Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure

MERCE GASA[1,7], RENAUD TAMISIER[1,2], SANDRINE H. LAUNOIS[1,2], MARC SAPENE[3], FRANCIS MARTIN[4], BRUNO STACH[5], YVES GRILLET[6], PATRICK LEVY[1,2] and JEAN-LOUIS PEPIN[1,2]

[1]INSERM U 1042, Joseph Fourier University, HP2 Laboratory (Hypoxia: Pathophysiology), La Tronche, France, [2]Sleep Laboratory and EFCR, Locomotion, Rehabilitation and Physiology Department, Grenoble University Hospital,Grenoble CEDEX 09, France, [3]Unité Sommeil et Vigilance, Polyclinique Bordeaux Cauderan, Bordeaux, France, [4]Unité des pathologies du sommeil, Centre hospitalier de Compiègne, Compiegne, France, [5]Service de pneumologie, Clinique Teissier, Valenciennes, France, [6]Pneumologie, Cabinet privé, Valence, France and [7]Sleep Unit, Department of Respiratory Medicine, Hospital Universitari de Bellvitge and Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain

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Correspondence
Jean Louis Pépin, MD, and Renaud Tamisier, MD, Laboratoire EFCR, CHU de Grenoble, BP217X, 38043 Grenoble cedex 09, France.
Tel.: (33+) 4-76-76-55-16;
fax: (33+)-4-76-76-55-86;
e-mails: jpepin@chu-grenoble.fr and rtamisier@chu-grenoble.fr

On behalf of the scientific council of The Sleep Registry of the French Federation of Pneumology, (FFP), PARIS, France.

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SUMMARY

Hypoxic brain damage might explain persistent sleepiness in some continuous positive airway pressure-compliant obstructive sleep apnea called residual excessive sleepiness. Although continuous positive airway pressure may not be fully efficient in treating this symptom, wake-promoting drug prescription in residual excessive sleepiness is no longer allowed by the European Medicines Agency. The aim of this study is to describe residual excessive sleepiness phenotypes in a large prospective sample of patients with obstructive sleep apnea. Residual excessive sleepiness was defined by an Epworth Sleepiness Scale score $\geq$ 11. Eligible patients from the French National Sleep Registry attending follow-up continuous positive airway pressure visits numbered 1047. Patients using continuous positive airway pressure < 3 h (n = 275), with residual apnea–hypopnea index > 15 h^{-1} (n = 31) or with major depression were excluded (n = 150). Residual excessive sleepiness prevalence in continuous positive airway pressure-treated obstructive sleep apnea was 13% (18% for those with an initial Epworth Sleepiness Scale score > 11), and significantly decreased with continuous positive airway pressure use (9% in $\geq$ 6 h $night^{-1}$ continuous positive airway pressure users, $P < 0.005$). At the time of diagnosis, patients with residual excessive sleepiness had worse subjective appreciation of their disease (general health scale, Epworth Sleepiness Scale and fatigue score), and complained more frequently of continuous positive airway pressure side-effects. Residual excessive sleepiness prevalence was lower in severe obstructive sleep apnea than in moderate obstructive sleep apnea (11% when AHI > 30 h^{-1} versus 18% when AHI 15–30, $P < 0.005$). There was no relationship between residual excessive sleepiness and body mass index, cardiovascular co-morbidities or diabetes. Continuous positive airway pressure improved symptoms in the whole population, but to a lower extent in patients with residual excessive sleepiness (fatigue scale: −5.2 versus −2.7 in residual excessive sleepiness− and residual excessive sleepiness+ patients, respectively, $P < 0.001$). Residual excessive sleepiness prevalence decreased with continuous positive airway pressure compliance. Hypoxic insult is unlikely to explain residual excessive sleepiness as obstructive sleep apnea severity does not seem to be critical. Residual

symptoms are not limited to sleepiness, suggesting a true 'continuous positive airway pressure-resistant syndrome', which may justify treatment by wake-promoting drugs.

INTRODUCTION

Obstructive sleep apnea (OSA) syndrome is characterized by recurrent episodes of partial or complete pharyngeal collapse occurring during sleep. It is an established health concern affecting up to 5% of middle-aged men and women in the general population (Young *et al.*, 2002).

Excessive daytime sleepiness (EDS), fatigue and altered attention are the most frequent symptoms experienced by patients with OSA. EDS can have a major impact on quality of life, as it can cause problems in psychological and cognitive function. Furthermore, it is associated with an increased risk of near misses and real motor vehicle accidents (see systematic review and meta-analysis; Tregear *et al.*, 2009). Several randomized controlled trials have established continuous positive airway pressure (CPAP) efficacy regarding sleepiness in OSA (Giles *et al.*, 2006; Marshall *et al.*, 2006; Patel *et al.*, 2003). The beneficial CPAP effect is generally obtained after only a few weeks of treatment, with quality of life returning to normal. However, residual excessive sleepiness (RES) in patients correctly treated with CPAP occurs in more than 12% of these patients (Pepin *et al.*, 2009). This RES has been postulated to be related to irreversible hypoxic brain damage affecting the locus coeruleus, median raphe and forebrain (Alchanatis *et al.*, 2004; Vernet *et al.*, 2011). This hypoxic neuron damage may account for persisting RES and cognitive dysfunction despite treatment. The existence of RES in correctly treated patients with OSA remains debatable. The majority of authors consider RES as a marker of irreversible hypoxic insult, while others consider this sleepiness as a prevalent complaint existing in the general population that is likely to be related to sleep duration and sleep hygiene (Ohayon, 2012; Stradling *et al.*, 2007).

Wake-stimulant medications improve RES in correctly treated OSA with CPAP (Weaver *et al.*, 2009) and are commonly prescribed in the USA. Yet the European Medicines Agency restricted the use of these medications to narcolepsy in November 2010. This decision was based on the unresolved question of RES specificity in patients with OSA correctly treated with CPAP, the lack of follow-up data on blood pressure, and on the absence of studies in large groups of patients. Hence, there is a need for a better description of RES and potential mechanisms in large samples of CPAP-treated OSA population.

The aim of this study was to investigate and describe the occurrence of RES in a CPAP-treated OSA patient sample obtained from the French National web-based Sleep Registry (www.osfp.fr). Patients were included in the database at the time of the initial visit, and the database was updated on follow-up visits. We analysed the association between RES and characteristics at initial and follow-up evaluations, including associated morbidities and CPAP compliance, in 1047 patients with OSA.

MATERIALS AND METHODS

Data source

The research database of the Observatoire Sommeil de la Fédération Francaise de Pneumologie (OSFP) is a large, high-quality, not-for-profit database administered by the French Federation of Pneumology. The database contains de-identified longitudinal medical records from more than 500 respiratory physicians in private practice, general and university hospitals (website: www.osfp.fr). This registry is a formatted web-based report collecting data from patients complaining about sleep, completed and validated by respiratory physicians. Participating physicians are trained in using computerized medical records and appropriate software. Periodic quality control checks are performed to ensure up-to-standard data recording. Demographic characteristics of the 36 000 patients included in the OSFP database at the time of analysis suggest that those patients are considered broadly representative of CPAP-treated patients in France (10% of the total number of CPAP-treated patients in the country).

Ethical committee approval was obtained from Le Comité consultatif sur le traitement de l'information en matière de recherche en santé (C.C.T.I.R.S n° 09.521) and authorization from the Commission Nationale Informatique et Liberté (C.N.I.L), the French information technology and personal data protection authority. The OSFP Independent Scientific Advisory Committee approved data use for this study.

Data collection and outcome measures

Patients' visits and clinical information collected in the OSFP include diagnoses, symptoms, procedures [i.e. respiratory polygraphy or polysomnography (PSG)], prescriptions issued at diagnosis and follow-up visits. Anthropometric data, Epworth Sleepiness Scale (ESS; Johns, 1992), Pichot fatigue scale and Pichot depression scale (Pichot and Brun, 1984; Pichot and Lemperiere, 1964) are recorded. In addition, a 10-cm visual analogue scale is used to assess the patient's general perception of health. For each subject, the score ranges from 0 (very poor perception of health) to 10 (excellent perception of health). Physical exam results were collected during every visit according to physician follow-up.

Effective CPAP pressure was determined for each patient by manual titration under PSG or by auto-CPAP titration procedures at home. CPAP nightly usage and residual apnea –hypopnea index (AHI) were obtained from the CPAP device

log. A specific questionnaire focused on CPAP side-effects was completed by each patient. These were collected during the follow-up CPAP visits.

Residual excessive sleepiness was defined by an ESS score at the follow-up CPAP visit equal to or above 11, while patients were adequately treated (i.e. residual AHI < 15 h^{-1}, compliant to treatment more than 3 h per day and non-depressive with a depression score < 7 without any anti-depressive medication).

Statistical analysis

Distribution normality and variance equality of the data were checked using tests of Skewness or Kurtosis and the Levene test, respectively. Data are expressed as mean ± standard deviation (SD) for continuous variables and as a percentage for categorical variables. Comparisons between RES + and RES− were performed using the unpaired *t*-test or Mann–Whitney test (depending on normality distribution). Comparisons between baseline and follow-up visit were tested using paired *t*-test or Wilcoxon test (depending on the normality of distribution). For discrete variable, the Chi-squared test or Fisher's test (if expected counts were < 5) were used. Multiple comparisons were performed using one-way ANOVA or the Kruskal–Wallis test depending on the normality of distribution. Bonferroni's correction was used for the *post hoc* tests. A *P*-value of < 0.05 was considered statistically significant. NCSS 97 software (Kaysville, Utah, USA) was used for statistical analysis.

RESULTS

Among the population of 36 000 patients included in the database, 14 969 patients had a diagnosis AHI of > 15 h^{-1}. From those patients, 5509 on CPAP treatment completed the follow-up visit (Fig. 1a). Complete data quality was achieved in 3313 patients and, of these, 1624 completed the follow-up visit between 3 and 24 months after CPAP initiation. Objective compliance data and residual AHI were obtained from the CPAP device log in 1503 patients. Patients were excluded from analysis when CPAP use was < 3 h day^{-1} (n = 275), when there was incomplete resolution of respiratory events, residual AHI > 15 (n = 31) or a depression scale > 7 at the follow-up visit (n = 150). The former exclusion criterion was applied because depression may interfere with subjective sleepiness perception. Therefore, analysis was performed in 1047 patients, with 912 patients assigned to the RES− group and 135 patients to the RES+ group depending on the ESS score (Fig. 1b). The relative percentages of RES were 13%, 18.3% and 5.6% for the whole group, the initially sleepy group and non-sleepy group, respectively. The flow chart of the study and RES prevalence are shown in Fig. 1a and b.

Baseline characteristics of the studied population are shown in Table 1 for the overall sample, and according to the presence or not of RES in Tables 2 (for the overall group)

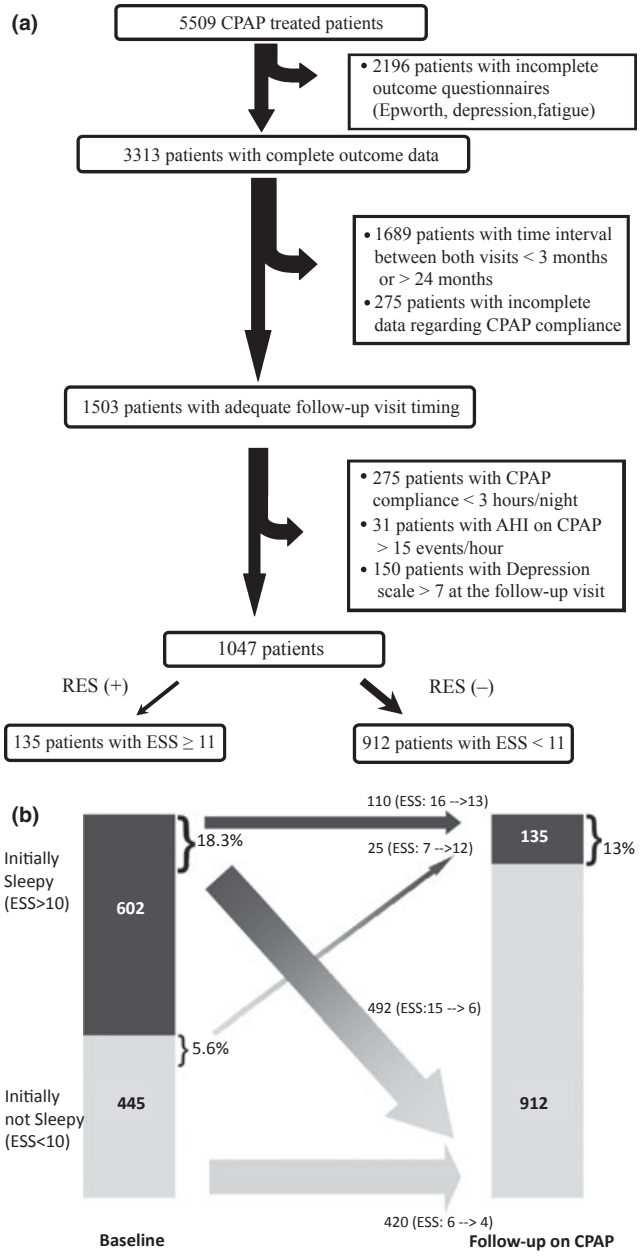

Figure 1. (a) Flowchart of the study. (b) Evolution of each subgroup of patients depending on the presence or not of an Epworth Sleepiness Scale (ESS) score > 10 between visit 1 and visit 2 [post-continuous positive airway pressure (CPAP)]. This figure illustrates how the proportion of initially sleepy patients changes with CPAP to a residual excessive sleepiness (RES) prevalence of 13%. Moreover, this highlights that 18.3% and 5.6% of patients exhibit RES at visit 2 among those initially sleepy or not, respectively. Delta changes in ESS are reported in parentheses for each subgroup, showing a decrease in ESS in all subgroups, but the one not initially sleep who became sleepy. AHI, apnea–hypopnea index.

and 3 (for patients with sleepiness at diagnosis). The 1047 patients studied had a mean age of 57 ± 12 years, mean body mass index (BMI) of 32 ± 7 $kg \cdot m^{-2}$ and a classic male predominance with a sex ratio M/F of 7/3. On average at diagnosis, the mean ESS score was 11 ± 5 and the mean AHI was 43 ± 20 $events \cdot h^{-1}$.

Table 1 Characteristics at diagnosis in the overall sample and according to the presence of sleepiness at diagnosis

	All patients N = *1047*	*ESS ≤ 10* *(n = 445, 43%)*	*ESS > 10* *(*n = *602, 57%)*	P-*value*
Anthropometrics				
Age (years)	57.38 ± 12.45	57.77 ± 13.05	57.09 ± 11.99	0.1748
Male/female (%)	70/30	68/32	71/29	0.3320
BMI (kg·m^{-2})	31.96 ± 6.59	32.15 ± 6.73	31.82 ± 6.49	0.6171
Subjective scale values at baseline				
ESS	11.33 ± 5.13	6.42 ± 2.90	14.96 ± 2.91	**<0.0001**
Depression	3.21 ± 3.44	3.00 ± 3.31	3.37 ± 3.53	0.2216
General health	5.88 ± 2.46	6.00 ± 2.64	5.85 ± 2.39	0.0564
Co-morbidities				
Hypertension (%)	49.9	47.6	51.5	0.1312
Arrhythmia (%)	8.4	8.8	8.1	0.9149
Stroke (%)	3.0	3.4	2.7	0.5526
Heart failure (%)	1.9	0.7	2.8	**0.0120**
Peripheral arterial disease (%)	2.0	2.0	2.0	0.9735
Ischaemic cardiomyopathy (%)	7.5	8.1	7.1	0.5663
Diabetes (%)	17.0	17.5	16.6	0.5436
PLM treatment (%)	0.4	0.0	0.7	0.1412
OSA severity				
Baseline AHI (events h^{-1})	42.65 ± 19.61	42.70 ± 18.73	42.62 ± 20.25	0.5528
Oxygen desaturation index (nb h^{-1})	34.59 ± 22.93	33.33 ± 22.08	35.57 ± 23.54	0.2527

Data expressed as mean ± standard deviation for continuous variables, and as a percentage for categorical variables. Test used: Student's *t*-test or Mann–Whitney test when appropriate for continuous variables; Chi-squared test or Fisher test when appropriate for categorical variables.
AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; PLM, periodic leg movement syndrome. *P* values in bold are statistically significant.

Table 2 Characteristics at diagnosis according to the presence of RES at follow-up

	*RES+(*n = *135, 13%)*	*RES−(*n = *912, 87%)*	P-*value*
Anthropometrics			
Age (years)	56.12 ± 11.55	57.56 ± 12.57	0.0909
Male/female (%)	60/40	71/29	**<0.01**
BMI (kg m^{-2})	31.14 ± 6.11	32.08 ± 6.65	NS
Subjective scale values at baseline			
ESS	14.17 ± 4.65	10.91V5.06	**<0.0001**
Depression	4.14 ± 3.91	3.08 ± 3.35	**<0.01**
Fatigue	14.50 ± 9.09	11.18 ± 7.91	**<0.0001**
General health	5.22 ± 2.39	5.98 ± 2.45	**<0.001**
Co-morbidities			
Hypertension (%)	45.19	50.55	NS
Arrhythmia (%)	8.15	8.44	NS
Stroke (%)	1.48	3.18	NS
Heart failure (%)	2.96	1.71	NS
Peripheral arterial disease (%)	2.22	1.97	NS
Ischaemic cardiomyopathy (%)	6.67	7.68	NS
Diabetes (%)	14.1	17.4	NS
PLM treatment (%)	0.74	0.33	NS
OSA severity			
Baseline AHI (events h^{-1})	40.60 ± 20.61	42.95 ± 19.45	**<0.05**
Oxygen desaturation index (nb h^{-1})	31.71 ± 23.22	34.99 ± 22.87	NS

Data expressed as mean ± standard deviation for continuous variables, and as a percentage for categorical variables. Test used: Student's *t*-test or Mann–Whitney test when appropriate for continuous variables; Chi-squared test or Fisher test when appropriate for categorical variables.
AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; PLM, periodic leg movement syndrome; RES, residual excessive sleepiness. *P* values in bold are statistically significant.

Table 3 Characteristics at diagnosis in patients with sleepiness at diagnosis and according to the presence of RES at follow-up

	RES+(n = 110, 18%)	*RES−(n = 492, 82%)*	P-*value*
Anthropometrics			
Age (years)	55.36 ± 11.55	57.48 ± 12.06	0.0948
Male/female (%)	59/41	74/26	**0.0021**
BMI (kg m^{-2})	30.94 ± 6.21	32.02 ± 6.54	NS
Subjective scale values at baseline			
ESS	15.79 ± 3.16	14.77 ± 2.82	**0.0019**
Depression	4.28 ± 3.89	3.17 ± 3.41	**0.0067**
Fatigue	15.13 ± 8.79	12.80 ± 8.03	**0.0099**
General health	5.50 ± 2.71	5.94 ± 2.30	0.3810
Co-morbidities			
Hypertension (%)	44.5	53.0	NS
Arrhythmia (%)	8.2	8.1	NS
Stroke (%)	1.8	2.8	NS
Heart failure (%)	3.6	2.6	NS
Peripheral arterial disease (%)	0.9	2.2	NS
Ischaemic cardiomyopathy (%)	4.5	7.7	NS
Diabetes (%)	13.7	17.3	NS
PLM treatment (%)	0.9	0.6	NS
OSA severity			
Baseline AHI (events h^{-1})	40.93 ± 21.40	42.99 ± 19.98	0.1005
Oxygen desaturation index (nb h^{-1})	32.10 ± 23.54	36.29 ± 23.51	0.0935

Data expressed as mean ± standard deviation for continuous variables, and as a percentage for categorical variables. Test used: Student's *t*-test or Mann–Whitney test when appropriate for continuous variables; Chi-squared test or Fisher test when appropriate for categorical variables.
AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; PLM, periodic leg movement syndrome; RES, residual excessive sleepiness. *P* values in bold are statistically significant.

Factors associated with RES on CPAP

Anthropometric data, symptoms and co-morbidities

In patients with RES, the percentage of females was significantly higher, but the two groups exhibited similar mean age and BMI. Regarding clinical complaints at the first visit, patients with RES had higher mean values of ESS, depression and fatigue scales, and reported worse general health status. No significant relationship was found between RES and cardiovascular co-morbidities or diabetes.

Severity of sleep apnea

The prevalence of RES among patients suffering from moderate OSA (baseline AHI between 15 and 30 events h^{-1}) was nearly twice the prevalence in the severe groups (baseline AHI between 30 and 50 events·h^{-1} and > 50 events h^{-1}; 18.1% versus 11.2%, $P < 0.01$ and versus 11.0%, $P < 0.05$, respectively).

CPAP side-effects and acceptance

Furthermore, patients with RES complained significantly more about mouth dryness, asphyxia and psychological discomfort, while the device was less tolerated by the patients' family (Table 4).

CPAP compliance and RES: a dose–response relationship

Continuous positive airway pressure treatment characteristics in the whole sample and according to the presence or not of RES are presented in Table 4. For the entire sample, the mean CPAP pressure was 8.8 ± 2.1 cmH_2O with a mean CPAP use of 5.7 ± 1.5 h·$night^{-1}$ and a mean residual AHI of 4.2 ± 3.0 h^{-1}. There were no differences in mean CPAP pressure levels and residual AHI values between both groups. However, patients with RES used their device on average 10.6% less than patients without RES ($P < 0.0001$). The overall prevalence of RES was 13%. However, as shown in Fig. 2a, the prevalence of RES decreased when CPAP use increased. The prevalence of RES was significantly lower in subjects who used CPAP more than 6 h $night^{-1}$ compared with those who used the device < 4 h $night^{-1}$ and 4–5 h $night^{-1}$ (8.7% versus 18.5%, $P < 0.01$ and versus 22.3%, $P < 0.0001$, respectively; Fig. 2b). This analysis was equivalent when taking into account only patients initially sleepy with an ESS score > 11 (Fig. 2b). The improvement in ESS from the initial visit to the CPAP follow-up visit increased with CPAP daily use (Fig. 2c).

The 'CPAP-resistant' syndrome

As stated above, at the time of diagnosis, patients with RES had a worse subjective appreciation of their disease (general

Table 4 CPAP-related characteristics in the overall sample and according to the presence or not of RES

	All patients N = *1047*	*RES+* (n = *135, 13%)*	*RES–* (n = *912, 87%)*	P-*value*
CPAP				
Residual AHI (events h^{-1})	4.19 ± 3.02	4.33 ± 3.19	4.17 ± 2.99	0.7408
Mean CPAP pressure (cmH_2O)	8.82 ± 2.11	8.78 ± 1.99	8.82 ± 2.13	0.9522
CPAP use (h day^{-1})	5.68 ± 1.51	5.14 ± 1.51	5.75 ± 1.50	**<0.0001**
Side-effects (%)	11.7	17.78	10.86	0.0619
Stuffy nose				
Eye irritation	6.2	10.37	5.59	0.0813
Dry mouth	21.7	34.07	19.85	**<0.0001**
Choking sensation	10.3	21.48	8.66	**<0.0001**
Psychological discomfort	10.8	17.04	9.87	**0.0407**
Headache	2.8	2.22	2.85	0.2699
Poor CPAP acceptance by the family	5.8	11.11	5.04	**0.0173**

Data expressed as mean ± standard deviation for continuous variables, and as a percentage for categorical variables. Test used: Student's *t*-test or Mann–Whitney test when appropriate for continuous variables; Chi-squared test or Fisher test when appropriate for categorical variables.
AHI, apnea–hypopnea index; CPAP, continuous positive airway pressure; RES, residual excessive sleepiness. *P* values in bold are statistically significant.

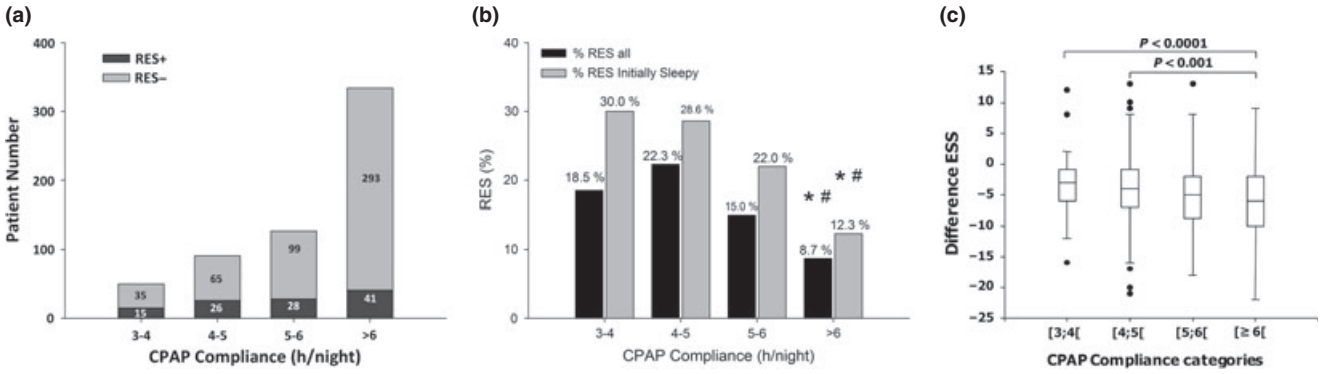

Figure 2. Residual excessive sleepiness (RES) among continuous positive airway pressure (CPAP) compliance. Test used: one-way ANOVA with *post hoc* Bonferroni correction (comparison of RES prevalence among categories). (a) The absolute distribution of patients among CPAP compliance categories and the prevalence of RES. The prevalence of RES decreased when CPAP use increased (test used: one-way ANOVA). (b) The percentage of patients with RES in all (dark) and in initially sleepy (grey) patients among CPAP compliance. Light grey bars represent the percentage of patients complaining of excessive sleepiness [Epworth Sleepiness Scale (ESS) > 10] initially (visit 1), and the dark grey bars represent all patients. Significant differences are expressed by * and # for comparison with 3–4 and 4–5 h, respectively. (c) ESS evolution among CPAP compliance categories. Box-plots represent the difference in ESS values between the initial visit and the CPAP follow-up visit. The average nightly use of CPAP (h) is shown in parentheses. Test used: one-way ANOVA with *post hoc* Bonferroni correction.

health scale, ESS and fatigue score). Mean values of ESS, depression, fatigue and global health perception scales significantly improved on CPAP for both groups (Table 5). However, CPAP improved symptoms to a lower extent in patients with RES.

DISCUSSION

The four main findings of this study are as follows. (i) The prevalence of RES in patients with OSA properly treated by CPAP was 13% for the whole group, but increased to 18% in the initially sleepy group, and was significantly decreased in patients with high CPAP usage (9% in ≥ 6 h $night^{-1}$ CPAP users, $P < 0.005$). (ii) At the time of diagnosis, patients with RES had a worse subjective appreciation of their condition with greater perceived impairment of their general health, and exhibited higher sleepiness and fatigue scale scores. (iii) CPAP improved a variety of symptoms and this was also true, albeit to a lesser extent, in patients with RES. (iv) RES prevalence was lower in severe OSA than in moderate OSA, suggesting that the severity of intermittent hypoxia is not the main determinant of RES in CPAP-treated patients.

The population under study in this manuscript was selected according to clinic attendance and data availability. However, our study is the largest in the field and it has the strength of including patients not only from academic centres but also from private practice respiratory physicians, thus reflecting a real-world management of patients with OSA. The observed

Table 5 Evaluation of mean health scale scores depending on the presence of RES

	RES+(n = 135)			*RES−(n = 912)*				
	Visit 1	*Visit 2*	P-*value*	*Visit 1*	*Visit 2*	P-*value*	*Delta change (IC)*	P-*value*
ESS	14.17 ± 4.65	12.69 ± 1.88	**<0.0001**	10.91 ± 5.06	5.02 ± 2.72	<0.0001	−4.4 (−5.3/−3.5)	**<0.0001**
Depression	4.14 ± 3.91	2.27 ± 2.03	**<0.0001**	3.08 ± 3.35	1.15 ± 1.68	<0.0001	−0.05 (−0.6/0.5)	0.7961
Fatigue	14.50 ± 9.09	12.09 ± 7.15	**<0.0001**	11.18 ± 7.91	4.83 ± 4.99	<0.0001	−3.9 (−5.2/−2.7)	**<0.0001**
General health	5.59 ± 2.70 (*n* = 111)	6.10 ± 2.62 (*n* = 111)	**0.0049**	5.99 ± 2.46 (*n* = 666)	6.73 ± 2.68 (*n* = 666)	<0.0001	0.2 (−0.2/0.7)	**0.0361**

Data are expressed as mean ± standard deviation. Test used: paired Student's *t*-test or Wilcoxon test when appropriate for comparison between both visits; unpaired Student's *t*-test or Mann–Whitney test when appropriate for comparisons of the variables 'difference' depending on the presence or absence of RES.
ESS, Epworth Sleepiness Scale; RES, residual excessive sleepiness. *P* values in bold are statistically significant.

13% prevalence of RES is consistent with previous work that reported a prevalence of RES between 6% and 14% in CPAP-compliant patients (Nguyen *et al.*, 2008; Pepin *et al.*, 2009). In addition, the prevalence of RES was clearly higher in patients suffering from moderate OSA than in those with severe disease. We may hypothesize that, at diagnosis, patients present to the clinic when their symptoms reach a certain level. If those symptoms are entirely due to sleep apnea, suggesting that sleep apnea is likely to be more severe, they may respond favourably to treatment. However, if the cause of their symptoms is multifactorial, it is possible that sleep apnea is less severe than in the first situation (because in addition to the sleep apnea, other problems have increased the symptoms to a critical level), and thus CPAP may be less effective on symptoms and therefore patients may be left with residual symptoms.

In a highly selected population of 208 morbidly obese, sleepy OSA patients, Koutsourelakis *et al.* (2009) found a 55% rate of RES with a significant relationship to depression as well as cardiovascular disease and diabetes. In our real-world population of OSA, including non-sleepy and sleepy patients at baseline, a history of cardiovascular disorder or diabetes was not a significant predictor for RES.

To adequately address the topic of RES in CPAP patients, the issue of treatment compliance is crucial. In the present study, patients with RES used CPAP less than those without RES (5.1 versus 5.8 h night^{-1}, $P < 0.001$), and there was an inverted dose response between CPAP usage and the risk of RES (Fig. 2). Patients with RES also complained more frequently about CPAP side-effects than those without RES. These side-effects might contribute to persistent sleep fragmentation because of leaks or discomfort, thus partly accounting for RES. This finding emphasizes the fact that, in any CPAP-treated OSA patient referred for persistent sleepiness, the first step is to optimize CPAP tolerance in order to obtain an optimal compliance.

It remains unclear if the residual sleepiness is an irreversible result of previous OSA and merits consideration for pharmacological treatment, or if residual sleepiness is due to the many and varied causes of sleepiness normally found in the community. Stradling *et al.* (2007) have used the ESS score in 572 patients on CPAP and compared them with a control group of 525 subjects from a community survey. There was no difference in the percentage of patients with an ESS score > 10 in the CPAP group compared with the controls (16.1 versus 14.3, $P = 0.54$). In the most recent studies in the general population, Pahwa *et al.* (2012) found that 21% of randomly selected individuals in a Canadian rural population had ESS scores > 10, while this prevalence of 10.9% was reported by Johns and Hocking (1997) in an Australian working population in 1997. Accordingly, in the Ohayon (2012) study, 19.5% of the randomly selected population reported severe excessive sleepiness, and 20% moderate excessive sleepiness, but the ESS was not used. In our study, because depression is a significant confounder, patients with severe depression scores have been excluded, but the crude rate of 13% of RES that we reported was not higher than in the community.

Patients with RES demonstrated a different phenotype at baseline, with remarkably worse overall health self-perception (worse scores in sleepiness, fatigue, depression and general health perception scales). Actually, CPAP improved symptoms in the whole group but to a lesser extent in patients with RES (fatigue scale: −5.2 versus −2.7 in RES− and RES+ patients, respectively, $P < 0.001$). Antic *et al.* (2011) had assessed the efficacy of 3 months of CPAP on ESS and other neurocognitive parameters in 174 patients with symptomatic moderate-to-severe OSA. They also found a positive dose–response effect between CPAP duration and decrease in ESS. However, these authors and others (Vernet *et al.*, 2011; Weaver *et al.*, 2009) reported that a substantial proportion of patients did not normalize neurobehavioural function even if CPAP compliance was optimal. Differential neurobehavioural vulnerability to sleep deprivation/disorders is trait-like, with genotypic involvement (Goel and Dinges, 2011; Goel *et al.*, 2010). Human leukocyte antigen (HLA) *DQB1*0602* is an allele that predicts inter-individual differences in sleepiness, physiological sleep and fatigue in response to chronic partial sleep deprivation in healthy adults. Further studies examining CPAP response in patients with OSA should evaluate whether a genetic biomarker may be able to predict CPAP-resistant syndrome. DQB1*0602 is

likely not to be a candidate as this has been explored by Vernet *et al.* (2011) in a population of 20 patients with OSA with RES, 20 patients with OSA without RES, and 20 healthy controls. In that study, DQB1*0602 did not represent a good genetic marker for RES as, in fact, it was slightly lower in the RES compared with the non-sleepy OSA group, 15% versus 25%, respectively. The substantial subgroup of OSA responding only partly to CPAP would be interesting to identify at the time of diagnosis, and there is a need to develop specific countermeasures and tailored treatments.

Although about 10% of patients expressed RES, only 8.7% of patients still complained about RES when CPAP use exceeded 6 h night^{-1}. This unexplainable residual sleepiness might be put in perspective with what has been recently observed in a representative sample of US population by Ohayon (2012). According to this report, there is a strong relationship between sleep duration and excessive sleepiness, as we report in the present results in OSA-treated patients.

Finally, some limitations of our study should be noted. Both polygraphy and PSG were used for OSA diagnosis. Despite the fact that this seems not to impact our analysis (same prevalence of RES in polygraphic versus PSG groups), we cannot rule out that in mild OSA, this may have some impact by underestimating the AHI during polygraphy for instance. Narcolepsy and restless legs syndrome were excluded at initial sleep recording and clinical assessment at follow-up, but not by a full PSG on CPAP. No evaluation of differential diagnosis of sleepiness-like behaviourally induced insufficient sleep syndrome was conducted. Some of the patients ESS scores worsened on CPAP. Because no sleep study was performed before the second visit, we cannot distinguish between sleep disturbances induced by CPAP and test–retest variability as a cause of higher ESS at the second visit.

CONCLUSION

Our study suggests that up to 10% of patients will not normalize sleepiness and fatigue despite seemingly adequate CPAP daily use. CPAP compliance associated with the lowest RES prevalence was > 6 h night^{-1}. Brain damage sequel due to hypoxic exposure is probably not the explanation for RES as OSA severity did not seem to be critical. However, we can not rule out a differential reactivity to hypoxic brain insult. Residual symptoms are not limited to sleepiness, suggesting the existence of a true CPAP-resistant syndrome, and justifying a thorough assessment of patients who remain sleepy following CPAP therapy where alternate aetiologies have been excluded and CPAP treatment has been optimal to improve compliance. The use of psychostimulants in patients with significant persistent complaints should be evaluated.

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CONFLICT OF INTEREST

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AUTHOR'S CONTRIBUTIONS

Dr Merce Gasa: analysis and interpretation, critical revision of the manuscript for important intellectual content; Dr Renaud Tamisier: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision; Dr Sandrine H. Launois: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision; Dr Marc Sapene: study concept and design, acquisition of data; Dr Francis Martin: study concept and design, acquisition of data; Dr Bruno Stach: study concept and design, acquisition of data; Dr Yves Grillet: study concept and design, acquisition of data; Dr Prof. Patrick Levy: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content; and Dr Prof. Jean-Louis Pepin: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision.

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