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ORIGINAL ARTICLE

Short- and long-term effects of CPAP on upper airway anatomy and collapsibility in OSAH

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Abstract
Rationale and aim In obstructive sleep apnea hypopnea (OSAH) patients, an increase of upper airway (UA) collapsibility has been described together with a reduced UA caliber due to inflammation, edema, and fat accumulation in pharyngeal walls. CPAP is the main treatment of OSAH and acts mechanically by increasing pressure inside UA. The aim of this study was to assess the short- and long-term effects of CPAP on UA caliber and collapsibility in severe OSAH patients.
Patients and methods Ten obese patients (nine male, age 55± 9 yr, BMI 35.1 ± 6.1, Epworth sleepiness scale 12.3 ± 3.6 point, AHI 58.8 ± 27.1) had measurements of oropharingeal junction area (OPJ), mean pharyngeal area (APmean), maximal pharyngeal area (APmax) by acoustic pharyngometry and determination of expired volume in the first 0.5 s after the application at the mouth of −5 cmH_2O negative expiratory pressure ($V,NEP_{0.5}$) during wakefulness in the supine position under basal conditions (baseline) and after 1 week and 6 months of CPAP treatment.
Results OPJ was 0.74 ± 0.28 cm^2 at baseline, 0.90 ± 0.24 cm^2 after 1 week and 1.05 ± 0.31 cm^2 after 6 months (1 week and 6 months vs baseline $p < 0.05$). APmax was 2.28 ± 0.74 cm^2 at baseline, 2.79 ± 0.90 cm^2 after 1 week and 2.94 ± 0.33 cm^2 after 6 months (1 week and 6 months vs baseline $p < 0.05$). APmean was 1.43 ± 0.46 cm^2 at baseline, 1.82 ± 0.45 cm^2 after 1 week and 1.94 ± 0.35 cm^2 after 6 months (1 week vs baseline $p < 0.01$; 6 months vs baseline; $p < 0.05$). $V,NEP_{0.5}$ was 290 ± 73 mL at baseline, 291 ± 65 mL after 1 week and 338 ± 67 mL after 6 months (6 months vs baseline $p < 0.05$; 1 week vs 6 months $p < 0.01$).
Conclusions Our data suggest that CPAP treatment might be effective in OSAH patients not only by causing a mechanical splint of UA but also by inducing an improvement on anatomical (early) and functional (later on) aspects of UA that can be observed during wakefulness.

Keywords CPAP · Upper airway caliber · Upper airway collapsibility · OSAH

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Introduction

In patients with obstructive sleep apnea hypopnea (OSAH) MRI studies have shown upper airway (UA) caliber reduction due to enlargement of the soft tissue, including tongue, uvula, tonsillar pillars, soft palate, blood vessels, lymphoid tissue, pharyngeal fat pads, muscles, and pharyngeal mucosa [1]. Soft tissue edema is considered as largely responsible for this thickening [2], possibly resulting from inflammation due to chronic trauma caused by the tissue vibration during snoring [3] and from increased neck veins pressure [4]. More easily and rapidly than MRI [5], acoustic pharyngometry can be used to assess the UA caliber [6] and its change in OSAH patients [7].

Increased intrinsic UA collapsibility that is generally observed in OSAH patients [8] is due to decreased transmural pressure and increased pharyngeal wall compliance. In normal awake subjects, the application of small

negative expiratory pressure (NEP) transients at the beginning of resting expiration does elicit neither reflex activity of genioglossus nor changes in UA resistance [9]. Under these conditions, the flow dynamics in early expiratory phase during NEP application are thought to reflect the mechanical behavior of the pharyngeal airway with a very low dilating muscle tone even during wakefulness. Therefore, the volume exhaled at the mouth during the first 0.5 s after application of NEP ($V,NEP_{0,5}$) at the onset of resting tidal expiration might be useful to estimate the degree of UA collapsibility [10] and its changes during CPAP in OSAH patients.

There is clear evidence that CPAP, working as a pneumatic splint to relieve UA obstruction during sleep, eliminates respiratory events [11], and reduces sleepiness in OSAH patients, with an improvement on the quality of life indices [12]. Persistence of a positive effect on respiratory events during sleep, however, has been shown also in the first night after CPAP treatment interruption [12], probably due to a sustained reduction of soft tissue edema and inflammation [13].

The aim of this study was to assess the effect of domiciliary CPAP on UA caliber and collapsibility in CPAP-naive OSAH patients during wakefulness in the supine position after short- and long-term period of treatment.

Materials and methods

Subjects

The patients were recruited from our Sleep Laboratory between June 2005 and March 2006. All patients with a sleep study showing severe OSAH (apnea-hypopnea index [AHI] >30) and naive to treatment were considered for the study. We excluded those with obvious anatomical defects such as cranio-facial and/or severe otorino-laryngoiatric abnormalities, or with neurological and endocrine diseases known to be causally associated with OSAH. Patients were not treated with drugs active on the central nervous system or suffered from chronic alcoholism. All patients, before being enrolled, underwent arterial blood gases analysis and spirometry in order to exclude the presence of resting hypercapnia ($PaCO_2 \geq 45$ mmHg) and/or ventilatory dysfunction. The presence of tidal intra-thoracic expiratory flow limitation (EFL) was excluded using the NEP technique.

The study was approved by the local Ethic Committee and all patients gave written informed consent.

Study protocol

During the afternoon before the overnight CPAP titration, the enrolled patients underwent evaluation of UA caliber by acoustic pharyngometry and UA collapsibility by NEP technique in the supine position during wakefulness. These measurement were repeated in the same conditions after 1 week and after 6 months of home treatment with CPAP. During the follow-up period, the patients' adherence to the CPAP treatment was assessed by downloading data from CPAP device and analyzing them by means of Compliance Maximizer Software (Fisher & Paykel, New Zealand).

Methods

Sleep study Embletta pds recorder (Flaga^{hf} Reykjavik, Iceland) was used to perform both the diagnostic sleep study and the CPAP titration sleep study to determine the optimal pressure to control OSAH. The CPAP device used was "CPAP Fisso HC221LE". Apnea was defined as a cessation of airflow at the nose and at the mouth for at least 10 s. Hypopnea scored as a decrease for at least 10 s of the amplitude of the ribcage and of the abdomen motion signals to less than 70% of the basal level before the event coupled with a fall of oxyhemoglobin saturation of 4% or more.

Arterial blood gas analysis Arterial blood gas (ABG) analysis was performed in sitting position before any pulmonary function test.

Spirometry A computerized water-sealed light-bell Stead-Wells spirometer (Biomedin, Padova, Italy) was used to perform pulmonary function testing (spirometry and maximal flow–volume curves). All the spirometric tests employed in the study fulfilled the ATS recommendations [14].

Acoustic pharyngometry UA anatomy was evaluated in the supine position by means of acoustic pharyngometry ('Eccovision' Hood Laboratories, Pembroke, MA, USA). It uses acoustic reflection (AR) technology to assess cross-sectional areas from the oral cavity to hypopharynx by calculating changes in acoustic impedance that occur along these UA with variable caliber. This technique is fully described elsewhere [7]. We obtained traces that represent UA cross-sectional area (UA-XSA) versus distance down the airway. Four technically acceptable traces (variability $\leq$ 10%) were taken at the end of resting expiration. Three UA-XSA were read off the traces: oropharyngeal junction (OPJ) represents the area of the junction between the back of the oral cavity and the oropharynx; maximal pharyngeal area (APmax) is the maximum area in the oropharynx, generally found behind the tongue radix; mean pharyngeal area (APmean) represents the mean area from the OPJ to the glottis. OPJ and APmax, representing the narrowest and the widest sections of the pharynx respectively, can be used as indicators of UA morphology, while APmean represents

a complete evaluation of pharyngeal caliber [15–17]. This technique has been validated against magnetic resonance imaging for assessment of the UA-XSA [5].

NEP test UA collapsibility was assessed by computing the volume exhaled at the mouth during the first 0.5 s of application of −5 cmH_2O NEP ($V,NEP_{0.5}$) [10]. This technique is fully described elsewhere [9]. Briefly, NEP was applied in the seated position and 10 min after assuming the supine position. In each position at least five NEP breath-tests were performed at intervals of five to ten respiratory cycles, always when the patient had resumed regular breathing. Initially, intra-thoracic tidal EFL was excluded in either position by the NEP technique checking that the flow during NEP was never superimposed on the flow during previous control tidal expiration. Then, the expiratory flow under each NEP application was recorded in order to compute, by time integration, the volume exhaled in the first 0.5 s. after the NEP start, henceforth labelled $V,NEP_{0.5}$ (Fig. 1). Subsequently, the mean value of $V,NEP_{0.5}$ was calculated, after discarding the highest and the lowest value, by averaging those obtained during at least three acceptable NEP maneuvers.

Statistical analysis

Analysis of variance for repeated measurements was performed. If significant variance was observed, paired *t*-test was performed after checking the normality of the data sets. Relationships between changes in $V,NEP_{0.5}$, OPJ, APmax, and APmean after 1 week and 6 months of CPAP treatment were examined by Pearson correlation. A $p < 0.05$ was considered significant. Data are presented as mean ± SD. Statistical analysis was performed using SPSS for Windows software version 13.0 (SPSS, Inc, Chicago, IL, USA).

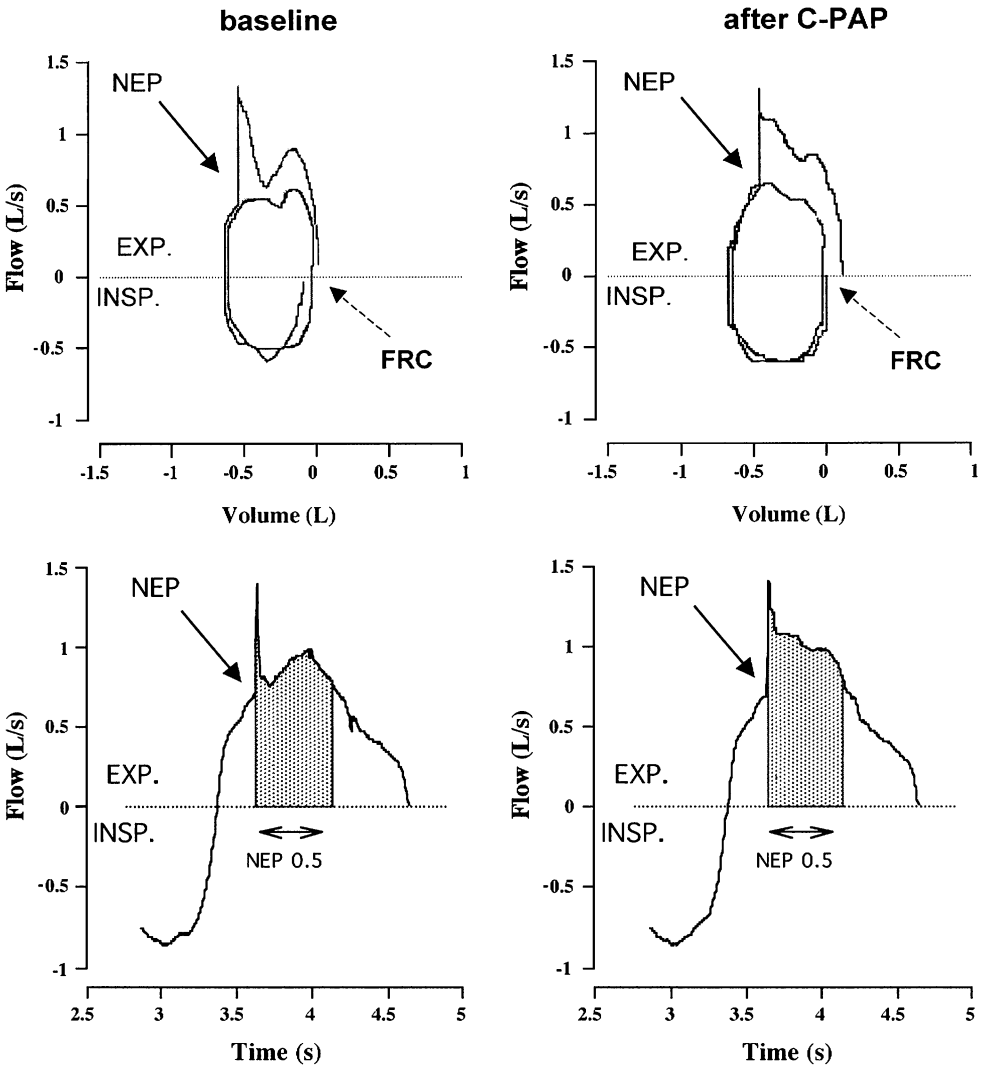

Fig. 1 Supine tidal flow–volume curves (control and during NEP of −5 cm H_2O) and corresponding flow–time curves (only during NEP) in a representative OSAH patient before and after 6-month treatment with CPAP. The hatched areas under the flow measure the volume exhaled in the first 0.5 s ($V, NEP_{0.5}$) after NEP application (*FRC* = functional residual capacity)

Results

Ten obese patients (nine male) aged 55 ± 9 year were enrolled and completed the study. Anthropometric characteristics at baseline and after 6 months of CPAP treatments are shown in Table 1. Two patients were current smokers, nine were treated for hypertension and five were diabetics without autonomic neuropathy. ABG analysis and pulmonary function tests were normal. The AHI was 58.8 ± 27.1, the percentage of time of sleep spent with an oxyhemoglobin saturation less than 90% and 80% was 38.8 ± 0.3% and 11.6 ± 0.2%, respectively. The level of CPAP applied to control OSA was 9.6 ± 1.2 cmH_2O. During 6 months CPAP usage was 85 ± 2.7% of the days. Compliant days (usage >4 h) were 81 ± 6.3%. Average compliance in the compliant days was 5.9 ± 0.8 h per night and average compliance for all days was 5.4 ± 1.1 h per night. The ESS decreased significantly after 6 months of CPAP treatment (from 12.3 ± 3.6 to 6.1 ± 4.1, $p < 0.01$).

There was a significant increase of OPJ, APmax, and APmean after 1 week of CPAP treatment, but no difference was found between 1 week and 6 months. On the contrary, $V,NEP_{0.5}$ decreased significantly only after 6 months. Values of OPJ, APmax, APmean, and $V,NEP_{0.5}$ at baseline, after 1 week and after 6 months of CPAP treatment are labelled in Table 1 and graphically shown in Fig. 2.

No correlations was found between changes in the UA caliber (OPJ, APmax, APmean) and changes in the UA collapsibility ($V,NEP_{0.5}$) after 1 week and after 6 months of CPAP therapy.

A subgroup of five patients was restudied after a longer period of CPAP treatment (22 ± 3 months). In these patients UA caliber and collapsibility were reassessed before and after 1 week of CPAP withdrawal. We chose these patients according to compliance to CPAP treatment and body weight stability (BMI, 34.3 ± 5.8 vs 35.3 ± 6.4 kg/m^2 at baseline). It is interesting that the withdrawn of CPAP treatment for 1 week in this sub-group induced a clear reduction of APmean (1.79 ± 0.38 vs 1.44 ± 0.39 cm^2,—at baseline 1.46 ± 0.53 cm^2) OPJ (0.99 ± 0.23 vs 0.83 ± 0.38 cm^2,—at baseline 0.66 ± 0.17 cm^2) and APmax (2.67 ± 0.61 vs 2.13 ± 0.61 cm^2,—at baseline 2.19 ± 0.83 cm^2), while $V,NEP_{0,5}$ (342 ± 93 vs 337 ± 66 mL,—at baseline 250 ± 63 mL) showed no change.

Discussion

The main purpose of this study was to evaluate the changes of UA caliber and collapsibility in awake supine OSAH patients after short-term (1 week) and long-term (6 months) treatment with CPAP. Following the application of CPAP the acoustic measurements of UA caliber improved after 1 week, remaining unchanged at 6 months, while $V,NEP_{0,5}$, that inversely reflects UA collapsibility, increased only after 6 months. Changes of indices of UA caliber and collapsibility did not correlate, suggesting two independent effects elicited by the CPAP treatment. This hypothesis seems to be corroborated by the different time-course of these modifications. In fact, the enlargement of UA occurs quickly and is detectable already in the first week according to the AR technique, indicating a rapid reduction of soft tissue edema to explain greater UA caliber [13]. Conversely, the reduction of UA collapsibility, as reflected by the $V,NEP_{0.5}$ increase, takes more time to be obtained, likely ensuing from different mechanisms possibly related to more efficient structure and function of UA dilating muscles [18, 19].

Differently from other previous studies [13, 20] in obese OSAH patients, we assessed simultaneously UA anatomy and collapsibility both after short- and long-term application of nasal CPAP showing clear different dynamics in their improvement.

Upper airway cross-sectional area (UA-XSA), whether assessed by acoustic pharyngometry, CT, or MRI, is usually smaller in awake patients with OSAH than in normal subjects and correlates inversely with the AHI [18]. UA

Table 1 Anthropometric, anatomical and functional characteristics of ten patients at baseline, after 1 week and 6 months of CPAP treatment

	Baseline	After CPAP (1 week)	After CPAP (6 months)
Weight, kg	99.5 ± 15.2	–	96.9 ± 14.9
BMI, kg/m^2	35.1 ± 6.1	–	34.1 ± 5.7
Neck circumference, cm	46.8 ± 6.5	–	44.7 ± 3.3
OPJ, cm^2	0.74 ± 0.28	0.90 ± 0.24*	1.05 ± 0.31*
APmax, cm^2	2.28 ± 0.74	2.79 ± 0.90*	2.94 ± 0.33*
APmean, cm^2	1.43 ± 0.46	1.82 ± 0.45**	1.94 ± 0.35*
$V,NEP_{0.5}$, mL	290 ± 73	291 ± 65	338 ± 67* #

OPJ Cross-sectional area at the oropharyngeal junction, *APmax* maximum pharyngeal cross-sectional area; *APmean* mean cross-sectional area from the OPJ to the glottis; *$V,NEP_{0.5}$* volume exhaled during first 0.5 s following the NEP application (−5 cmH2O). Data are mean ± SD
*$p < 0.05$ vs baseline; **$p < 0.01$ vs baseline; #$p < 0.01$ vs 1 week

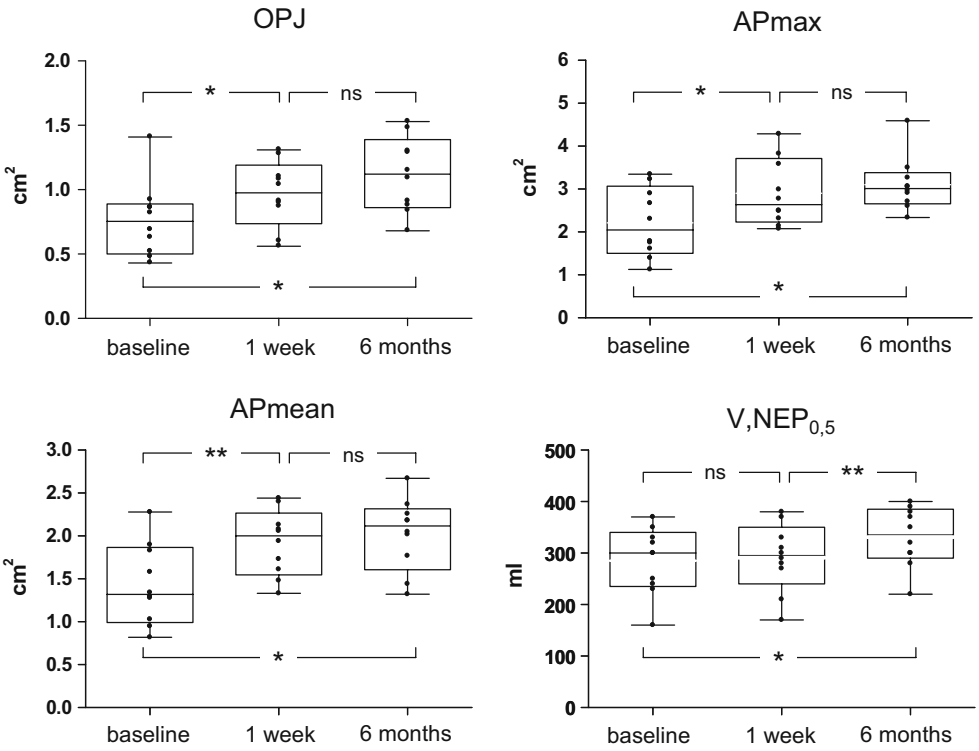

Fig. 2 Values of volume exhaled at the mouth during first 0.5 s. following the NEP application (−5 cmH2O) (V,$NEP_{0.5}$), and measurements of oropharyngeal junction area (OPJ), maximum pharyngeal area (APmax) and mean cross-sectional area from the OPJ to the glottis (APmean) are shown at baseline, after 1 week and 6 months of CPAP treatment. The boundary of the *boxes* closest to zero indicates the 25th percentile, the *line* within the box marks the median, and the boundary farthest to zero indicates the 75th percentile. *Whiskers* above and below the box indicate the 95th and 5th percentiles (*$p < 0.05$; **$p < 0.01$)

narrowing is often caused by increased surrounding soft tissue due to edema, inflammation, and fat accumulation in the lateral pharyngeal walls. UA-XSA is inversely related to thickness of the lateral pharyngeal walls [1]. Pharyngeal mucosal edema has been ascribed to inflammatory changes secondary to vibration-induced trauma occurring during snoring [21, 22]. As a result, compared to age- and weight-matched controls, OSAH patients have higher UA resistances and compliance [23]. Furthermore, their UA are more collapsible when exposed to negative pressure during wakefulness, or during sleep [24, 25].

The efficacy of nasal CPAP relies on the degree of positive pressure applied to the upper airway. Sullivan originally proposed that nasal CPAP acts as a 'pneumatic splint' into the upper airway [26]. It has been observed that also 'tracheal tug' due to lung volumes (namely functional residual capacity) increase could stretch and stabilize pharyngeal walls [27]. Moreover, some evidence is provided that the effect of CPAP is not only related to the physical enlargement of the upper airway caliber since some studies indicate that OSAH patients show an improvement of their disease even if CPAP is discontinued after a period of chronic treatment [12, 28]. Previous studies found an increase of UA caliber during wakefulness after long-term CPAP treatment using CT and MRI [2, 20]. This was attributed to the reduction of the UA edema and mucosa inflammation because of removal ceasing and disappearance of repeated mechanical trauma induced by marked intraluminal pharyngeal pressure swings during upper airway collapse.

In our study we assessed UA caliber changes using AR technique that provides instantaneous measurement independent from breathing pattern. Although AR cannot assess the retro-palatal pharynx, the segment most susceptible to collapse during sleep, the variations of OPJ area may provide an indirect estimation of retro palatal area changes, both areas being affected by the possible swelling of soft palate and tongue. There is a second main site that often collapses in OSAH located behind the tongue radix that corresponds to the AR parameter named maximum pharyngeal area (APmax), the greatest area in normal hypopharynx. In this study we found that patients exhibited a rapid and progressive enlargement of OPJ and APmax after CPAP treatment.

Increased UA collapsibility in OSAH patients tends to promote UA narrowing when low negative pressure is applied at the mouth during NEP test, so reducing V,$NEP_{0,5}$ values as compared with controls [10]. In this study we observed that V,$NEP_{0,5}$ increased after 6 months of treatment with CPAP, but not after 1 week.

Recently, Boyd has demonstrated that inflammatory cell infiltration and denervation changes affect the UA mucosa and muscles of patients with OSAH [29]. It is important to recognize that inflammatory cell infiltration of skeletal muscles, together with the production of proinflammatory mediators, such as cytokines and oxygen free radicals, can cause significant muscle weakness, neural toxicity, and denervation. These abnormalities could prevent dilating muscles activity to maintain UA patency during sleep. In

OSAH patients an abnormally high ratio of type IIa fatigue-susceptible to type I fatigue-resistant fibers has been described and treatment of OSAH with long-term CPAP was able to reduce the proportion of type IIa fibers [30]. In addition, intermittent hypoxia may provoke the shift to a more fatigable fiber type in OSAH patients [31].

Limitations of the study First, there was no control group in the study. This was due to the fact that the Ethics Committee of our Institution did not allow a sham treatment because of the OSAH severity of these patients and length of the study. On the other hand, it is highly improbable that measurements obtained by objective techniques such as AR and NEP could be influenced by the chance rather than CPAP treatment in the absence of significant BMI variations. Secondly, the UA collapsibility and its changes were assessed by applying a small negative pressure at the mouth at the beginning of tidal resting expiration, looking at the exhaled volume in the first 0.5 s. The NEP technique is an indirect method to study the UA mechanical behavior that, however, has been frequently used to distinguish among normals, snorers, and OSAH patients [10, 32–35]. Although different NEP-related parameters have been adopted to measure the amount of collapse of the upper airways suddenly exposed to negative pressure, the results of all these studies indicate that this technique is able to detect abnormal tendency to narrowing of UA in the presence of OSAH. So we are confident that V,$NEP_{0.5}$ values may well reflect the degree of UA collapsibility and its longitudinal change in the same individuals with OSAH.

Further studies will be required to verify how long the favorable, anatomical and functional, changes we found in the upper airways by applying CPAP can last in OSAH patients once CPAP treatment is withdrawn to envisage an alternate-day CPAP therapy or its interruption during the week-end period.

In this respect, interesting results were recently reported in a group of 20 moderate-to-severe OSAH patients with BMI of 36 ± 6, treated with CPAP for at least 12 months and with self-reported nightly use >4 h. In these subjects, the withdrawal from CPAP treatment for a week was shown to induce a progressive worsening of AHI, nightly SaO2 and daytime sympathetic activity, as measured by urinary noradrenaline (UN), with no changes in circulating levels of cytokines or vascular endothelial growth factor [36]. However, deterioration of AHI and SaO2 (not of UN) was present in the first night after CPAP suspension only on half of the patients, resulting more marked for the majority of them after 7 days. These results suggest a time-dependent, not abrupt disappearance of the beneficial effects of CPAP treatment in OSAH that likely cannot be limited to a simple splint mechanism. Moreover, in a subgroup of our patients the interruption of the CPAP therapy for 1 week showed a rapid UA anatomical derangement while the improvement of UA collapsibility was still maintained

In summary, the findings of this study show that the local effect of CPAP in obese patients with OSAH is not confined to a temporary UA dilation caused by its mechanical action but also to anatomical and functional improvement that can be perceived even during wakefulness. The former, that is increased UA caliber, is detectable after few days, the latter, which is decreased UA collapsibility, only after a relatively long-term treatment with CPAP.

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Conflict of interest statement None of the authors have a conflict of interest to declare in relation to this work.

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