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Should flow-volume loop be monitored in sleep apnea patients treated with continuous positive airway pressure?

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Summary Nasal continuous positive airway pressure (nCPAP) has been widely established in the treatment of obstructive sleep apnea syndrome (OSAS). However, only few studies have evaluated long-term effects of this treatment on lung function. This study assesses the effect of nCPAP on lung function parameters and response to bronchodilators in 50 OSAS patients. Spirometry and arterial blood gas measurements were performed before starting nCPAP and after 16.8 ± 8 months of treatment. Of the 50 study patients (55 ± 12 years, with an apnea/hypopnea index of $47 \pm 34\,h^{-1}$), 15 had asthma, 13 had chronic obstructive pulmonary disease (COPD) and 22 had no obstructive airway disease (NOAD). In the entire population, significant decreases in FEF_{50} (from $69 \pm 38\%$ to $61 \pm 30\%$, $P < 0.005$), FEF_{25} (from $53 \pm 34\%$ to $46 \pm 28\%$, $P < 0.05$) and FEF_{25-75} (from $65 \pm 33\%$ to $57 \pm 27\%$, $P < 0.005$) were observed after treatment. No impairment of lung function was found in COPD and asthmatic patients. In contrast, lung function was changed in the NOAD group where FEF_{50}, FEF_{25} and FEF_{25-75} as well as FEV_1 and FEV_1/VC ratio were significantly reduced. Moreover, bronchial hyperresponsiveness occurred in five of 22 patients of this group. These results suggest that tolerance of nCPAP should be handled by long-term follow-up of flow-volume loops.

Introduction

Obstructive sleep apnea syndrome (OSAS) represents an important health problem because of a prevalence of at least 1–4%,[1] frequent association with obesity,[2] systemic hypertension[3] and increased mortality without treatment.[4,5] Since the first publication in 1981,[6] nasal continuous positive airway pressure (nCPAP) has been widely established in the treatment of OSAS. However, only few studies have evaluated long-term effects of this treatment on lung function.[7–9] In patients with chronic obstructive pulmonary disease (COPD), both positive end-expiratory pressure and CPAP have been shown to reduce the work of breathing by minimizing dynamic airway collapse during expiration.[10–12] In asthmatic subjects in whom bronchospasm was induced by histamine, CPAP is thought to reduce pulmonary resistance and inspiratory muscles work.[13] More recently, nCPAP was shown to improve bronchial smooth muscle hyperreactivity to methacholine.[14] However, the effectiveness of CPAP in asthma is still conflicting. Interestingly, bronchial hyperreactivity to histamine has been reported in some patients treated by nCPAP for OSAS,[15] but no other adverse effect of

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long-term nCPAP on lung function has been described.

The aim of this study was to assess the effect of nCPAP on lung function parameters and airway responsiveness (response to bronchodilators) in 50 OSAS patients with or without obstructive spirographic pattern.

Methods

Patient selection

Two hundred patients with sleep respiratory disorders have been screened in our center for a 4-year period. Among them, 50 patients were included in this study. All these patients gave informed consent. The inclusion criteria were an apnea/hypopnea index (AHI) of more than 10 per hour at baseline, the normalization of the AHI (i.e. AHI <10) and the disappearance or a clear improvement of the related symptoms (snoring, excessive daytime sleepiness) resulting of nCPAP use and the acceptance of home nocturnal nCPAP.

Study protocol

All patients underwent two full polysomnographies, performed at baseline without nCPAP and with nCPAP. Polysomnography included electroencephalography (C4-A1, C3-A2, T4-O2), electrooculography, chinelectromyography, electrocardiography, nasal flow and oxygen saturation monitored via a finger probe. Neurophysiological and ventilatory signals were recorded using a CID 108-102 device (CIDELEC, Angers, France).

Patients were health screened at entry with uniform medical history and physical examination along with blood gases, spirometry, chest radiography and electrocardiography.

Spirometry (including bronchodilator testing) and arterial blood gas measurements were performed before starting nCPAP and after 17 ± 8 months of treatment.

Spirometry measurements and flow-volume curves were obtained using a body plethysmograph (PF/DX 1085D; MedGraphics, St. Paul, MN) with a heated pneumotachometer for flow measurement. The highest values of three technically satisfactory forced expirations were used. The spirometry technique met international standards and references values were those of the European Respiratory Society.[16] Results are expressed as absolute volumes (ml) and as percentages of predicted values (% pred).

Bronchial hyperresponsiveness was defined by an increase of FEV_1 of 200ml and more than 12% or an increase of FEF_{25}, FEF_{50} and FEF_{25-75} of more than 50% (without change in VC) after inhalation of 200 μg Salbutamol.

Arterial blood was drawn from the radial artery with the patient awake and semi-supine. The blood sample was analyzed for pH, pCO_2 and pO_2 (1306 IL; Paris, France).

In view of the presence of patients with obstructive airway disease, three groups were defined: those with an history or clinical evidence of asthma, those with COPD defined by airway obstruction [obstructive spirographic pattern with FEV_1/VC ratio (forced expiratory volume in one second/vital capacity) $<70\%$] and those without obstructive airway disease (no obstructive airway disease [NOAD]).

Statistics

Data were expressed as mean $\pm$ SD. Comparisons of the three groups according to the health status were made using analysis of variance (ANOVA). We also used the χ^2 test to compare the distribution of smoking habits between the three groups. Baseline and follow-up values were compared using Student's paired *t*-test. Non-parametric tests (Wilcoxon rank sum and Mann–Whitney tests) were used for small groups. Values were different with significance set at the $P<0.05$ level.

Results

Patients characteristics

The 50 patients were 55 ± 12 years, with a body mass index (BMI) of $36\pm8\,kg\,m^{-2}$ and an AHI of $47\pm34\,h^{-1}$. Baseline anthropometric, polysomnographic and lung function data before nCPAP treatment are summarized in Table 1. Of the 50 study patients, 15 had asthma, 13 had COPD and 22 were NOAD. Among all data, smoking habit, FEV_1, FEF_{50} (forced expiratory flow at 50% vital capacity), FEF_{25} (forced expiratory flow at 25% vital capacity), FEV_1/VC, VC and PaO_2 were significantly different between NOAD and COPD or asthma ($P<0.02$). FEF_{25-75} (forced expiratory flow between 25% and 75% of the vital capacity) was significantly different in the three groups ($P<0.02$).

Mean nCPAP level needed to treat patients was 8.9 ± 2.3 cm H_2O. The compliance to nCPAP treatment, expressed by the cumulated time of using, was 5.9 ± 0.9 h/night.

Table 1 Anthropometric, polysomnographic and lung function data before nCPAP treatment (mean ± SD).

	Asthma ($n = 15$)	COPD ($n = 13$)	NOAD ($n = 22$)	ANOVA or χ^2†
Age (year)	51 ± 11	56 ± 14	56 ± 12	NS
Sex (M/F)	8/7	9/4	16/6	NS
BMI ($kg\,m^{-2}$)	39 ± 7	37 ± 8	35 ± 9	NS
Smokers (*n*)	11/15	12/13	9/22	$P < 0.005$
Smoking history (pack year)	28 ± 27	33 ± 21	9 ± 17	$P < 0.005$
AHI (h^{-1})	47 ± 27	35 ± 26	53 ± 42	NS
PaO_2 (mmHg)	69 ± 16	67 ± 11	79 ± 10	$P < 0.05$
$PaCO_2$ (mmHg)	44 ± 6	43 ± 4	41 ± 5	NS
FEV_1/VC (%)	62 ± 14	66 ± 15	79 ± 10	$P < 0.005$
FEV_1 (% pred)	64 ± 22	70 ± 24	98 ± 26	$P < 0.0001$
FEF_{50} (% pred)	42 ± 25	53 ± 29	96 ± 31	$P < 0.0001$
FEF_{25} (% pred)	28 ± 20	42 ± 20	77 ± 33	$P < 0.0001$
FEF_{25-75} (% pred)	34 ± 19[a]	56 ± 25[a]	94 ± 21[a]	$P < 0.0001$
VC (% pred)	81 ± 16	83 ± 17	101 ± 21	$P < 0.005$
FRC (% pred)	95 ± 21	99 ± 24	92 ± 24	NS
TLC (% pred)	93 ± 17	93 ± 12	97 ± 17	NS
RV (% pred)	121 ± 34	115 ± 32	102 ± 32	NS

NOAD: no obstructive airway disease, BMI: body mass index, AHI: apnea/hypopnea index. Lung function parameters are expressed as the percentages of predicted values (% pred). FEV_1/VC: forced expiratory volume in one second/vital capacity, FEF_x: forced expiratory flow at *x*% vital capacity, VC: vital capacity, FRC: functional residual capacity, TLC: total lung capacity and RV: residual volume.
[a]Values were significantly different in the three groups ($P < 0.02$).

Lung function changes

In the entire study population of the 50 patients, significant decreases in FEF_{50} (from 69 ± 38% to 61 ± 30%, $P < 0.005$), FEF_{25} (from 53 ± 34% to 46 ± 28%, $P < 0.05$) and FEF_{25-75} (from 65 ± 33% to 57 ± 27%, $P < 0.005$) were observed. A significant increase in PaO_2 and decrease in $PaCO_2$ were seen (respectively, from 73 ± 13 to 76 ± 11 mmHg for PaO_2, $P < 0.01$, and from 43 ± 5 to 41 ± 4 mmHg for $PaCO_2$, $P < 0.01$). However, BMI, FEV_1/VC, FEV_1, VC, FRC (functional residual capacity), RV (residual volume) and TLC (total lung capacity) [% pred and ml] did not change significantly.

When health status was taken into account (Fig 1A), lung function was significantly worse in the NOAD group. FEV_1, FEF_{50}, FEF_{25} (% pred and mL), FEF_{25-75} (% pred) and FEV_1/VC ratio were significantly reduced. Moreover, no statistical difference was observed in PaO_2 and $PaCO_2$ before and after follow-up in the NOAD group. In contrast, PaO_2 was improved in the asthma group (from 69 ± 17 to 75 ± 9 mmHg, $n = 13$, $P < 0.05$) and in the COPD group (from 67 ± 11 to 75 ± 13 mmHg, $P < 0.005$), and $PaCO_2$ was reduced in asthmatic patients (from 45 ± 6 to 43 ± 5 mmHg, $n = 13$, $P < 0.05$).

Bronchial responsiveness

Bronchial hyperresponsiveness occurred in five of 22 patients of the NOAD group (Fig 1B). These five patients were not smokers. Their age, BMI, AHI and nCPAP level were not different from the NOAD group. Their BMI was stable during the follow-up

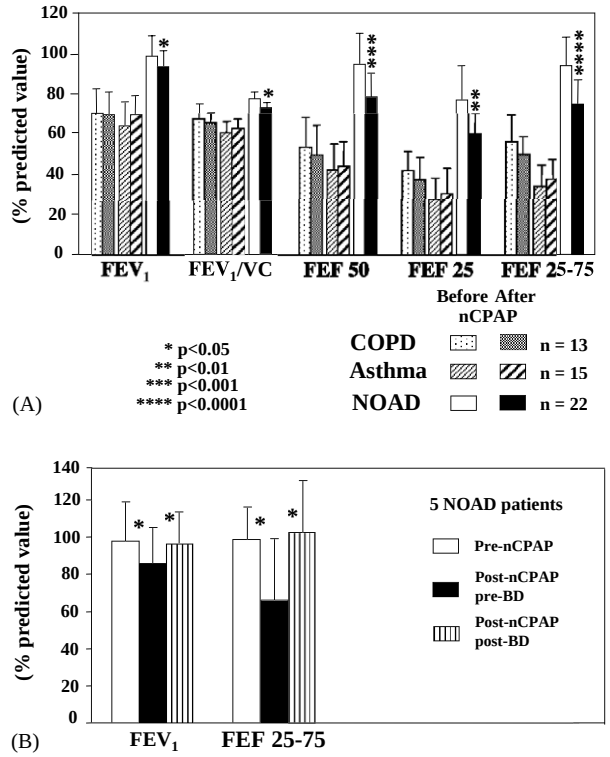

Figure 1 (A) Lung function changes. Mean values (+2 SEM) of FEV_1, FEV_1/VC, FEF_{50}, FEF_{25} FEF_{25-75} before and after nCPAP treatment in COPD, asthma and NOAD patients. (B) Bronchial responsiveness observed in five patients of the NOAD group. Mean values (+2 SEM) of FEV_1 and FEF_{25-75} before nCPAP (pre-nCPAP), after nCPAP (post-nCPAP) and before bronchodilator (pre-BD), after nCPAP and after bronchodilator (post-BD). NOAD = no obstructive airway disease group, FEV_1/VC = forced expiratory volume in one second/vital capacity, FEF_x = forced expiratory flow at x% vital capacity.

period and no difference in VC, FRC, RV and TLC (% pred and ml) were observed. All had nCPAP with humidification systems. Three of these five patients had history of chronic rhinitis. One of these patients, who developed a severe obstructive spirographic pattern, needed bronchodilator and corticosteroid treatment.

Discussion

The main result of the present study is that lung function and bronchial responsiveness may be impaired by long-term treatment of OSAS by nCPAP. The impairment is observed only in patients with normal initial lung function.

To our knowledge, this is the first study that describes a decrease of forced expiratory flows in NOAD patients treated by nCPAP for OSAS. Chaouat et al.[9] reported a significant decrease of FEV_1 after long-term nCPAP treatment (64±6 months) related to high percentage of smokers and ex-smokers (77%). In our study, the shorter period of follow-up (17±8 months) and the lower percentage of smokers (64%) do not support this hypothesis. Five cases of bronchial hyperresponsiveness were observed among 22 NOAD patients. Wenzel et al.[15] reported cases of bronchial hyperreactivity but after short-term follow-up and in lower proportion. No case of bronchial responsiveness like in our study was described elsewhere.

One hypothesis for the occurrence of obstructive spirographic pattern is that CPAP may irritate airway epithelia and induce airway inflammation. In animal models, prolonged exposure to high intermittent positive pressure ventilation induces airway remodeling and airway hyperreactivity as tested in vitro with carbachol.[17] Although level of CPAP was low in our study, chronic exposure to positive pressure ventilation might produce similar effects in man. The second hypothesis is that long-term nCPAP may act as a mechanical alteration of the nasal mucosa and creates a change in small airway resistance via a nasobronchial reflex.[18] No bronchoconstriction reflex after nasal histamine or allergenic provocation has been observed in patients with allergenic rhinitis associated with asthma. However, increased airway hyperreactivity after nasal allergenic provocation test is well known.[19,20] The role of proinflammatory mediators secreted by nasal epithelial cells is also evoked. These results suggest a link between upper airway inflammation and bronchial airway hyperreactivity. This hypothesis may explain our results in at least three patients with chronic rhinitis history. However, upper airway inflammatory disease was not systematically evaluated in our study population, and bronchial hyperreactivity was not assessed.

For the entire population, no change in FEV_1, VC, FRC and TLC was observed. Although the 50 patients included in our study were similar to other series of OSAS patients with regard to initial lung function and arterial blood gases,[7–9] differences in long-term follow-up were seen. Young et al.[8] reported a significant fall of TLC, FRC and RV after 1 year of nCPAP and suggested that this decrease of lung volume was consistent with change in respiratory muscle tone of initially hyperinflated patients. In our study, patients were not hyperinflated. Finally, the decrease of FEF_{50}, FEF_{25} and FEF_{25-75} observed in our patients was not reported elsewhere.

Conclusions

This study shows that long-term nCPAP may modify flow-volume loops of patients without initial obstructive spirographic pattern. Prospective studies evaluating airway responsiveness to β2-agonists and hyperreactivity to methacholine are needed to further explore the pathophysiological mechanisms involved. These results suggest that tolerance of nCPAP should be controlled by long-term follow-up of flow-volume loops and compared to new protocols of treatment.

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