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Impact of CPAP on asthmatic patients with sleep apnea

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Abstract

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

Methods: We performed a prospective study comparing the changes in airway responsiveness and quality of life, in stable asthmatic sleep apnea patients, before and 6 weeks after their nocturnal CPAP treatment.

Results: Twenty subjects (11 males, 9 women) completed the study. With the nocturnal CPAP treatment, the apnea-hypopnea index (AHI) dropped from 48.1 ± 23.6 /h to 2.6 ± 2.5 /h ($p < 0.001$). There were no significant changes in airway responsiveness (PC20 = 2.5 (1.4-4.5) mg/ml) after CPAP treatment compared with baseline (PC20 = 2.2 (1.3-3.5) mg/ml ($p=0.3$)). There was no significant change in FEV_1 either. However, the asthma quality of life (QOLAs) of the subjects improved from 5.0 ± 1.2 at baseline to 5.8 ± 0.9 at the end of the study ($p= 0.001$).

Conclusion: Nocturnal CPAP treatment did not alter airway responsiveness or FEV_1 in subjects with stable mild-to-moderate asthma and newly-diagnosed obstructive sleep apnea. However, nocturnal CPAP treatment did improve asthma quality of life.

Keywords: asthma, sleep apnea, CPAP, airway responsiveness, asthma quality of life

Introduction

The prevalence of asthma varies widely depending on the country studied[1]. In Canada, the 1998/1999 National Population Health Survey (NPHS) 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 apnea-hypopnea score of 15 /h or higher is 4% in women and 9% in men[3].

Asthma and obstructive sleep apnea (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 gastroesophageal reflux 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, sleep apnea, or both[11-12].

It is well known that 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 apneic patients[14-15-16]. Two studies reported an improvement of airway responsiveness with CPAP treatment, respectively in 4 out of 20 apneic non-asthmatic patients[17] and in 9 stable asthmatic non-apneic patients[18]. However, a deleterious effect of CPAP on airway responsiveness was reported in 6 out of 31 OSA patients[19]. To the best of our knowledge, no study has specifically evaluated the effects of CPAP treatment on airway responsiveness of asthmatic sleep apnea patients.

The primary aim of this prospective study was to observe the changes in airway responsiveness in stable asthmatic sleep apnea 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 and OSA.

Study design:

Before entering into the study, subjects underwent 3 serial methacholine inhalation challenges – measured 2 or 3 days apart. Baseline questionnaires on asthma and OSA-related quality of life were completed. An atopic status was assessed using skin prick tests to common inhalants. Gastroesophageal symptoms and/or anti-reflux 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 utilization 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 specific quality of life questionnaires for asthma and apnea were re-assessed as performed at baseline.

Material and methods:

SUBJECTS

Individuals of eighteen years of age and older with stable asthma and a new diagnosis of OSA syndrome were considered for enrollment in two centers (Hôpital du Sacré-Coeur de Montréal and Hôpital Laval de Québec) 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 criteria[20]. Acceptable asthma control was defined by occasional respiratory symptoms and absence of asthma exacerbation without any change in the maintenance therapy in the month preceding the study. All subjects showed airway responsiveness defined by a provocative concentration of methacholine, inducing a 20% fall in forced expiratory volume in one second (FEV_1) ≤ 8 mg/ml (PC_{20}).

All patients complained of symptoms suggestive of OSA syndrome and their apnea hypopnea index (AHI) was determined during one in-laboratory PSG, the recording of which was ≥ 15 /h.

EXCLUSION CRITERIA

Initially, subjects were not eligible to continue the study if the variation between the lowest and the highest measure of PC_{20} was more than 2 dilutions, which assumed that their asthma was not optimally controlled or that the methacholine challenge could not be reproducible in these patients.

WITHDRAWAL CRITERIA

No changes in the subjects' 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 vaporization and/or medication against gastroesophageal reflux.

Patients were withdrawn during the course of the study if compliance to their CPAP treatment was considered inadequate (average daily use < 4 hours / night) or if asthma exacerbations unrelated to CPAP use occurred (for example: respiratory tract infection, allergenic exposure and recurrence of smoking).

METHACHOLINE CHALLENGES

Spirometry was performed according to the American Thoracic Society standards[21]. Methacholine challenges were performed according to previously described standardized techniques [22].

SLEEP STUDIES

Initial polysomnographic recordings consisted of in-lab continuous acquisition of electroencephalogram, electrooculogram, submental electromyogram, arterial oxyhemoglobin saturation by transcutaneous pulsed oxymetry, naso-oral airflow with thermistors, nasal pressure with nasal cannula, chest and abdominal movements by impedance plethysmography (RespitraceTM, Ambulatory Monitoring Inc., Ardsley, NY), electrocardiogram, and breathing sounds. Sleep position was continuously assessed by the attending technician using an infrared camera. All variables were digitally recorded (Sandman EliteTM System, Mallinckrodt, Kenilworth, NJ). 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 apneic and hypopneic 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. The CPAP devices all included a heated-humidifier (ambient-tracking), a ramp function and a microprocessor allowing for time of usage measurement. A nasal or a facial mask could be used.

QUALITY OF LIFE QUESTIONNAIRES

Validated asthma (miniAQLQ) and OSA specific quality of life questionnaires were used[24-25]. Scores were reported on a scale of 7, higher scores meaning better quality of life. The asthma quality of life questionnaire was divided into four sections: emotional function, environmental stimuli, symptoms, and activity limitation.

DATA ANALYSIS

All values were expressed as the mean ± standard deviation. PC_{20} values were log-transformed and mean of 3 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 3 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%. The analysis was performed using the SPSS 10.0 statistical package (Chicago, IL).

Results

Thirty-three (33) patients were invited to participate in the study. Six (6) were excluded because of a high variability of PC_{20} results during the screening visits. Seven (7) were withdrawn during the study for different reasons: CPAP use < 4 hours/night (3), a upper respiratory tract infection (2), resumed smoking (1), and elective orthopedic surgery (1). A total of 20 patients completed the study. The baseline characteristics of these

patients are summarized in table 1. No differences were observed in the baseline characteristics between patients who completed or not the study.

Following 6 weeks of nocturnal CPAP used on an average of 6.7 ± 0.9 hours at a mean pressure of 9.3 ± 2.8 cm H_20, the AHI significantly dropped from 48.1 ± 23.6 /h at the baseline to 2.6 ± 2.5 /h on control PSG ($p < 0.001$). All patients used CPAP with a nasal interface, except one. The clinical and functional characteristics related to OSA and asthma before and 6 weeks after the CPAP treatment are summarized in table 2.

We did not find any significant change in airway responsiveness before (PC20 = 2.2 mg/ml with 95 % CI :1.3-3.5) and after 6 weeks of CPAP (PC20 = 2.5 mg/ml with 95 % CI :1.4-4.5), (p=0.3) (figure 1). In three patients, we noticed a reduction of airway responsiveness after 6 weeks of CPAP, as reflected by a two-fold increase in PC_{20} . Compared to 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) than the subjects who did not have any change in airway responsiveness (1.7 mg/ml), (p=0.02). There were no significant changes in the mean FEV_1 before (82.2 ± 13.6% predicted value) and after 6 weeks of CPAP (80.4 ± 13.6% predicted value). The OSA quality of life (QOLAp) statistically and clinically improved from 4.1 ± 1.4 at the baseline to 6.0 ± 1.0 at the end of the study ($p<0.001$). The asthma quality of life (QOLAs) also improved statistically and clinically from 5.0 ± 1.2 at the baseline to 5.8 ± 0.9 at the end of the study (p= 0.001), (figure 2). Clinical improvement for each QOL questionnaire is established by a

score increase ≥ 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 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

We 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 quality of life specific to asthma. This improvement was greater in obese patients and in patients with a high AHI at baseline.

We decided to enroll only stable asthmatic subjects in order to avoid potential variations in airway responsiveness related to poorly-controlled asthma. Indeed, one

must remember that the primary aim of this study was to assess the effect of CPAP on airway responsiveness and not the control of asthma.

Twenty subjects may appear to be quite a small sample size, but we feel that it was enough to allow us to detect a clinically-significant change in PC_{20} with greater than twofold dilutions after CPAP use to a 99% power, with an alpha error of 5%. Therefore, we believe that if there was a major effect of CPAP on airway responsiveness, we would have been able to detect it.

The number of patients excluded because of insufficient use of nocturnal CPAP (3/23) 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 around 70-80% [26]. It is important to notice that patients had a heated-humidifier integrated to their CPAP unit, thus preventing the effects of nasopharyngeal congestion in all but one subject.

An important variability in PC_{20} (greater than 2 methacholine dilutions) was found in 6 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 our results and those from others studies, which found an improvement in PC_{20} after CPAP treatment[17-18]. In those studies, PC_{20} was measured on only one occasion before and 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 comprised of stable asthmatic patients without OSA prevents us from concluding with any certainty that the improvement of QOLAs following CPAP utilization 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 quality of life specific to asthma cannot be explained by an overall feeling of well-being consecutive to sleep normalization 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 if whether or not BMI and AHI are independent contributors to QOLAs and its improvement with CPAP treatment.

Further randomized controlled studies including moderate to severe asthmatic patients with and without sleep apnea need to be conducted in order to assess the impact of CPAP on asthma quality of life and its control.

Patients	who completed the study (mean ± SD)	who did not complete the study * (mean ± SD)
n	20	13
Age (years)	49 ± 9	52 ± 11
Sex (M:W)	11 M : 9 W	9 M : 4 W
BMI (kg/m^2)	37 ± 9	41 ± 7
Smoker status : c/s ; ex (p-y)	1 ; 11 (22 ± 19)	3 ; 6 (36 ± 26)
GERD (symptoms or medication)	n= 6	n=2
Atopy	n=15	n=10
AHI	48 ± 24	45 ± 31
FEV_1 (% of predicted value)	82 ± 14	81 ± 20
Maintenance therapy for asthma	None (n= 9) ICS (n= 3) ICS + LABA (n= 6) LTRA + LABA (n=1) ICS + LABA + theophylline + prednisone (n=1)	None (n= 9) ICS (n= 1) ICS + LABA (n= 1) ICS + theophylline (n=1) ICS + LABA + prednisone (n=1)
Equivalent of fluticasone (mg/day) among ICS users	600 ± 376	500 ± 0

Table 1. **Characteristics of the subjects at baseline.** *Legend* ⇒ BMI: body mass index, c/s: current smoker, ex : ex-smoker, p-y : packs a year (among current and ex-smokers) GERD: gastroesophageal reflux, AHI: apnea-hypopnea index, FEV_1: forced expiratory volume in one second, ICS : inhaled corticosteroïds, LABA : Long Acting β_2-Agonists, LTRA : Leukotriene Receptor Antagonists.

* No difference was observed in baseline characteristics of patients who completed or not the study. Among the 13 patients, 6 were initially excluded because their PC_{20} had more than 2 dilution variations following the 3 serial methacholine inhalation challenges.

	Pre CPAP	**Post CPAP** (after 6 weeks of treatment)
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)	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 *

Table 2. Functional and clinical characteristics of the subjects at baseline and after 6 weeks of treatment with CPAP. *Legend* ⇒ FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, PC_{20}: methacholine concentration causing a 20% fall in FEV_1; AHI: apnea-hypopnea index, QOLAs: Quality Of Life specific to Asthma; QOLAp : Quality Of Life specific to OSA; * : $p \leq 0{,}001$. Data are expressed as mean value ± standard deviation, except PC_{20} values which are expressed as the geometric means (95% CI) (average of 3 individual geometric means before and after CPAP).

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