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Impact of CPAP on asthmatic patients with obstructive sleep apnoea

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ABSTRACT: The impact of continuous positive airway pressure (CPAP) treatment on the airway responsiveness of asthmatic subjects with obstructive sleep apnoea (OSA) has scarcely been studied.

A prospective study was performed comparing the changes in airway responsiveness and quality of life in stable asthmatic OSA patients, before and 6 weeks after their nocturnal CPAP treatment.

A total of 20 subjects (11 males and nine females) participated in the study. With the nocturnal CPAP treatment, the apnoea/hypopnoea index dropped from 48.1±23.6·h^{-1} to 2.6±2.5·h^{-1}. There were no significant changes in airway responsiveness after CPAP treatment (provocative concentration causing a 20% fall in forced expiratory volume in one second (FEV_1; PC_{20} 2.5 mg·mL^{-1} (1.4–4.5)) compared with baseline (PC_{20} 2.2 mg·mL^{-1} (1.3–3.5)). There was no significant change in FEV_1 either. However, the asthma quality of life of the subjects improved from 5.0±1.2 at baseline to 5.8±0.9 at the end of the study.

In conclusion, nocturnal continuous positive airway pressure treatment did not alter airway responsiveness or forced expiratory volume in one second in subjects with stable mild-to-moderate asthma and newly diagnosed obstructive sleep apnoea. However, nocturnal continuous positive airway pressure treatment did improve asthma quality of life.

KEYWORDS: Airway responsiveness, asthma, asthma quality of life, continuous positive airway pressure, obstructive sleep apnoea

The prevalence of asthma varies widely depending on the country studied [1]. In Canada, the 1998/1999 National Population Health Survey reported a prevalence of physician-diagnosed asthma in 8.4% of the overall population [2]. The estimated prevalence of sleep nocturnal breathing disorder, defined as an apnoea/hypopnoea score $\geqslant$15·h^{-1}, is 4% in females and 9% in males [3].

Asthma and obstructive sleep apnoea (OSA) syndrome are two prevalent diseases that may coexist [4] and adversely affect health-related quality of life [5]. A high body mass index (BMI) may be an impediment in both conditions [6]. Furthermore, nasal symptoms and gastro-oesophageal reflux that are often reported in OSA [7, 8] may exacerbate asthma [9, 10]. In patients suffering from both conditions, nocturnal breathing disorder may be related to asthma, OSA or both [11, 12].

It is well known that continuous positive airway pressure (CPAP) is the most effective treatment for OSA [13]. It has also been reported to be effective in reducing nocturnal asthma attacks in asthmatic and apnoeic patients [14–16]. Two studies reported an improvement of airway responsiveness with CPAP treatment in four out of 20 apnoeic nonasthmatic patients [17] and in nine stable asthmatic nonapnoeic patients [18], respectively. However, a deleterious effect of CPAP on airway responsiveness was reported in six out of 31 OSA patients [19]. To the best of the present authors' knowledge, no study has specifically evaluated the effects of CPAP treatment on airway responsiveness of asthmatic OSA patients.

The primary aim of the present prospective study was to observe the changes in airway responsiveness in stable asthmatic OSA patients before and 6 weeks after CPAP treatment. The secondary aim was to study the impact of CPAP on quality of life specific to asthma (QOLAs) and OSA (QOLAp).

MATERIAL AND METHODS

Study design

Before entering the study, subjects underwent three serial methacholine inhalation challenges measured 2–3 days apart. Baseline QOLAs and

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QOLAp questionnaires were completed. An atopic status was assessed using skin-prick tests to common inhalants. Gastro-oesophageal symptoms and/or antireflux medication usage were assessed by way of open questionnaires.

CPAP titration was completed during a full-night polysomnography (PSG). Afterwards, CPAP treatment was started at home. After the second and fourth week of nocturnal treatment with CPAP, patients were contacted by the research nurse to verify the control of their asthma and their adaptation to the CPAP treatment.

After 6 weeks of nocturnal treatment with CPAP, objective CPAP utilisation was determined by downloading information from the CPAP unit. An in-laboratory PSG was repeated with CPAP therapy as prescribed at home. The airway responsiveness and QOLAs and QOLAp questionnaires were reassessed as performed at baseline.

Subjects

Individuals aged $\geqslant$18 yrs with stable asthma and a new diagnosis of OSA syndrome were considered for enrolment in two centres (Sacre-Coeur Hospital, Montreal and Laval Hospital, Quebec, QC, Canada) between October 2001 and March 2005. The study was approved by the research ethics committee of each participating centre. All subjects gave their written consent.

Inclusion criteria

Asthma was defined according to the American Thoracic Society (ATS) criteria [20]. Acceptable asthma control was defined by occasional respiratory symptoms and absence of asthma exacerbation without changes in the maintenance therapy in the month preceding the study. All subjects showed airway responsiveness defined by a provocative concentration of methacholine causing a 20% fall in forced expiratory volume in one second (FEV_1) $\leqslant 8$ mg·mL^{-1} (PC_{20}).

All patients complained of symptoms suggestive of OSA syndrome and their apnoea/hypopnoea index (AHI) was determined during one in-laboratory PSG, the recording of which was $\geqslant 15 \cdot h^{-1}$.

Exclusion criteria

Initially, subjects were not eligible to continue the study when the variation between the lowest and the highest measure of PC_{20} was more than two dilutions. This assumed that their asthma was not optimally controlled or that the methacholine challenge could not be reproduced in these patients.

Withdrawal criteria

No changes in the patients' maintenance therapy for asthma were allowed during the study (which included changes in inhaled or systemic steroids, long-acting inhaled β_2-agonists, theophylline or leukotriene receptor antagonists) nor were the addition of steroids in nasal vaporisation and/or medication against gastro-oesophageal reflux.

Patients were withdrawn during the course of the study when compliance to their CPAP treatment was considered inadequate (average daily use <4 h·night^{-1}) or when asthma exacerbations unrelated to CPAP use occurred (*e.g.* respiratory tract infection, allergenic exposure and recurrence of smoking).

Methacholine challenges

Spirometry was performed according to the ATS standards [21]. Methacholine challenges were performed according to previously described standardised techniques [22].

Sleep studies

Initial PSG recordings consisted of in-laboratory continuous acquisition of electroencephalogram, electro-occulogram, submental electromyogram, arterial oxyhaemoglobin saturation by transcutaneous pulsed oxymetry, naso-oral airflow with thermistors, nasal pressure with nasal cannula, chest and abdominal movements by impedance plethysmography (Respitrace^{TM}; Ambulatory Monitoring Inc., Ardsley, NY, USA), ECG and breathing sounds. Sleep position was continuously assessed by the attending technician using an infrared camera. All variables were digitally recorded (Sandman Elite^{TM} System; Mallinckrodt, Kenilworth, NJ, USA). Sleep and respiratory variables were manually scored according to standard criteria [23].

During the CPAP titration sleep study, airflow was recorded *via* a pneumotachograph connected to a tightly fitting nasal CPAP mask. The titration procedure was manually completed by the attending technician, who adjusted the pressure level in order to abolish apnoeic and hypopnoeic obstructive events, snoring and inspiratory flow-limited events (effective pressure level).

CPAP apparatus

The units used at home (Fisher-Paykel, Auckland, New Zealand) were set at the effective pressure level. All the CPAP devices included a heated humidifier (ambient tracking), a ramp function and a micro-processor allowing for time of usage measurement. A nasal or a facial mask could be used.

Quality-of-life questionnaires

Validated QOLAs and QOLAp questionnaires were used [24, 25]. Scores were reported on a scale of 1–7, with higher scores equating to better quality of life. The QOLAs questionnaire was divided into four sections: emotional function, environmental stimuli, symptoms and activity limitation.

Data analysis

All values were expressed as mean$\pm$SD. PC_{20} values were log-transformed and the mean of the three serial methacholine challenges before and after CPAP was calculated on this transformation to get one representative value before and after CPAP. Statistical results from PC_{20} before and after treatment were expressed with the log-transformed values as the geometric means (average of three individual geometric means before and after CPAP) and 95% confidence interval (CI). Different correlations were examined by a Spearman rank-order test. Significance was accepted at the level of 95%.

RESULTS

In total, 33 patients were invited to participate in the study. Six were excluded due to the high variability of their PC_{20} results during the screening visits. Seven were withdrawn during the study due to CPAP use <4 h·night^{-1} (n=3), an upper respiratory tract infection (n=2), resumed smoking (n=1) or elective orthopaedic surgery (n=1). A total of 20 patients completed the study. The baseline characteristics of these

TABLE 1 Characteristics of the subjects at baseline

Characteristics	Completed the study	Did not complete the study
Subjects n	20	13
Age yrs	49±9	52±11
Male/female	11/9	9/4
BMI kg·m^{-2}	37±9	41±7
Smoker status		
Current smoker	1	3
Ex-smoker	11	6
Pack-yrs[#]	22±19	36±26
GERD[¶]	6	2
Atopy	15	10
AHI	48±24	45±31
FEV$_1$ % pred	82±14	81±20
Maintenance therapy for asthma	None[+]	None[+]
	ICS[§]	ICS[f]
	ICS+LABA[##]	ICS+LABA[f]
	LTRA+LABA[f]	ICS+theophylline[f]
	ICS+LABA+theophylline+prednisone[f]	ICS+LABA+prednisone[f]
Equivalent of fluticasone mg·day^{-1} among ICS users	600±376	500±0

Data are presented as n and mean±SD, unless otherwise stated. BMI: body mass index; GERD: gastro-oesophageal reflux disease; AHI: apnoea/hypopnoea index; FEV$_1$: forced expiratory volume in one second; % pred: % predicted; ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; LTRA: leukotriene receptor antagonists. Among the 13 patients who did not complete the study, six were initially excluded because their PC$_{20}$ had more than two dilution variations following the three serial methacholine inhalation challenges. [#]: among current and ex-smokers; [¶]: symptoms and/or medication; [+]: n=9; [§]: n=3; [f]: n=1; [##]: n=6.

patients are summarised in table 1. No differences were observed in the baseline characteristics between patients who completed the study and those who did not.

Following 6 weeks of nocturnal CPAP used on an average of 6.7±0.9 h at a mean pressure of 9.3±2.8 cmH_2O, the AHI significantly dropped from 48.1±23.6·h^{-1} at the baseline to 2.6±2.5·h^{-1} on control PSG ($p<0.001$). All patients except one used CPAP with a nasal interface. The clinical and functional characteristics related to OSA and asthma before and 6 weeks after the CPAP treatment are summarised in table 2.

TABLE 2 Functional and clinical characteristics of the subjects at baseline (pre-) and after 6 weeks of treatment (post-) with continuous positive airway pressure (CPAP)

	Pre-CPAP	Post-CPAP
FEV$_1$ % pred	82.2±13.6	80.4±13.6
FEV$_1$/FVC %	77.3±8.3	76.3±10.1
PC$_{20}$ mg·mL^{-1}	2.2 (1.3–3.5)	2.5 (1.4–4.5)
AHI	48.1±23.6	2.6±2.5***
QOLAs	5.0±1.2	5.8±0.9***
QOLAp	4.1±1.4	6.0±1.0***

Data are presented as mean±SD or geometric means (95% confidence interval), *i.e.* average of three individual geometric means before and after CPAP. FEV$_1$: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; PC$_{20}$: provocative methacholine concentration causing a 20% fall in FEV$_1$; AHI: apnoea/hypopnoea index; QOLAs: quality of life specific to asthma; QOLAp: quality of life specific to obstructive sleep apnoea. ***: $p \leqslant 0.001$.

No significant change in airway responsiveness before (PC$_{20}$ (95% CI) 2.2 mg·mL^{-1} (1.3–3.5)) and after 6 weeks of CPAP (PC$_{20}$ 2.5 mg·mL^{-1} (1.4–4.5); $p=0.3$; fig. 1a) was found. In three patients, a reduction of airway responsiveness was noticed after 6 weeks of CPAP, as reflected by a two-fold increase in PC$_{20}$. Compared with the other patients, no differences were found in their age, effective CPAP pressure, CPAP compliance, BMI, AHI, gastric reflux, atopy or quality-of-life scores. However, their baseline PC$_{20}$ was higher (7.3 mg·mL^{-1}) than the subjects who did not have any change in airway responsiveness (1.7 mg·mL^{-1}; $p=0.02$). There were no significant changes in the mean FEV$_1$ before (82.2±13.6% predicted) and after 6 weeks of CPAP (80.4±13.6% pred). The QOLAp statistically and clinically improved from 4.1±1.4 at baseline to 6.0±1.0 at the end of the study ($p<0.001$). The QOLAs also improved statistically and clinically from 5.0±1.2 at baseline to 5.8±0.9 at the end of the study ($p=0.001$; fig. 1b). Clinical improvement for each QOL questionnaire is established by a score increase $\geqslant 0.5$. The QOLAs at baseline were inversely correlated with the patient's BMI (rho=-0.5, $p=0.02$). Following the CPAP treatment, an improvement in QOLAs was positively correlated with the BMI (rho=0.5, $p=0.03$) and the AHI at baseline (rho=0.5, $p=0.03$).

There was no correlation between the BMI and the baseline AHI, or between BMI and baseline PC$_{20}$. Furthermore, following the CPAP therapy, no relationship was observed between the changes in QOLAs and QOLAp as well as

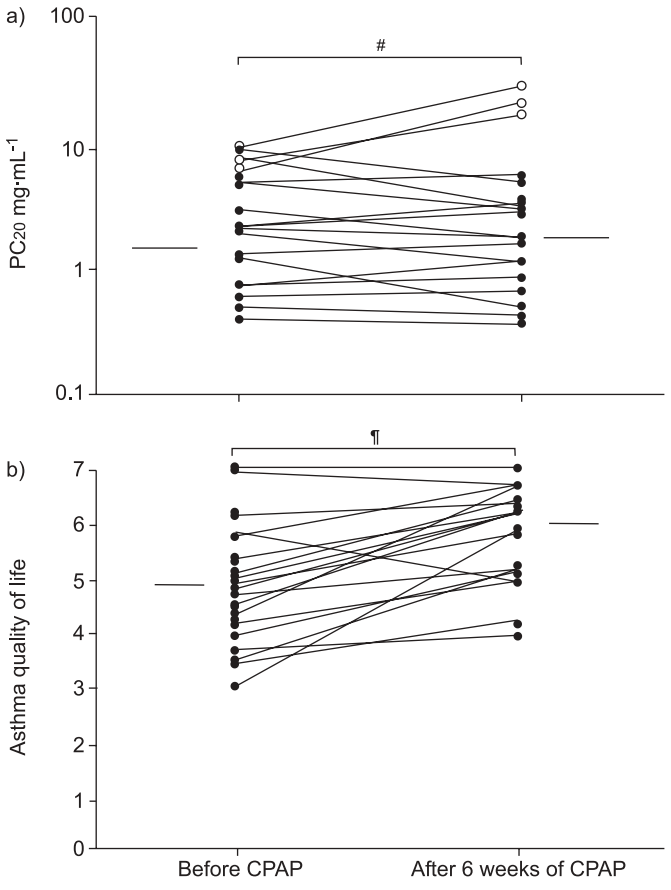

FIGURE 1. a) Changes in provocative concentration causing a 20% fall in forced expiratory volume in one second (PC_{20}) after 6 weeks of treatment with continuous positive airway pressure (CPAP). PC_{20} is calculated as the geometric mean of the three serial methacholine challenges performed. ○: patients with more than a two-fold increase in methacholine dilutions. b) Changes in asthma quality of life after 6 weeks of treatment with CPAP. Horizontal bars represent the mean. #: p=0.3; ¶: p=0.001.

between the changes in QOLAs and PC_{20}. Following CPAP use, the BMI was correlated with the improvement of the emotional (rho=0.5, p=0.02) and the environmental (rho=0.5, p=0.01) domains of QOLAs. The AHI at baseline was correlated with the improvement of the symptomatic (rho=0.6, p=0.01), the emotional (rho=0.6, p=0.01) and the environmental (rho=0.5, p=0.05) domains of QOLAs.

DISCUSSION

It was found that nocturnal CPAP treatment used with a heated humidifier in patients with stable asthma and newly diagnosed OSA did not modify the respiratory functional parameters, such as PC_{20} or FEV_1. Nevertheless, the CPAP treatment improved the QOLAs. This improvement was greater in obese patients and in patients with a high AHI at baseline.

The present authors decided to enrol only stable asthmatic subjects in order to avoid potential variations in airway responsiveness related to poorly controlled asthma. Indeed, it must be remembered that the primary aim of the present study was to assess the effect of CPAP on airway responsiveness and not the control of asthma.

A total of 20 subjects may appear to be quite a small sample size, but the present authors feel that it was enough to allow detection of a clinically significant change in PC_{20} with greater than two-fold dilutions after CPAP use to a 99% power, with an α-error of 5%. Therefore, it is believed that should a major effect of CPAP on airway responsiveness occur, the present study would have been able to detect it.

The number of patients excluded due to insufficient use of nocturnal CPAP (three out of 23) is less than the CPAP drop-out rate reported among OSA patients, since the acceptance rate of CPAP treatment among OSA patients, at large, is considered to be ~70–80% [26]. It is important to notice that patients had a heated humidifier integrated into their CPAP unit, thus preventing the effects of nasopharyngeal congestion in all but one subject.

An important variability in PC_{20} (more than two methacholine dilutions) was found in six patients at baseline in spite of a clinically adequate control of asthma. These patients were excluded from the study. This exclusion criterion may explain the discrepancy between the present results and those from other studies, which found an improvement in PC_{20} after CPAP treatment [17, 18]. In those studies, PC_{20} was measured on one occasion before and one after CPAP treatment. Therefore, a spontaneous PC_{20} variability may have occurred, which could be unrelated to CPAP treatment.

The lack of a control group comprising stable asthmatic patients without OSA prevents the present authors from concluding with certainty that the improvement of QOLAs following CPAP utilisation is specifically related to CPAP treatment. Indeed, this improvement may be due to other factors, such as a placebo effect of CPAP or improvement of adherence to asthma treatment during the study. The lack of correlation between the changes in QOLAs and QOLAp suggests that the improvement in QOLAs cannot be explained by an overall feeling of well-being consecutive to sleep normalisation following OSA treatment with CPAP. The interdependence of the questionnaires should not be completely excluded and should be addressed by experts in a future study. In a future larger study, additional analysis could possibly and more accurately determine whether BMI and AHI are independent contributors to QOLAs and its improvement with CPAP treatment.

Further randomised controlled studies including moderate-to-severe asthmatic patients with and without obstructive sleep apnoea need to be conducted in order to assess the impact of continuous positive airway pressure on asthma quality of life and its control.

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