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Original Article

Effect of continuous positive airway pressure on respiratory drive in patients with obstructive sleep apnea

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ABSTRACT

Objective: Patients with obstructive sleep apnea (OSA) have an altered control of breathing during wakefulness. Thus far, whether and how treatment with continuous positive airway pressure (CPAP) may restore these abnormalities has been poorly understood. The aim of this study was to investigate the long-term effects of CPAP on the breathing pattern, ventilatory drive (VDr), and chemoreceptor sensitivity in OSA patients.

Patients and methods: This was a prospective, observational study, carried out in an academic sleep outpatient clinic. A total of 62 patients with OSA (mean age [SD], 51 [11] years) underwent polysomnography (PSG), breathing pattern assessment, mouth occlusion pressure, ventilatory response to hypoxemia (V_e/SaO_2), and hypercapnia ($V_e/PETCO_2$) before and after CPAP titration and during 12-month follow-up. A total of 48 age-matched healthy subjects served as controls. Patients with good ($\geq$6 h/night) and poor (<6 h/night) compliance with CPAP were also compared.

Results: At baseline, VDr as well as thoracic and inspiratory impedances were greater in patients with OSA compared with controls and were reduced by CPAP treatment, starting from the night of titration ($P < 0.01$), especially in patients with good compliance with CPAP. Baseline V_e/SaO_2 was higher in OSA patients ($P < 0.05$) and was progressively normalized during CPAP treatment ($P < 0.001$). The pathophysiological changes were mainly due to a reduction in tidal volume. The remaining breathing pattern parameters were unaltered by CPAP treatment and were similar between groups.

Conclusion: In OSA patients, the mechanics of breathing are inefficient because of an imbalance of the VDr. Regular CPAP treatment improves the efficiency of the respiratory system and normalizes the hypoxemic stimulus.

1. Introduction

During sleep, patients with obstructive sleep apnea (OSA) have periodic fluctuations in upper airway muscle activity, upper airway resistance, and ventilation [1–3]. Moreover, pharyngeal anatomy, upper airway muscle responsiveness, arousal threshold, and loop gain may all contribute to apnea presence and severity [4]. Loop gain is a measure of the stability of a system, and sleep disordered breathing has been suggested to be a consequence of an instability in ventilatory control [5]. Abnormalities in the chemoreflex ventilatory response are often present in patients with OSA [6]; they are expressed through an increase in peripheral chemoreflex sensitivity, which is in turn associated with a selective potentiation of the autonomic and hemodynamic response [7]. One of the major determinants of ventilatory stability is represented by the controller gain [8], that is, the ventilatory response to hypoxia and hypercapnia, which are related to chemosensitivity control and drive the open-loop response, reflecting a system's dynamic gain [9]. Available data on ventilatory responses to chemical changes in

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patients with OSA are conflicting. Previous research demonstrated blunted chemoreflexes due to sleep fragmentation in patients with OSA [10–12], with an impaired hypercapnic ventilatory response and mouth occlusion pressures. On the other hand, normocapnic OSA patients showed normal respiratory responses during stimulation with carbon dioxide (CO_2) [13–15], whereas the ventilatory CO_2 response was depressed in OSA patients with chronic hypercapnia [14–16]. Wang and coworkers [5] showed that the degree of apnea/hypopnea events was directly related to an increased ventilatory response to hypercapnia in asymptomatic patients [5]. Hudgel and colleagues demonstrated differences in the central dynamic control of breathing but similar chemosensitivity to hypercapnic stimuli in OSA patients and healthy subjects [9]. Notably, Benlloch and coworkers [17] showed a respiratory pattern characterized by both increased mouth occlusion pressure and respiratory drive in OSA patients at rest.

Nasal continuous positive airway pressure (CPAP) can reduce nocturnal respiratory events, nighttime symptoms, and cardiovascular morbidity [18,19] and is therefore considered the first-choice treatment for patients with OSA. However, the long-term effects of CPAP on the control of breathing are poorly understood, and the available data appear to be conflicting [12,20–26].

The primary aim of the present study was to investigate the medium- and long-term effects of CPAP treatment on the ventilatory pattern and ventilatory drive in patients with OSA. The secondary aim was to explore whether the ventilatory pattern and ventilatory drive of OSA patients could be affected by compliance with CPAP therapy.

2. Patients and methods

This was a prospective, observational study, carried out in the academic sleep outpatient clinic center of the L. Sacco University Hospital, Milan (Italy). Between January 2011 and December 2014, we studied 62 patients with newly diagnosed moderate to severe OSA and 48 healthy volunteers who formed the control group. Previous reports did not show an age or sex effect on hypercapnic or hypoxic ventilatory responses [5] or on breathing pattern [27]. To control for confounding factors such as body mass index (BMI) in patients with OSA, healthy subjects with anthropometric characteristics comparable to those of patients with OSA were enrolled with a pragmatic approach. Inclusion criteria for patients were >18 years of age; diagnosis of moderate to severe OSA, as determined by an apnea–hypopnea index (AHI) index of ≥15 according to current standards [28]; and the ability to perform the pathophysiological testing required by the study. Exclusion criteria were a diagnosis of concomitant chronic or acute respiratory diseases such as chronic obstructive pulmonary disease, asthma, bronchiectasis, or interstitial pneumonia; daytime hypercapnia (ie, a partial pressure of arterial carbon dioxide [PaCO2] of >45 mmHg) and BMI >30, to avoid any possible interference in the stimulated ventilatory response in patients with hypoventilation syndrome; severe cognitive impairment; alcohol and drug addiction; and any known contraindication to CPAP treatment. Smoking cessation was required for all participants for at least six months before study enrollment, and alcohol consumption was prohibited at least 24 h before the study day. The study was conducted in accordance with the amended Declaration of Helsinki (2013), and all participants signed an informed consent form.

2.1. Study protocol

Consecutive patients referring to the Sleep Outpatient Clinic with clinical suspicion of OSA were screened with baseline diagnostic polysomnography (PSG). The morning after, patients with a diagnosis of moderate and severe OSA underwent the following pathophysiological measurements: arterial blood gas (ABG) analysis, static and dynamic lung volumes, respiratory pattern at rest, mouth occlusion pressure (P0.1), and ventilatory response to normocapnic hypoxemia and normoxic hypercapnia.

The same pathophysiological measurements were performed after the night of CPAP titration and after 1, 3, and 12 months of CPAP therapy. PSG tests were performed in the sleep laboratory as detailed in section 2.2, and results were downloaded and analyzed the next morning. During the follow-up period, compliance with CPAP therapy was assessed by analyzing the flash memory card of each CPAP machine. Good compliance with CPAP was defined as ≥6 h of CPAP use per night, whereas poor compliance was defined as <6 h of use per night [29]. BMI was checked at each study visit; patients were not exposed to diet therapy, and no new hypnotic or neuroleptic drugs were introduced after study enrollment. At baseline, healthy subjects underwent the same sleep and respiratory function testing. An overview of the study protocol is presented in Fig. 1.

2.2. Sleep study

The sleep study was performed and analyzed using a computer-assisted device (Medatec, PA.ME.LA., Brussels, Belgium). Equipment measured electroencephalogram, electro-oculogram, electrocardiogram, submental and tibial electromyogram, body movement, nasal and oral airflow, respiratory effort via thoracic and abdominal bands, and oximetry pulse rate (Pulsox 7 Minolta, Osaka, Japan). The transducers and lead wires allowed normal position changes during sleep. Snoring sounds were recorded by an air-coupled subminiature microphone (sensitivity threshold of 20 dB UIL at 125 Hz), which was taped to the skin at the level of the larynx. The PSG was performed in our sleep laboratory, which consisted of a sound-attenuated room with temperature control.

OSA was defined as cessation of airflow for ≥10 s, with continued chest and abdominal movement. Hypopnea was defined as ≥30% reduction in airflow for ≥10 s, accompanied by a 4% decrease in SpO_2 and/or followed by an arousal, with continued chest and abdominal movement. AHI was defined as the number of obstructive apnea or hypopnea episodes per hour of sleep, and arousals were scored according to the American Academy of Sleep Medicine criteria [30]. The percentage of sleep time spent having an SpO_2 <90% (ST90) was calculated. The oxygen desaturation index (ODI) was defined as the number of episodes of a fall ≥4% in SpO_2 per hour of sleep. For snoring evaluation, quiet breathing was recorded at a level of <50 dB; any deflections synchronous with respiration in the microphone channel and >50 dB were counted as snores, and the percentage of total sleep time spent snoring was calculated. CPAP titration was performed according to current recommendations [31].

2.3. Respiratory function tests

All tests were performed at rest, in the sitting position. Static and dynamic lung volumes were assessed by means of a constant-volume plethysmograph (VMAX 227 Autobox V6200, Sensor Medics, Yorba Linda, CA, USA) according to current guidelines [32].

The respiratory pattern analysis was performed during the second of 3 min of quiet breathing and analyzed breath by breath. Patients were connected to a mouthpiece and a flow meter while wearing a nose clip. The following parameters were measured: tidal volume (VT), respiratory rate (RR), inspiratory time (Ti), expiratory time (Te), total respiratory time (Ttot), mean inspiratory flow (Vt/Ti), and respiratory duty cycle (Ti/Ttot). Minute ventilation (Ve) was calculated by multiplying the Vt by RR. P0.1 was measured

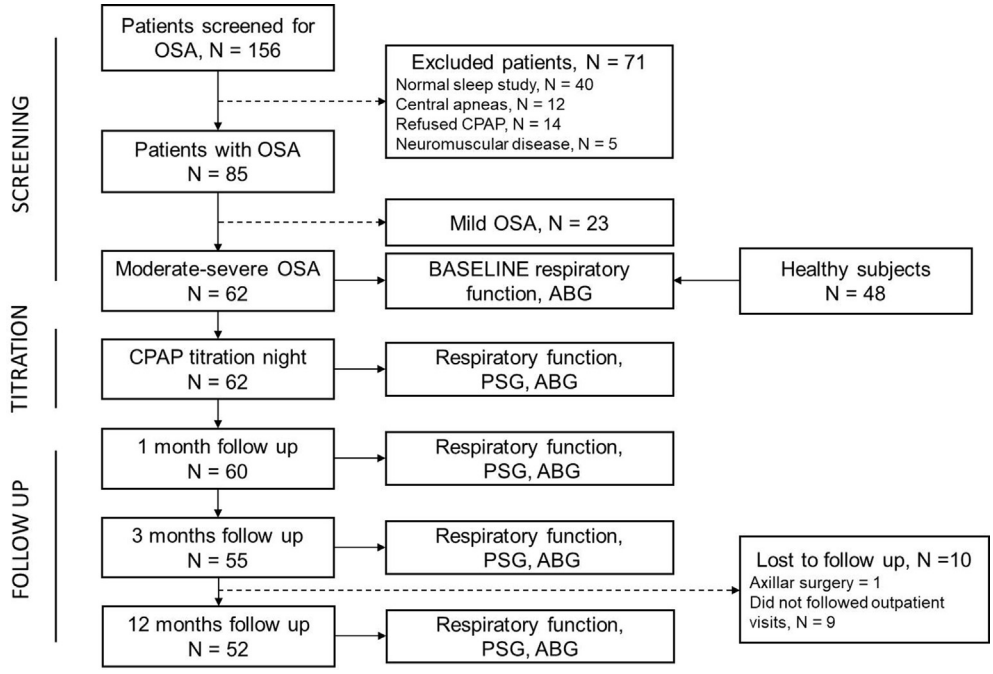

Fig. 1. Flow chart describing the study protocol. Dotted lines represent patients excluded from the study because they did not meet the inclusion criteria. ABG, arterial blood gas analysis; OSA, obstructive sleep apnea.

at rest in the sitting position at functional residual capacity; measurements were performed randomly every five breaths during the third minute of quiet breathing (VMAX 227 Autobox V6200, Sensor Medics, Yorba Linda, CA, USA).

Both Ve and Vt/Ti were correlated with P0.1; these relationships reflect the efficiency of the thoracic pulmonary system in converting the neuromuscular drive (ie, P0.1) in ventilatory and inspiratory flow, and are considered indicators of the effective impedance of the inspiratory and thoracic pulmonary system [33,34].

Ventilatory responses to normocapnic hypoxia and normoxic hypercapnia were assessed while subjects were connected to a rebreathing circuit through a mouthpiece, as previously described [17]. To measure the response to hypoxic normocapnia, a rebreathing bag containing a gas mixture of 7% CO_2, 23% O_2, and nitrogen balance was connected to the circuit. End-tidal CO_2 ($PETCO_2$) was kept constant by passing a portion of the expired air into a scrubbing circuit before returning it to the rebreathing bag. Ventilatory response to normoxic hypercapnia was assessed following a modified version of the Reid rebreathing method [35]. The rebreathing bag concentration of O_2 was brought to 50%, and oxygen saturation (SpO_2%) was maintained at a value of approximately 96%. To achieve this, the inspired oxygen fraction was constantly measured by means of a rapid oxygen sensor (Morgan Italia srl, San Lazzaro di Savena, Bologna, Italy). During both tests, $PETCO_2$ was continuously measured with a capnograph connected to the mouthpiece (LB2 Beckman, Fullerton, CA, USA), while SpO_2% was assessed by a pulse oximeter (pulsox 7, Minolta, Osaka Japan). Flow was continuously measured by a heated Fleisch pneumotachograph (MFP 1TS; Nihon Kohden, Tokyo, Japan) connected to a differential pressure transducer (RS part N 395-257; RS Components, Corby, UK) in series to the expiratory part of the rebreathing circuit. Baseline parameters were collected before each rebreathing test, and participants were asked to breathe room air through the mouthpiece while disconnected from the rebreathing circuit. RR, Vt, and Ve were measured breath to breath. The chemoreflex sensitivity to hypoxia or hypercapnia was obtained from the slopes of the linear regression of minute ventilation and SpO_2% or $PETCO_2$, respectively.

The ABG values were measured with the patient in the sitting position at rest, sampling the radial artery in room air conditions. Samples were analyzed by an automated, computerized micro blood gas and acid–base analyser (BG3, Instrumental Laboratory, Paderno Dugnano, Italy).

2.4. Statistical analysis

Data are presented as the mean and standard deviation (SD). Paired *t* test and Pearson's χ^2 test were performed to assess the differences between anthropometrical characteristics, respiratory function test, and ABG in healthy subjects and OSA patients, as appropriate. Analysis of variance for repeated measures was performed to establish changes in lung function in healthy controls and OSA patients during follow-up. The Tukey honestly significant difference test for unequal sample sizes (Spjötvall and Stoline test) was used to compare differences between groups considered in the analysis of variance.

The relationships between the variables were evaluated using the Spearman rank correlation. All statistical tests were two sided, and *P* values less than 0.05 were considered statistically significant. Data were analyzed using STATISTICA (data analysis software system), version 10 (StatSoft Inc. 2011, www.statsoft.com).

Given the pivotal and exploratory nature of the study and the absence of longitudinal data in the literature, we hypothesized that doubling the population of the study by Bennloch and coworkers [17] would allow us to detect long-term significant differences in the ventilatory function in patients with OSA treated with CPAP.

3. Results

A total of 156 patients with suspected OSA were screened, and 62 were enrolled in the study (59.7% men). A total of 71 patients were initially excluded because of a negative sleep study (40 patients), prevalent central apneas (12 patients), refusal to start CPAP

therapy (14 patients), and new diagnosis of neuromuscular disorders (five patients). An additional 23 patients were excluded because they had mild OSA (Fig. 1). The control group consisted of 48 healthy subjects (52.1% men). Ten patients were lost after 12 months of follow-up (Fig. 1). Baseline anthropometric characteristics, lung function, and blood gas parameters of patients with OSA did not differ from those of healthy controls (Table 1). The proportion of OSA patients on antipsychotics, benzodiazepines, and selective serotonin reuptake inhibitor antidepressants did not differ compared with those of healthy subjects (3%, 18.2%, and 6.1%, vs 2.8%, 16%, and 5%, respectively). BMI at baseline was similar in healthy controls and OSA patients (mean [SD], 25 [2] vs 26 [3] kg/m^2, $P = 0.694$). In OSA patients, BMI did not change during follow-up; the mean (SD) BMI at 12 months was 26 (2) kg/m^2.

As expected, at diagnosis, OSA patients had significantly higher AHI, desaturation time, and snoring time as compared with healthy subjects (Table 1).

The mean (SD) CPAP titration pressure was 10.5 (2.5) cmH_2O, and the average nighttime use of CPAP treatment was 8.0 (1.0), 7.5 (0.8), and 6.8 (1.5) hours per night after the 1, 3, and 12 months of follow-up, respectively. Of the 52 OSA patients who completed the follow-up, 40 (76.9%) had good compliance with CPAP treatment.

After the night of CPAP titration, patients with OSA experienced a significant improvement in nocturnal oxygenation, paralleled by a normalization of the event rate and snoring time, which appeared comparable to healthy subjects at the end of the follow-up period (Fig. 2). In patients with OSA, treatment with CPAP also significantly improved the mean nocturnal SpO_2 (Table 2). Conversely, no difference between healthy subjects and OSA patients was observed for PaO_2, $PaCO_2$, or HCO_3^- at baseline. The latter parameters did not change during the follow-up period (Table 2).

Compared with healthy subjects, patients with OSA showed an increased central respiratory drive at baseline as expressed with P0.1 or with Vt/Ti (Table 3 and Fig. 3). Both P0.1 and Vt/Ti progressively decreased with CPAP treatment, and this was paralleled by a reduction of Ve. The reduction in Vt/Ti and Ve was caused exclusively by a progressive reduction in Vt (Table 3 and Fig. 3), whereas RR and duty cycle remained stable during the follow-up period (Table 3).

At baseline, the normocapnic hypoxic ventilatory response was higher in patients with OSA compared with healthy subjects, and progressively and significantly decreased after the introduction of CPAP therapy (Fig. 4), whereas the normoxic hypercapnic ventilatory response did not differ between the two groups. The slope values of P0.1/Ve and P0.1/Vt/Ti were lower in OSA patients compared with healthy subjects, indicating a higher thoracic and inspiratory impedance (3.38 ± 0.8 vs 2.31 ± 0.9 and 0.36 ± 0.07 vs 0.19 ± 0.08, respectively; all $P < 0.05$).

In patients with OSA, the ventilatory drive, expressed as P0.1 and Vt/Ti, significantly and positively correlated with the AHI score and snoring time. Moreover, the hypoxic ventilatory response significantly correlated with ST90, ODI, and AHI (Table 4).

At the end of the follow-up period, 10 patients showed poor compliance whereas 42 patients had good compliance with the CPAP treatment. The respiratory drive and the inspiratory and thoracic impedance of patients with good compliance were comparable to those of healthy subjects, whereas patients with poor compliance did not demonstrate any significant change in the aforementioned parameters (Table 5).

Table 1
Anthropometric and lung function parameters in patients with obstructive sleep apnea and healthy subjects.

	Healthy (n = 48)	OSA (n = 62)	*P*
Sex, male/female	25/23	37/25	0.724
Age, yr	50 (12)	51 (11)	0.881
BMI, kg/m^2	25 (2)	26 (3)	0.694
VC, % predicted	87 (3)	88 (7)	0.986
FEV_1, % predicted	92 (9)	87 (3)	0.471
TLC, % predicted	104 (9)	103 (10)	0.762
$PaCO_2$, mm Hg	39 (2)	40 (2)	0.862
PaO_2, mm Hg	86 (3)	85 (5)	0.716
HCO_3^-, mmol/L	24 (2)	26 (3)	0.435
Nocturnal SpO_2, %	96 (2)	91 (2)*	0.002
ODI, events/h	3 (1)	34 (6)*	<0.001
ST90, %	3 (1)	22 (5)*	<0.001
AHI, events/h	2 (2)	38 (10)*	<0.001
Snoring time, %TST	6 (2)	42 (12)*	<0.001

Data are expressed as mean (SD) or as a proportion when appropriate.
BMI, body mass index; FEV_1, forced expiratory volume in 1 s; TLC, total lung capacity; VC, vital capacity.
*p<0.05.

4. Discussion

The main findings of the present study can be summarized as follows: (1) patients with moderate and severe OSA had an increased respiratory drive, paralleled by an augmented response to the hypoxemic stimulus and an abnormal increase in respiratory impedance compared with healthy subjects; (2) the breathing pattern of OSA patients differed from that of healthy volunteers only in Vt, which was significantly larger; (3) beginning with the first month of nocturnal CPAP therapy, OSA patients experienced a tendency toward a normalization of the hypoxic response and of the inspiratory and thoracic impedance with a reduction of the Ve during daytime, mainly due to a progressive reduction in Vt; and (4) the improvement in the latter physiological parameter is limited to patients with a good compliance to CPAP therapy (≥6 h/night).

An increase in the output drive in OSA patients has already been reported in the literature [16,22,36], but data were often limited to obese or obstructed patients. Our data suggest that in OSA patients, there is an increase in respiratory drive that persists in the morning hours, independent of the presence of obesity or bronchial obstruction [37,38].

In contrast to healthy subjects, OSA patients showed increased Ve, which was associated with a rise in Vt. The P0.1 was also increased, which could be considered a consequence of an increased baseline condition of the neuromuscular impulses trying to overcome the mechanical alterations that occur in such patients.

Recurrent upper airway obstruction increases inspiratory resistive load, increases diaphragmatic fatigue [39], and causes intermittent hypoxemia that has been shown to facilitate inspiratory muscle fatigue during inspiratory load [40]. Furthermore, sleep loss has been shown to impair inspiratory muscle endurance, which can be improved by restorative sleep [41].

As expected, the OSA patients recruited in the present study, who were normocapnic and without any conditions that could influence the ventilatory response (eg, hypertension, obesity, diabetes, or cigarette smoking) [29,42], did not have a different ventilatory response to hypercapnia as compared with healthy subjects. On the other hand, the increased ventilatory response to hypoxia could be explained by the chronic exposure to intermittent hypoxia due to upper airway obstruction, as was shown to occur both in animals and in humans [43]. Furthermore, physiologic studies [44] have demonstrated that acute intermittent hypoxia, but not sustained hypoxia, induces a long-term increase in respiratory motor output. The correlations between P0.1 and Ve and P0.1 and Vt/Ti (thoracic and inspiratory impedance), which express the efficiency of the thoracopulmonary system to convert the neuromuscular drive in ventilation or inspiratory flow, were slightly but significantly decreased in OSA patients compared with healthy

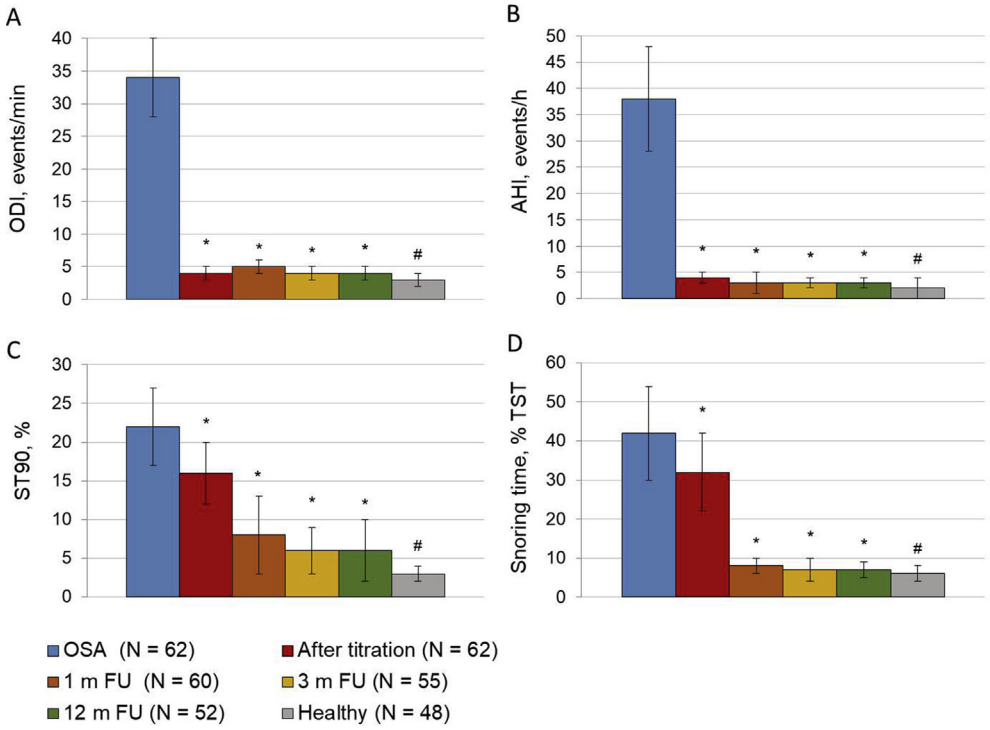

Fig. 2. Sleep study parameters in healthy subjects and patients with OSA. Baseline, following CPAP titration, and follow-up data are shown. (A) Oxygen desaturation index (ODI). (B) Apnea– hypopnea index (AHI). (C) Percentage of sleep time with peripheral oxygen saturation <90% (ST90). (D) Percentage of total sleep time with snoring events (%TST). Vertical bars represent standard deviation.

Table 2
ABG and nocturnal SpO_2 in healthy subjects and OSA patients at baseline and during the follow-up period.

	Healthy (n = 48)	OSA (n = 62)	OSA post-titration (n = 62)	1-mo (n = 60)	3-mo (n = 55)	12-mo (n = 52)	*P*
$PaCO_2$, mm Hg	39 (2)	40 (2)	41 (3)	40 (2)	38 (3)	39 (2)	0.714
PaO_2, mm Hg	86 (3)	85 (5)	86 (4)	85 (3)	86 (3)	86 (3)	0.826
HCO_3^-, mmol/L	24 (2)	26 (3)	27 (3)	27 (3)	25 (2)	25 (2)	0.311
Nocturnal SpO_2, %	96 (2)	91 (2)[a]	93 (3)[b]	95 (4)	96 (3)	96 (4)	0.173

Data are expressed as mean (standard deviation).
ABG, arterial blood gas; HCO_3^-, plasma bicarbonate; OSA, obstructive sleep apnea; $PaCO_2$, carbon dioxide arterial pressure; PaO_2, oxygen arterial pressure; ST90%, sleep time spent of SpO_2% <90%.
[a] (A) vs (B) at baseline ($P < 0.05$).
[b] OSA patients at baseline vs posttitration ($P < 0.05$).

controls. The efficiency of the inspiratory muscles in OSA patients can be reduced for at least two reasons: first, an obstructed airway and the subsequent asphyxia may lead to increased inspiratory efforts and hence the chronic overload of inspiratory muscles [45]; and second, the repetitive deoxygenation–reoxygenation pattern in OSA patients may induce free radical production and oxidative stress, causing muscle damage [46]. The indirect evidence of hyperstimulation of respiratory muscles is given by the increased

Table 3
Breathing pattern in healthy subjects and patients with OSA at baseline, after the CPAP titration, and during follow-up.

	Healthy (n = 48)	OSA (n = 62)	OSA after titration (n = 62)	1-mo Follow-up (n = 60)	3-mo Follow-up (n = 55)	12-mo Follow-up (n = 52)	*P*
Vt, mL	770 (235)	880 (202)[a]	850 (200)[b]	807 (198)[b,c]	795 (210)[b,c]	800 (206)[b,c]	0.001
Ti, s	1.50 (0.4)	1.49 (0.4)	1.51 (0.5)	1.49 (0.6)	1.52 (0.5)	1.50 (0.4)	0.751
Te, s	2.01 (0.8)	1.97 (0.7)	2.01 (0.9)	1.99 (0.9)	2.01 (0.8)	2.01 (0.8)	0.684
Ttot, s	3.51 (1.1)	3.46 (1.2)	3.52 (0.8)	3.48 (1.0)	3.53 (0.9)	3.51 (1.0)	0.592
Ti/Ttot	0.42 (0.5)	0.42 (0.6)	0.43 (0.7)	0.43 (0.8)	0.43 (0.6)	0.43 (0.7)	0.871
RR, events/min	18.0 (4.0)	18.3 (3.2)	18.1 (4.2)	18.9 (3.2)	18.3 (4.0)	18.0 (4.0)	0.218

Data are expressed as mean (standard deviation).
CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; RR, respiratory rate; Te, expiratory time; Ti, inspiratory time; Ttot, breathing cycle; Ve: minute ventilation; Vt: tidal volume.
[a] Post hoc comparison between healthy subjects and OSA patients at recruitment ($p < 0.05$).
[b] Post hoc comparison between OSA patients at recruitment ($p < 0.05$).
[c] Post hoc comparison with OSA patients after night of CPAP titration ($p < 0.05$).

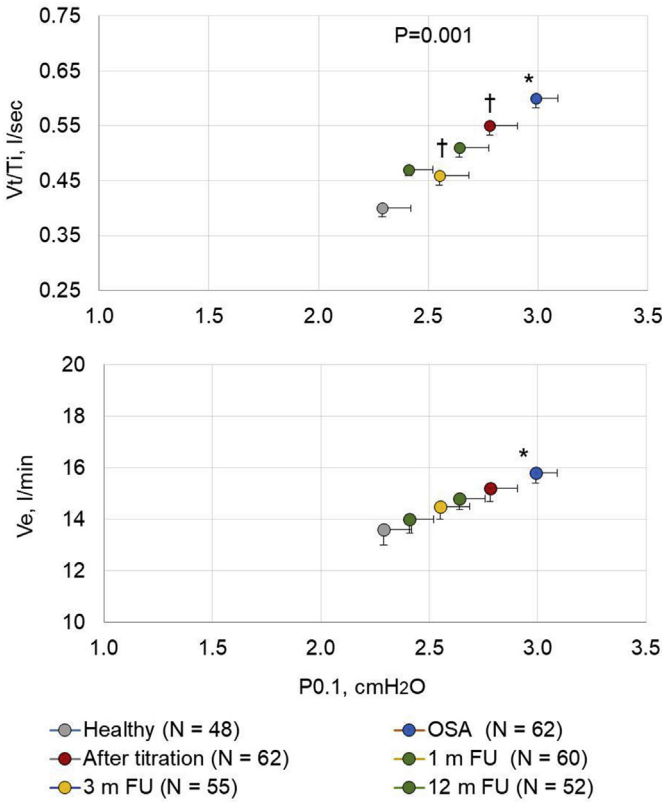

Fig. 3. Ventilatory drive in healthy subjects and patients with OSA. Baseline, following CPAP titration, and follow-up data are shown. Vertical and horizontal bars represent standard errors. CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; P0.1 = mouth occlusion pressure after 0.1 sec; Ti = inspiratory time; Ve = minute ventilation; Vt = tidal volume. *$P < 0.05$ vs healthy subjects; †$P < 0.05$ vs OSA patients at enrollment.

nocturnal energy expenditure in OSA patients that returned to normal after six months of CPAP treatment [47].

The correlation between P0.1 and VT/Ti with AHI, snoring time, ODI, ST90, and the hypoxic ventilatory response is well documented, since the increase of the respiratory work due to the presence of repeated apneas and oxygen desaturation affects the respiratory drive [25].

To our knowledge, this is the first study to investigate the long-term effect of CPAP treatment in terms of respiratory mechanics,

Table 4
Spearman rank correlation for ventilatory drive and polysomnographic parameters in patients with OSA.

AHI, events/h	*r*	*P*
VT/Ti	0.70	<0.001
P0.1, cm H_2O	0.73	<0.001
Snoring time, % TST		
VT/Ti	0.58	<0.01
P0.1, cm H_2O	0.60	<0.01
Hypoxic ventilatory response		
ST90, %	0.51	<0.05
ODI, events/h	0.70	<0.001
AHI, events/h	0.66	<0.01

Only significant correlations are shown.
AHI, apnea–hypopnea index; ODI, oxygen desaturation index; P01, mouth occlusion pressure; ST90%, sleep time spent of SaO_2% <90%; Vt/Ti, mean inspiratory flow.

breathing pattern, and chemoreflexes in a substantial number of normocapnic, nonobese patients with OSA. Our data are in contrast with those of a previous study by Lin [48], who demonstrated a reduced hypoxic drive at baseline only in hypercapnic OSA patients, whereas CPAP treatment had no effect on the sensitivity of the hypoxic and hypercapnic chemoreflex in eucapnic patients [48]. Similarly, Berthon-Jones and coworkers [20] studied 19 patients with OSA (10 of whom had daytime hypercapnia) and found that after two weeks of treatment with CPAP, only patients with hypercapnia had changed ventilation in response to the hypercapnic stimulus, whereas no changes were observed in normocapnic patients.

Finally, Verbraecken and colleagues [26] studied the hypercapnic ventilatory response in a small group of patients with OSA, and found a small but significant increase in the response compared with that in patients with untreated OSA.

Some important differences between the latter studies and ours may have influenced the results. In fact, beside the small sample size [20,26,48], most of the patients enrolled were obese (34.1 ± 2.1, [48]; 34 ± 1 [26]; 149 ± 15%, and 172 ± 5% of predicted weight in patients without and with baseline hypercapnia [20]).

Conversely, our results are in line with those published by Spicuzza and colleagues [25]. They studied 25 normocapnic patients with moderate to severe OSA and found a reduction in the hypoxic drive after a month of CPAP therapy, with no effect on the hypercapnic ventilatory response. However, the study sample was small (10 patients), follow-up was limited to one month, and healthy controls were not enrolled. Finally, data on respiratory drive in this study were lacking [25].

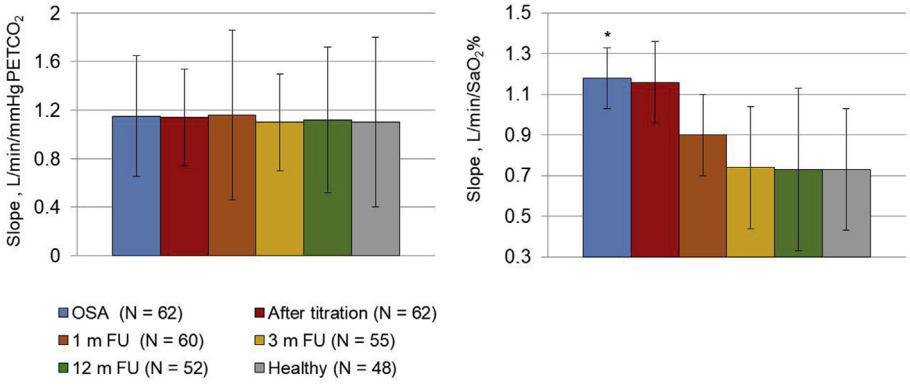

Fig. 4. Chemoreflex response in healthy subjects and obstructive sleep apnea (OSA) patients. Hypercapnic normoxic ventilatory response (left panel) and normocapnic hypoxic ventilatory response (right panel) in healthy subjects and patients with OSA at baseline, after CPAP titration, and during follow-up. Vertical bars represent standard deviation. *$P < 0.05$ vs healthy subjects.

Table 5
Ventilatory drive and thoracic and inspiratory impedance in healthy subjects at baseline and in patients with OSA at baseline and after 12 months of CPAP therapy.

	Healthy (n = 48)	<6 h/Night baseline (n = 10)	<6 h/Night 12-mo (b) (n = 10)	*p*	≥6 h/Night Baseline (n = 42)	≥6 h/Night 12-mo (a) (n = 42)	*P*	*P*[a] (Δa vs Δb)
V_t/T_i, L/s	0.40 (0.11)	0.60 (0.15)	0.53 (0.10)	0.094	0.59 (0.10)	0.41 (0.09)	0.001	0.043
P0.1, cm H_2O	2.29 (0.9)	2.99 (0.9)	2.60 (0.7)	0.145	2.98 (0.8)	2.36 (0.8)	0.002	0.038
Inspiratory impedance, cm H_2O/L/s	3.38 (0.8)	2.30 (0.9)	3.14 (0.7)	0.074	2.30 (0.9)	3.36 (0.6)	<0.001	0.041
Thoracic impedance, cm H_2O/L/m	0.36 (0.07)	0.19 (0.8)	0.25 (0.06)	0.089	0.19 (0.7)	0.36 (0.08)	<0.001	0.021

Data are expressed as mean (standard deviation). Patients are divided depending on poor (<6-h) or good (≥6-h) compliance with CPAP treatment. P values refer to parameters of OSA patients before and after CPAP treatment.
CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; P0.1, mouth occlusion pressure; Ti, inspiratory time; Ve, minute ventilation; Vt, tidal volume.
[a] Between-group changes.

Our study introduced, for the first time, compliance with CPAP as a determinant of treatment effect in OSA patients. Indeed, only patients with good compliance with CPAP (checked by smart card) experienced significant changes in respiratory drive and inspiratory impedance. This may also justify the similar results obtained by Spicuzza and colleagues, who reported a mean CPAP use of 6.0 ± 1.1 h per night [25]. In previous studies, a compliance with CPAP of ≥4 h per night has been considered acceptable. However, large prospective studies [50,51] have shown that a CPAP compliance of ≥6 h is preferable, in terms of reduction of both cardiovascular events and mortality. As pointed out by other authors [29], we considered that a cutoff of 6 h per night could be a clinical and mechanistically reasonable threshold to reflect changes associated with the CPAP intervention.

In OSA patients, the use of CPAP for >6 h night, which is associated with normalizing of AHI, ODI, snoring time, and ST90, may improve the efficiency of the inspiratory muscles, and within 12 months may return VT/Ti and P0.1 to values similar to those of healthy subjects.

The progressive reduction of the ventilatory response to hypoxia induced by CPAP treatment reflects a change in the chemoreflex sensitivity and not simply changes in blood gases, since Ve, SaO_2%, and $PaCO_2$ did not vary during the follow-up. In fact, previous studies have shown that peripheral but not central chemoreflex sensitivity is increased in eucapnic OSA patients [7,25]. In line with these results, we observed a restoration of normal nocturnal respiratory conditions with CPAP.

Our data confirm previous reports [52] that demonstrated how, in OSA patients, the normocapnic hypoxic ventilatory response positively correlates with the AHI and the nocturnal SaO_2%. Therefore, it appears conceivable that the normalization of nocturnal levels of PaO_2 may result in the recovery of the sensitivity of carotid bodies. Furthermore, in OSA patients, the increase in sympathetic activity reduces arterial baroreflex sensitivity [6,53]. It is also possible that the chronic reduction in baroreflex sensitivity observed in OSA patients may be linked to increased chemoreflex sensitivity [53]. Therefore, the decrease in sympathetic activity and the increase in baroreflex sensitivity induced by CPAP treatment [53–55] may be associated with a decrease in chemoreflex sensitivity.

We observed that treatment with CPAP allowed for a gradual improvement in the inspiratory and thoracic impedance at the end of 12 months of follow-up, with values very close to those measured in healthy subjects. This incomplete normalization of inspiratory and thoracic impedance despite CPAP therapy observed in our OSA patients could be due to inadequate CPAP compliance in about one-third (12/40) of our OSA patients. Further confirming this hypothesis, the present study showed that OSA patients with a compliance of ≥6 h per night had an inspiratory and thoracic impedance similar to that observed in healthy subjects. In this group of OSA patients, at the end of 12 months of CPAP therapy, only P0.1 remained slightly increased as compared with that in healthy subjects, likely because of persistently elevated upper airway resistance despite the normalization of AHI and snoring time [56], both of which were induced by bronchial and upper airway inflammation and possibly, in some cases, by a nonspecific bronchial hyperresponsiveness caused by the continuous CPAP airflow [57].

The present study has several limitations. The low number of patients in the poor compliance group limits the statistical inference and the possibility for further speculation on the effect of good compliance with CPAP in OSA patients. Obese subjects often represent a consistent proportion of patients undergoing sleep studies and CPAP therapy; these patients were excluded from the study to avoid a substantial effect of possible BMI reduction on pulmonary mechanics during the follow-up. Further prospective double-blind studies with broader inclusion criteria are warranted to better reflect real-life circumstances.

The coefficient of variation (CV) for breathing pattern parameters has been the object of thorough investigations. Data on CV values for volume, time, and respiratory drive in healthy subjects at rest have been published elsewhere [27,58], showing a reduced variability for the fractional inspiratory time and progressively higher CVs for respiratory rate and Vt/Ti. Furthermore, a recent model proposed by Jaworski and Bates [59] has demonstrated that the highest variability of breathing pattern CV is attributable to variations in airway resistance and impairment of gas exchange. The hypoxic ventilatory response was found to have a consistent repeatability and equal variability between individuals and between different days [60,61]. In our study, we performed repeated measurements in equal ambient conditions in a substantial number of patients over different months and found statistically significant changes in hypoxic drive, respiratory drive, and respiratory impedance during the follow-up period for treated OSA patients compared with healthy subjects. Unfortunately, according to the study design, healthy subjects underwent the physiological measurements only once at baseline; thus, a comparison between the mean CV for OSA patients and healthy controls would not be feasible.

The impact of the circadian system on OSA patients is still under investigation but has been demonstrated to influence apnea occurrence and duration [62]. We are aware that in animals, measurements of resting minute ventilation made in the morning and evening hours have produced discordant results [63], but in awake humans, the same measurements did not result in significant differences [64]. It is now accepted that ventilation and breathing pattern follow a circadian rhythm, with the night hours characterized by a drop in metabolic rate, a large decrease in Ve, and a slight increase in the alveolar and arterial partial pressures of CO_2 [65]. However, the correlation between variations in Vt and the

circadian patterns of parameters reflecting metabolism (eg, body temperature, activity, oxygen consumption, and carbon dioxide production) is still unknown. Respiratory impedance and mechanics have also been investigated in terms of circadian oscillations, as they are able to modify the downstream signal of the neural output and respiratory muscle activation. Lung volumes in healthy subjects are known to be affected by sleep. Airway resistance was found to increase during nighttime, with a negative peak during the early hours of the day and better values in the afternoon. This feature is especially evident in patients with asthma and chronic obstructive pulmonary disease and has been correlated with body temperature and cholinergic tone, although a clear causative relationship for those events is still obscure [63,66]. In patients with OSA, circadian rhythm plays a fundamental role in apnea/hypopnea initiation, with the longest events and lowest AHI demonstrated in the early morning, whereas in the afternoon/evening hours, the apnea events were shortest and the AHI highest [67]. The same was true for critical closing pressures [68]. Finally, chemosensitivity has also been shown to reflect a circadian pattern, with the highest sensitivity to both hypoxic and hypercapnic stimuli around 17:00 and the lowest at around 05:00. [69], with no effect on the metabolic rate and hence hyperventilation [63]. In our study, all respiratory tests (for both OSA patients and healthy subjects) were performed the morning after the PSG (only at baseline for the control group) between 09:30 and 12:00. The timing was based on outpatient clinic organization and patient availability. Considering that patients underwent the testing well outside the critical window of the early morning hours and that we compared tests performed in similar daytime conditions for all follow-up visits, we believe that the effect of the time of the day, if present, could be reasonably low for baseline values, without jeopardizing the significant differences in breathing pattern and chemosensitivity obtained during the follow-up in OSA patients.

5. Conclusion

Our data suggest that in OSA patients, there is an increase in respiratory drive that persists even in the morning hours, independent of the presence of obesity or bronchial obstruction.

We hypothesize that the increase in respiratory drive stimulates respiratory muscles in OSA patients and results in a reduced efficiency due to the increase in the inspiratory resistive load, diaphragmatic fatigue, and the frequent intermittent hypoxemia.

The hyperstimulation of the ineffective respiratory musculature may result in the increase in the impedance of the thoracopulmonary system that is resolved only after long-term CPAP therapy.

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Conflict of interest

The authors declare that they have no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.05.019.

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