies - Depression) scale score greater than 16 before the initiation of medication was considered to classify a patient in the depression group [12]. In all cases we communicated with the patient’s psychiatrist to ask for the CES-D scale score and ensure the diagnosis of depression. When this communication was impossible, a sleep physician (I.K.) filled the CES-D scale score from patient’s recall. Diabetes was defined according to current criteria [13]. Finally, alcohol use was defined as the ingestion of two or more alcoholic drinks per day [14], and smokers were defined as current smokers if any type of tobacco product was systematically used during the preceding month. All data were ultimately validated from adjudicated chart review by a sleep physician (I.K.). The second assessment comprised an in-laboratory polysomnography for the manual titration of CPAP. A prescription for an appropriate CPAP pressure and a suitable fitting mask were then given to all participants. Subjects were asked to start using CPAP that included internal usage (time at pressure) recording capability. All patients had follow-up appointments at 1 and 3 months at the outpatient clinic to encourage compliance, unless earlier difficulties with therapy were encountered. Moreover, they were supplied with a telephone number to contact the medical team in case of questions. None of the patients was informed of the recording capability of the CPAP unit but they were told to bring it to every follow-up visit. The third assessment took place at follow-up visit after at least 6 months of CPAP use and included a polysomnographic CPAP review...
study to ensure that CPAP was appropriately titrated. CPAP usage data were then downloaded into a personal computer using proprietary software (Encore pro; Respironics Inc., Murrysville PA). Subsequently, all patients underwent a review of the clinical screening and self-administered ESS for a second time.

**Baseline overnight diagnosis study**

All the patients underwent an overnight polysomnography (EMBLA S7000; Medcare Flaga, Reykjavik, Iceland). In order to determine the stages of sleep, an electroencephalogram (with four channels: C4-A1, C3-A2, O2-A1 and O1-A2), an electro-oculogram and an electromyogram of the submentalis muscle were obtained. Arterial blood oxyhaemoglobin was recorded with the use of a finger pulse oximeter. Thoracoabdominal excursions were measured qualitatively by respiratory effort sensors (XactTrace; Medcare Flaga) placed over the rib cage and abdomen. Snoring was detected with a vibration snore sensor, and body posture with a body position sensor. Airflow was monitored using an oral thermistor and a nasal cannula/pressure transducer. All variables were recorded with a digital acquisition system (Somnologica 3.3; Medcare Flaga). An experienced technician using standard criteria scored obstructive respiratory events. Thus, apnoea was defined as the absence of inspiratory airflow for more than 10 s in the presence of rib cage and abdominal excursions [15], whereas hypopnoea was defined as an at least 30% reduction in airflow as compared to baseline, lasting more than 10 s, and leading to a decrease in hemoglobin saturation of at least 4% or an arousal [16]. An arousal was defined as an abrupt shift in electroencephalogram frequency for at least 3 s [15]. Respiratory effort-related arousal was defined as a sequence of breaths characterized by increasing respiratory effort leading to an arousal that does not meet criteria for apnoea or hypopnoea [15]. The number of episodes of apnoeas, hypopnoeas and respiratory effort-related arousals per hour of sleep is referred to as the RDI. OSAS was diagnosed if RDI was > 5 events/h [15].

**CPAP titration study**

Following the baseline diagnostic evaluation, a manual titration of CPAP was performed using a full-polysomnography setting. All patients were instructed in the use of CPAP before the night of CPAP titration. The best-fitting mask was chosen, and the patients were familiarized with the CPAP treatment with the help of staff physicians. The optimal CPAP pressure was the minimum pressure needed to abolish snoring and obstructive respiratory events. The adequate titration of CPAP pressure was checked at polysomnographic CPAP review study that took place at follow-up assessment.

**Apparatus and CPAP compliance**

All participants were prescribed a CPAP device (RemStar Auto; Respironics Inc., Murrysville PA), which automatically turned on when the patients breathed into the mask and shut off when the mask was removed. The CPAP device contains a built-in time counter, which records the time spent at effective pressure. At the completion of follow-up, objective compliance was assessed by the mean value of hours of daily use spent at effective pressure. Patients were considered having good compliance whenever their CPAP daily use was \( \geq 4 \) hours per day during follow-up period, and patients were considered having poor compliance whenever their CPAP daily use was < 4 hours per day during follow-up period. The cutoff value of 4 hours per day has been identified as the threshold above which further improvement in subjective sleepiness is less likely to occur [17]. Nevertheless, because the actual time needed for CPAP in order to achieve normal values of sleepiness is probable to be individually determined rather than generally applicable [17], and the cutoff value of
4 hours per day for definition of compliance may be low if a population with long habitual sleep hours is addressed, we also evaluated those patients with CPAP daily use ≥ 5 and ≥ 6 hours per day.

**Subjective sleepiness and CPAP treatment response**

Subjective tendency for sleepiness was evaluated by means of the validated Greek version [18] of the ESS [19], at initial assessment and at follow-up assessment at least 6 months later. Higher ESS scores indicate greater subjective tendency for daytime sleepiness. Excessive daytime subjective sleepiness is commonly considered present whenever ESS score is > 10 [19], and this limit was also adopted in the present study to define excessive daytime sleepiness. CPAP treatment response was assessed on the basis of post-treatment level of subjective sleepiness, which is regarded as the primary outcome for the clinical management of OSAS [20]. Thus, patients who exhibited after CPAP treatment normal ESS score (< 11) were defined as CPAP responders, whereas those who exhibited after CPAP treatment abnormal ESS score (> 10) thus demonstrating residual excessive daytime sleepiness, were defined as CPAP non-responders.

**Statistical analysis**

Quantitive data are reported as means ± SD. The normality of the data distributions was assessed by the Kolmogorov-Smirnov test. Differences in means of quantitive variables between CPAP responders and CPAP non-responders were assessed by unpaired t-test, whereas differences in categorical values were assessed by the Yates corrected Chi-square or Fisher’s exact test when appropriate.

Univariate logistic regression analysis was performed in order to determine the contribution of each variable to residual excessive daytime sleepiness after CPAP therapy. Multivariate logistic regression analysis followed in order to identify the variables that were independently associated with residual excessive daytime sleepiness after CPAP therapy. The stepwise procedure was used to select the best logistic regression model, and the goodness of fit of this model was assessed by the Hosmer-Lemeshow test. The independent variables included in the model were those, which showed significant difference in the univariate comparison between CPAP responders and CPAP non-responders; body mass index, stroke and alcohol use were also included in the model despite lack of significance, because of their potential importance [10, 14]. A p value of less than 0.05 was considered to indicate statistical significance.

**Results**

Among 1017 patients screened, 311 did not meet the inclusion criteria (109 had RDI ≤ 5 events/h and 202 had ESS score < 11). Of 706 eligible patients, 498 were excluded from analysis (13 had a sleep disorder other than sleep apnoea, 43 were shift workers, 33 were taking hypnotic medication, and 409 fulfilled other exclusion criteria; fig. 1). The resulting cohort of 208 patients was stratified in CPAP responders (94 patients, 45%) and CPAP non-responders (104 patients, 55%). Clinical characteristics and polysomnographic data of these two groups of patients determined at baseline assessment are summarized in table 1. Age, ESS score, average and lowest oxygen saturation, and percentages of diabetes, depression, heart disease and COPD were higher, whereas percentage of males and RDI were lower in CPAP non-responders than in CPAP responders. Of 44 patients with depression (all CPAP non-responders), in 36 the CES-D scale score was documented by their psychiatrist, whereas in the rest the CES-D scale score was taken from patient’s recall. Follow-up evaluation took place after 8.2±1.2 months for CPAP responders.
and 9.1±1.5 months for CPAP non-responders. At follow-up assessment, body mass index remained unchanged for CPAP responders (34.4±6.7 kg⋅m⁻²) and CPAP non-responders (34.3±8.1 kg⋅m⁻²). Additionally, treatment for various diseases, e.g., diabetes or heart disease, did not substantially change during follow-up. CPAP responders exhibited after CPAP treatment a mean decrease of ESS score of 8.4±2.7, whereas CPAP non-responders presented after CPAP treatment a mean decrease of ESS score of 2.4±2.4 (p < 0.001). Additionally, objective compliance was not significantly different between the two groups: 6.1±1.0 hours per night for CPAP responders (mean CPAP pressure prescribed 8.4±1.2cmH₂O) and 5.9±0.9 hours per night for CPAP non-responders (mean CPAP pressure prescribed 6.7±1.6 cmH₂O). Finally, RDI at follow-up CPAP review polysomnography was within normal limits (2.2±1.1 for CPAP responders and 3.1±0.9 for CPAP non-responders).

Multivariate logistic regression analysis was performed to identify the independent predictors of residual excessive daytime sleepiness after CPAP therapy. Demographic, clinical and polysomnographic parameters determined at baseline assessment that showed significant difference in the univariate comparison between CPAP responders and CPAP non-responders (and also body mass index, stroke and alcohol use) (table 1) were entered into a forward, stepwise, logistic regression model. Since depression offered a near complete discrimination between CPAP responders and CPAP non-responders (0% of CPAP responders and 38.6% of CPAP non-responders had a history of depression), it was not included in the logistic regression model because maximum likelihood estimation could not be achieved. By examining the effect of the other variables, multivariate logistic regression analysis revealed that the independent predictors of residual subjective sleepiness after CPAP therapy were the presence of diabetes, heart disease, higher ESS score and lower RDI at baseline assessment (table 2). The Hosmer-Lemeshow test indicated that the fit of the model was good (p = 0.68). Backward procedure gave identical results.

By performing ad-hoc analysis it was found that, if the cutoff value for CPAP good compliance was set at 5 hours per day, the resulting cohort included 125 patients divided in 89 CPAP responders (71%) and 36 CPAP non-responders (29%), whereas if the cutoff value for CPAP good compliance was set at 6 hours per day, the cohort consisted of 94 patients stratified in 69 CPAP responders (73%) and 25 CPAP non-responders (27%). Clinical characteristics and polysomnographic data of these two cohorts of patients determined at baseline assessment are summarized in tables 1S and 2S of the online supplement, respectively. For most variables, the results were identical with those of our original cohort (table 1), because age, and percentages of diabetes, depression, heart disease and COPD were higher, whereas RDI and percentage of males were lower in CPAP non-responders than in CPAP responders. Additionally, by applying univariate and multivariate logistic regression models (table 3S of the online supplement), the results obtained did not differ between the three cohorts. Indeed, the odds ratios and 95% confidence intervals that describe the magnitude of the effects were reasonably similar. Minimal changes that were observed in multivariate logistic models, e.g., the effect of heart disease was slightly weaker in the two cohorts derived from ad-hoc analysis than in the original cohort and not statistically significant, could be explained by sample size reduction and the consequent power loss.

**Discussion**

The present study demonstrated that in adequately CPAP-treated OSAS patients residual excessive daytime sleepiness after effective CPAP therapy is
Independently associated with a history of depression, diabetes and heart disease, and the presence of higher ESS score and lower RDI at initial assessment.

The literature reports a variety of clinical and polysomnographic factors in addition to apnoeas, which are associated with increased subjective sleepiness of OSAS patients [10, 11, 14]. However, none of these studies has examined directly the contribution of these factors to subjective sleepiness of OSAS patients who remain subjectively somnolent despite the implementation of CPAP therapy and the ensuing abolishment of sleep-disordered breathing. Moreover, some previous studies [5, 9, 17, 21, 22] have highlighted residual excessive sleepiness of OSAS patients after CPAP implementation, but none has examined the determinants of this sleepiness beyond factors related to sufficient CPAP therapy [5, 17, 21, 22]. The present study adds to the current literature by employing strict exclusion criteria, which aimed to convincingly eliminate the effect of apnoeas on subjective sleepiness, and thus render the contribution of the rest of factors more apparent.

Daytime sleepiness refractory to adherent use of CPAP is of paramount importance for patients with OSAS, their relatives and physicians but also for insurance companies, as even modest levels of sleepiness may have a substantial negative effect on daytime functioning, quality of life and safety [7, 8]. Despite its significance, the prevalence of residual excessive daytime sleepiness in patients with OSAS who are under CPAP treatment remains unknown. The present study was not designed to evaluate the prevalence of this condition, as it enrolled only patients who used adequately titrated CPAP for more than 4 hours daily during at least 6 months. Indeed, of 706 OSAS patients who met the inclusion criteria, 498 were excluded from further analysis for various reasons (fig. 1). Therefore, due to selection bias associated with the high percentage of excluded patients, this study could not evaluate the residual excessive daytime sleepiness in unselected CPAP-treated patients. Literature reports different percentages of residual excessive daytime sleepiness in treated OSAS patients. WEAVER et al demonstrated that subjective sleepiness persisted in 34% of patients despite using CPAP [17], whereas GUILLEMINAULT et al reported that 5% of patients with sleep-disordered breathing still complained of daytime tiredness, fatigue and/or sleepiness despite various treatment strategies (CPAP, oral appliances, surgery) [6]. In our study, the percentage of patients with remaining subjective sleepiness after mean daily CPAP use ≥ 4 hours was high (55%). However, if the time for definition of good compliance were set at ≥ 5 or ≥ 6 hours per day, subjective sleepiness persisted in only 29% and 27% of patients, respectively (tables 1S and 2S), percentages that are similar to that previously reported (34%) [17]. In fact, although WEAVER et al considered 4 hours as the cutoff value for CPAP good compliance, they pointed out that the actual time needed for CPAP in order to achieve normal values of sleepiness is likely to be individually determined rather than generally applicable [17]. Thus, it appears that in a population with long habitual sleep hours as probably was the one we studied, the cutoff value of 4 hours per day for definition of CPAP compliance may be low, and that the cutoff values of 5 or 6 hours per day might better reflect the level of good CPAP compliance.

Interestingly, nearly 40% of CPAP non-responders had a history of depression, whereas none of CPAP responders had such a history (table 1) suggesting that residual excessive sleepiness in adequately CPAP treated OSAS patients is associated with the presence of depression. Accordingly, it appears that sleep physicians should not always anticipate complete resolution of subjective sleepiness in OSAS patients with depression after the implementation of CPAP. Importantly, the overlap of OSAS and depression is not unusual as SCHWARTZ et al documented that 39% of patients with
OSA referring to a sleep unit were receiving antidepressant treatment [23]. The possible causal pathways linking persistent sleepiness with depression in CPAP treated OSAS patients have been suggested by SANTAMARIA et al who highlighted primarily the disturbances in pathways involved in the regulation of sleep and wakefulness induced by depression per se but also the sedative effect of antidepressant treatment and the poor compliance to CPAP therapy [24].

Diabetes also proved to be a significant determinant of CPAP-resistant excessive daytime sleepiness. The association between diabetes and daytime sleepiness is not novel and has been documented in population-based studies, where diabetes was more prevalent in patients with excessive daytime sleepiness [14]. Although epidemiologic studies can only establish an association rather than a causal pathway, a diminished cerebral use of glucose and an increased sympathetic tone has been suggested to link subjective sleepiness with impaired glucose tolerance [25]. Combining these data it is plausible to suggest that diabetes should always be ranked in the differential diagnosis of persistent daytime sleepiness despite CPAP therapy in OSAS patients.

A history of heart disease was found to predict the occurrence of residual excessive sleepiness in CPAP-treated OSAS patients. This finding is consistent with previous reports that documented an association of daytime sleepiness with the use of medication for congestive heart failure [26] and the occurrence of hypertension [27]. Additionally, it has been suggested that in patients with heart disease, daytime sleepiness derives from disturbed sleep continuity and poor sleep quality [26].

Lastly, increased ESS score and lower RDI at initial assessment proved to be determinants of residual excessive daytime sleepiness. In other words, OSAS patients with more subjective sleepiness and less severe apnoea were more likely to continue to experience subjective sleepiness after optimal CPAP treatment. This finding seems partially contradictory to the results of a meta-analysis of placebo-controlled trials demonstrating the more severe apnoea and sleepiness, the biggest benefit obtained in terms of resolution of subjective sleepiness [2]. Indeed, although our result about apnea severity is in line with that of meta-analysis [2], our finding about subjective sleepiness severity seems divergent. However, this discrepancy could be attributed to the patient cohort of the current study, which didn’t include patients with normal ESS score at initial assessment and patients with OSAS who were not compliant to CPAP use, as well as to the dichotomous patient stratification in CPAP responders and CPAP non-responders.

Inadequate CPAP use and the presence of residual respiratory events due to insufficient CPAP titration have been considered leading candidates of residual daytime sleepiness in OSAS patients [21, 22]. Despite the fact that 4 hours of CPAP use is the threshold above which further improvement in daytime sleepiness is less likely [17], one could argue that inadequate mean daily CPAP use might contribute to residual sleepiness in some patients of the present study, because the cutoff value of 4 hours per day adopted for definition of CPAP compliance may be low in a population with long habitual sleep hours. We cannot exclude this possibility, because during ad-hoc analysis we found that the percentage of patients with remaining subjective sleepiness decreased from 55% to 29% and 27% if the time for definition of good CPAP compliance were set at ≥ 5 or ≥ 6 hours per day, respectively. This was due to the fact that more patients with mean daily CPAP use ≥ 4 and < 5 hours were CPAP non-responders than CPAP responders [78 vs 5 patients; the correspondent numbers for patients with mean daily CPAP use ≥ 5 and < 6 hours were 11 vs 20 patients (table 1, and tables 1S and 2S)], raising the suspicion that several patients with mean daily
CPAP use ≥ 4 hours might have persisted subjective sleepiness because of inadequate duration of daily CPAP use. Nevertheless, independent predictors of residual excessive daytime sleepiness after CPAP therapy (i.e., a history of depression, diabetes and heart disease, and higher ESS score and lower respiratory distress index at initial assessment) were exactly the same regardless of whether the cutoff value for CPAP compliance were set at 4, 5 or 6 hours, indicating that the results of the present study stand, in spite of the definition of CPAP compliance. Given that 14 days of CPAP use is sufficient for patients in order to resume regular alertness [22], a minimum of 6-month follow-up of the present study, makes it unlikely that residual subjective sleepiness observed in our study sample could be explained by inadequate duration of CPAP use. Additionally, the contribution of arousals and residual respiratory events can also safely be excluded, because all patients underwent a follow-up CPAP titration review study to ensure the adequate titration of CPAP pressure. Other potential sources of residual daytime sleepiness include intermittent hypoxemia [11, 28, 29], age [14], obesity [9, 10, 14], and a history of stroke [10], COPD [10, 30], and alcohol use [10, 14]. All these factors failed to be identified as independent determinants of residual daytime sleepiness after CPAP therapy in the present study, and their role to residual sleepiness in this clinical condition should rather be considered as minimal or negligible.

Some methodological issues must be acknowledged and warrant consideration in the current study. Firstly, the mean nightly duration of CPAP use in our study is higher in comparison with previous studies [17]. That is because the study sample we aimed to investigate included only patients with objective compliance to CPAP ≥ 4 hours per day. Thus, it does not represent an estimate of general CPAP use. Secondly, sleepiness was assessed by ESS, a simple self-administered questionnaire that quantifies subjective sleep propensity. Yet, it remains unclear if the results would have persisted if an objective measure of sleepiness such as the multiple sleep latency test were employed. However, methods used in routine clinical practice and recommended by the American Academy of Sleep Medicine [15] were employed.

In conclusion, the results of the present study suggest that a history of depression, diabetes and heart disease, and the presence of higher ESS score and lower RDI at initial assessment can predict those OSAS patients who may experience excessive daytime sleepiness even after adequate (≥ 4 hours daily) CPAP use. Clinicians should consider these factors in order to sufficiently anticipate the resolution or persistence of excessive daytime sleepiness of OSAS patients.
Table 1. Demographic, clinical and polysomnographic features of the OSAS patients with excessive daytime sleepiness (ESS score > 10) determined at baseline assessment. Patients who exhibited after CPAP treatment (mean daily use ≥ 4 hours during follow-up period) normal ESS score (< 11) were defined as CPAP responders, whereas those who exhibited after CPAP treatment abnormal ESS score (> 10) thus demonstrating residual excessive daytime sleepiness were defined as CPAP non-responders.

Continuous data are presented as mean ± SD and median (interquartile range), whereas categorical data are presented as % (95% confidence interval). #: p<0.05 versus CPAP responders; *: p<0.01 versus CPAP responders;**: p<0.001 versus CPAP responders. ESS: Epworth sleepiness scale; COPD: chronic obstructive pulmonary disease; TST: total sleep time; REM: rapid eye movement sleep; SWS: slow wave sleep.

Table 2. Odds ratios for variables independently associated with residual excessive daytime sleepiness after CPAP therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (0 = no, 1 = yes)</td>
<td>6.87</td>
<td>2.50-18.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart disease (0 = no, 1 = yes)</td>
<td>2.94</td>
<td>1.41-6.15</td>
<td>0.004</td>
</tr>
<tr>
<td>Epworth sleepiness scale score</td>
<td>1.31</td>
<td>1.15-1.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory disturbance index</td>
<td>0.97</td>
<td>0.96-0.98</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI: confidence interval.
All variables were determined at baseline assessment. Results were calculated with the use of stepwise, forward, multivariate logistic regression analysis. Variables that showed significant difference in the univariate comparison between CPAP responders and CPAP non-responders (and also body mass index, stroke and alcohol use) were entered in the model. Depression was not included in the model because it offered a near complete separation between CPAP responders and CPAP non-responders and maximum likelihood estimation was not achieved. Among patients, the odds of having residual excessive daytime sleepiness after CPAP therapy increased with the presence of diabetes, heart disease, and higher Epworth sleepiness scale score and lower respiratory disturbance index at baseline assessment.

References

**Screened patients**
1017 patients suspected for sleep-disordered breathing

- 311 patients with RDI ≤5 or ESS score < 11

**Eligible patients**
706 patients with RDI > 5 and ESS score > 10

- 89 patients with concomitant sleep disorder or shift workers or taking hypnotic medication
- 85 patients declined CPAP treatment
- 123 patients withdrew during follow-up
- 201 patients with poor CPAP compliance or inadequate CPAP pressure

**Studied patients**
208 patients compliant to CPAP treatment for at least 6 months

**Figure 1.** Flowchart showing the selection process for the studied patients. RDI: respiratory distress index; ESS: Epworth sleepiness scale; CPAP: continuous positive airway pressure.