ORIGINAL INVESTIGATION

Marked Improvement in Nocturnal Gastroesophageal Reflux in a Large Cohort of Patients With Obstructive Sleep Apnea Treated With Continuous Positive Airway Pressure

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Background: Nocturnal gastroesophageal reflux (nGER) is common in patients with obstructive sleep apnea (OSA). Small, short-term studies have shown that treatment with nasal continuous positive airway pressure (CPAP) decreases esophageal acid exposure.

Objective: To examine the relationship between OSA and nGER, and the effect of CPAP on nGER, in a long-term follow-up study of a large cohort of patients with OSA and nGER.

Methods: We prospectively studied 331 patients diagnosed as having OSA between October 1, 1993, and November 30, 2000. At baseline, patients graded their frequency of nGER symptoms on a scale of 1 (never) to 5 (always). All patients were prescribed CPAP for their OSA. At follow-up, the frequency of nGER symptoms was obtained by telephone interview.

Results: Of the 331 patients with OSA, nGER was present in 204 (62%) before treatment with CPAP. Follow-up was obtained in 181 patients (89%). Of these 181 patients, 165 (91%) were still using CPAP and 16 (9%) were not, forming the treatment and control groups, respectively. The patients compliant with CPAP had a significant improvement in nGER score, from a mean of 3.38 before CPAP treatment to 1.75 after treatment (48% improvement; $P<.001$), while patients not using CPAP (control subjects) showed no improvement (mean, 3.56 to 3.44; $P=.55$). There was a strong correlation between CPAP pressure and improvement in nGER score (correlation, $r=0.70$; $P<.001$), with patients with higher CPAP pressures demonstrating a greater improvement in nGER score.

Conclusions: Nocturnal GER is common in patients with OSA. Treatment with nasal CPAP decreases the frequency of nGER symptoms by 48%. Higher nasal CPAP pressures are associated with greater improvement in nGER.

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GASTROESOPHAGEAL reflux disease (GERD) is characterized by heartburn and regurgitation caused by the reflux of gastric contents into the esophagus. The pathogenesis of GERD involves abnormal function of the lower esophageal sphincter (LES). Reflux is a common problem, with 20% of the population reporting weekly symptoms.[1] Nighttime reflux causes substantial morbidity. In a large recent national survey, 10% of respondents reported frequent nocturnal gastroesophageal reflux (nGER).[2] These patients had significantly worse health-related quality of life than patients with GERD without nocturnal symptoms.

Obstructive sleep apnea (OSA) is a disorder characterized by repetitive sleep-induced pharyngeal collapse, with airflow ceasing despite a continued respiratory drive. Patients with OSA have a high frequency of nGER that ranges from 54% to 76%.[3,4] The reasons for this association are not fully understood. Possible explanations include obesity predisposing to both conditions, decreased intrathoracic pressure during apneic episodes promoting reflux, and increased arousals coupled with decreased sleep efficiency triggering transient LES relaxation.[5,6]

Although the role of OSA in the pathogenesis of GERD is unclear, the ability of nasal continuous positive airway pressure (CPAP) to reduce GER measures has been reported.[5-7] Kerr and colleagues[8] have also demonstrated the ability of CPAP to reduce nGER measures in patients without OSA, suggesting a direct effect on the esophagus rather than an indirect effect of resolving the OSA.

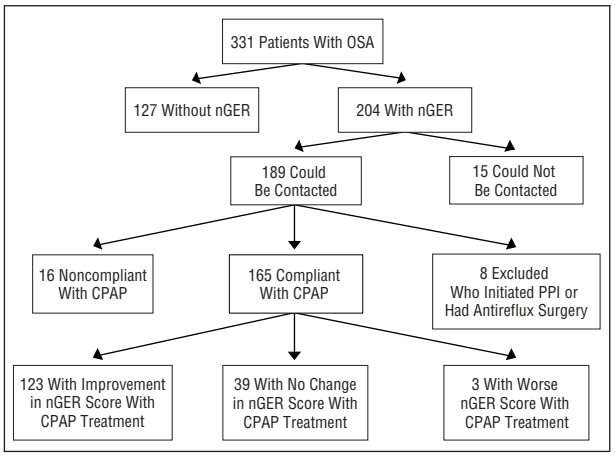

Figure 1. Flow diagram describing patient selection and outcomes of patients treated with nasal continuous positive airway pressure (CPAP). nGER indicates nocturnal gastroesophageal reflux; OSA, obstructive sleep apnea; and PPI, proton pump inhibitor.

However, published studies to date are small and have focused on the ability of CPAP to reduce esophageal acid exposure, as measured by ambulatory pH testing. They have not addressed patient symptoms, and follow-up has been short-term. We present the first, to our knowledge, prospective long-term follow-up study of a large cohort of patients with OSA and nGER to examine the relationship between OSA and nGER, and the effect of nasal CPAP on nGER.

METHODS

We prospectively studied 331 patients diagnosed as having OSA between October 1, 1993, and November 30, 2000, at the University of South Alabama Sleep Disorders Center, Mobile. All patients had been referred for polysomnography to evaluate for OSA, which was performed in the laboratory (Compumedics S Series Sleep System V4.0; Compumedics, Minneapolis, Minn). The respiratory disturbance index (RDI; a measure of the severity of sleep apnea) was determined in all studies. The RDI is the total number of apneas and hypopneas divided by the total sleep time and is interchangeable with the apnea-hypopnea index. Subjects were defined as having OSA if the RDI was greater than 15.

All patients either had nasal CPAP titrated on the initial study or returned for a second study with titration. Titration is a process in which the CPAP pressure is gradually increased to achieve a normalization of OSA. Patients who were unable to tolerate an initial trial of CPAP, did not return for titration, or could not have their OSA controlled with the initial titration were excluded from this analysis.

Immediately before the initial visit, patients were asked to fill out a questionnaire regarding sleep-related symptoms. The instructions ask the respondent to "consider each question as applying to the past 6 months of your life." The questions were answered by circling a number from 1 to 5, with the following key: 1, never; 2, rarely; 3, sometimes; 4, usually; and 5, always. The nocturnal reflux question states, "My sleep is disturbed by severe heartburn and choking ('regurgitation' bringing up bitter stomach fluid)." The symptoms of heartburn and acid regurgitation are considered to be specific for GERD and are widely accepted for use in population-based research.[9-11] Patients who either failed to answer this question or failed to return the questionnaire were excluded from the study. Patients with an initial response to the nocturnal reflux question of 2 or greater (ie, had nocturnal reflux symptoms) were then contacted by telephone by a single investigator (B.T.G.).

Table 1. Initial Characteristics of Patients With OSA With and Without nGER

	With nGER	Without nGER	*P* Value
Patients, No.	204	127	. . .
Sex, No.			
Male	131	85	.61
Female	73	42	
Age, y*	49.3 (11.3)	50.4 (13.3)	.30
Weight, kg*	111 (24.4)	108 (26.7)	.09
Height, m*	2.02 (4.36)	1.71 (0.11)	.70
BMI*	38.0 (9.21)	37.2 (9.08)	.32
RDI*	43.1 (29.0)	43.3 (29.2)	.92
PPI, No.	27	5	.005
H_2RA, No.	19	2	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); H_2RA, histamine$_2$ receptor antagonist use before continuous positive airway pressure treatment; nGER, nocturnal gastroesophageal reflux; OSA, obstructive sleep apnea; PPI, proton pump inhibitor use before continuous positive airway pressure treatment; RDI, respiratory disturbance index.
*Mean (SD).

The follow-up ranged from 5 to 98 months (mean, 39 months) after the initial study. After being read the same instructions, patients were asked the same gastroesophageal reflux question. They were also questioned about their current use of CPAP, their CPAP pressure, proton pump inhibitor (PPI) use, histamine$_2$ receptor antagonist (H_2RA) use, tobacco use, and whether they had had reflux surgery in the interim. The investigator (B.T.G.) was not involved in the care of any of the patients, and they were not informed of his position as a physician. They also were not informed of the purpose of the study. After 4 unsuccessful attempts to contact the patients by telephone, they were considered lost to follow-up.

Demographic and clinical data obtained at the time of the initial polysomnography included age, sex, height, weight, RDI, PPI use, H_2RA use, and tobacco use. These data were extracted from the patient chart.

The institutional review board of the University of South Alabama approved the study. Data were analyzed by means of standard statistical techniques: χ^2 for categorical data and either *t* tests or rank sum tests for continuous data. A *P* value of less than .05 was considered significant.

RESULTS

Obstructive sleep apnea was present in 331 patients (**Figure 1**). Nocturnal gastroesophageal reflux was present in 204 (62%) of these patients, while it was absent in 127. The characteristics of patients with OSA with and without nGER are summarized in **Table 1**. Patients with OSA with and without nGER were similar with respect to sex, age, weight, height, body mass index (BMI), and RDI. As expected, PPI and H_2RA use before treatment with nasal CPAP was significantly greater in subjects with nGER than those without. The mean RDI of greater than 40 in our patients suggests that most patients had moderately severe to severe OSA.

Follow-up was obtained on 189 (93%) of the 204 patients with OSA and nGER at time intervals ranging from 5 to 98 months (mean, 39 months). The reasons for which 15 patients could not be contacted included

Table 2. Characteristics of Patients With OSA With nGER Who Were Not Using CPAP

	Patients	Controls	*P* Value
Patients, No.	165	16	
Sex, No. (%)			
Male	108 (65.5)	11 (68.8)	>.99
Female	57 (34.5)	5 (31.2)	
Age, y*	48.9 (10.9)	52.7 (11.0)	.20
BMI*	38.6 (9.25)	36.2 (7.66)	.32
RDI*	44.3 (30.3)	28.7 (11.6)	.04
Follow-up, mo*	39.9 (21.6)	34.8 (17.2)	.35
nGER score*			
Pretreatment	3.38 (0.89)	3.56 (1.03)	.50
Posttreatment	1.75 (0.99)	3.44 (0.81)	<.001
P value for change	<.001	.55	. . .
CPAP pressure, cm H_2O*	9.15 (1.52)	. . .	. . .
Posttreatment nGER, No. (%)			
Better	123 (74.5)	5 (31.2)	<.001
Same	39 (23.6)	8 (50.0)	
Worse	3 (1.8)	3 (18.8)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CPAP, continuous positive airway pressure; nGER, nocturnal gastroesophageal reflux; OSA, obstructive sleep apnea; RDI, respiratory disturbance index.
*Mean (SD).

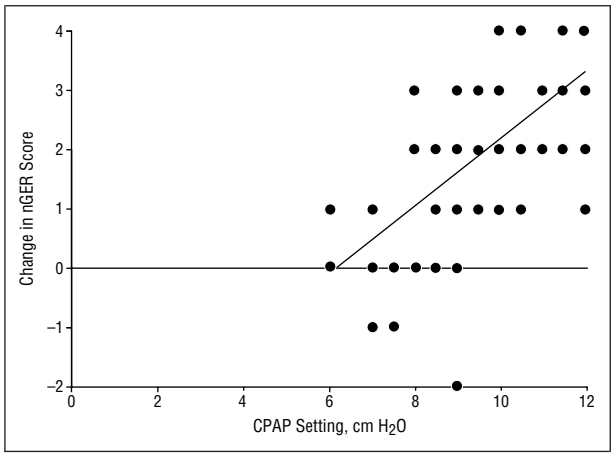

Figure 2. Scatterplot showing the change in nocturnal gastroesophageal reflux (nGER) score after continuous positive airway pressure (CPAP) treatment. Trend line (least squares) demonstrates that higher CPAP settings result in greater improvement in nGER.

Table 3. Characteristics of Patients With OSA Who Had an Increase in nGER Score With CPAP (Responders) and Those Who Had Either a Decrease or No Change in nGER Score (Nonresponders)

	Responders	Nonresponders	*P* Value
Patients, No.	123	42	. . .
Age, y*	48.4 (11.1)	50.7 (10.3)	.35
BMI*	38.7 (38.7)	38.2 (10.1)	.35
Pre-CPAP nGER*	3.53 (0.83)	2.93 (0.89)	<.001
Change in nGER with CPAP*	2.22 (0.82)	−0.010 (24.2)	<.001
Pre-CPAP RDI*	48.3 (31.3)	32.8 (24.2)	<.001
CPAP pressure, cm H_2O*	9.64 (1.29)	7.38 (0.82)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CPAP, continuous positive airway pressure; nGER, nocturnal gastroesophageal reflux; OSA, obstructive sleep apnea; RDI, respiratory disturbance index.
*Mean (SD).

the following: no current telephone or address (10 patients), died of myocardial infarction (3 patients), and died in a motor vehicle accident (2 patients). There was no significant difference in sex, age, weight, height, BMI, RDI, PPI use, H_2RA use, or nGER score before treatment between patients who could and could not be contacted. The similarity of these groups makes response bias unlikely. Eight patients currently using CPAP were excluded from further analysis, because they either had undergone antireflux surgery or had begun using a PPI during follow-up. Any change in nGER score after treatment with CPAP in these patients would be difficult to interpret and could potentially bias the results.

Of the remaining 181 patients with OSA and nGER, 165 (91%) were still using nasal CPAP and 16 (9%) were not. The reasons given for discontinuing CPAP were discomfort with the mask in 14 patients and nasal dryness in 2 patients. Patients who were not compliant with CPAP acted as a control group for this analysis. The characteristics and results of patients who were and who were not using CPAP are summarized in **Table 2**. The patients compliant with CPAP had a 48% improvement in nGER score, from a mean of 3.38 before CPAP treatment to 1.75 after treatment ($P<.001$), while patients not using CPAP (control subjects) did not (mean, 3.56 to 3.44; $P=.55$). Among the group of patients compliant with CPAP, 75% (123/165) showed improvement in their nGER scores, compared with only 31% (5/16) in the control group ($P<.001$). The compliant group also had fewer patients with a worsening in nGER score (3/165 [2%]) than the control group (3/16 [19%]), a difference that was also statistically significant ($P<.001$). The RDI was significantly greater in patients compared with controls. There was no significant difference between the groups in any other measures, including sex, age, weight, height, BMI, duration of follow-up, PPI, and H2RA use.

An important finding of our study was a strong correlation between the change in nGER score and CPAP pressure (correlation, $r=0.70$; $P<.001$), with patients with higher CPAP pressures demonstrating a greater improvement in nGER score (**Figure 2**). There was also a weak correlation between the RDI and the pretreatment nGER score (correlation, $r=0.22$; $P=.004$). Patients with more severe OSA, as evidenced by a higher RDI, had more severe nGER before treatment. There was no significant correlation between BMI or age and pretreatment nGER ($P=.42$ and .05, respectively).

The data were analyzed categorically by response or nonresponse after CPAP use. The 123 patients with an improvement in nGER score with CPAP (*responders*) were compared with the patients in whom the nGER score either did not change (39 patients) or worsened (3 patients) (collectively termed *nonresponders*) (**Table 3**). The mean CPAP pressure was 31% greater in responders than in nonresponders (9.64 vs 7.38 cm H_2O; $P<.001$). The mean pretreatment GER score was significantly higher in the responders than in the nonresponders

(3.53 vs 2.93; $P<.001$), as was the mean RDI (48.3 vs 32.8; $P<.001$).

COMMENT

The 62% incidence of nocturnal GER in our cohort of patients with OSA is consistent with the findings of other studies (53% to 76%).[4,5] The reasons for this strong association are not completely understood. It is evident that obesity predisposes to both conditions. Gastroesophageal reflux has been found to be more frequent and prolonged in patients with OSA than in BMI-matched controls.[7] Obstructive sleep apnea has been postulated to trigger acid reflux episodes by producing decreased intrathoracic pressure during apneic episodes and/or increased arousals and decreased sleep efficiency causing LES relaxation.[7] Kerr et al[6] found that arousals, movement, and swallowing were more frequent within 30 seconds before GER events. They also found that nadir intrathoracic pressure was lower before GER episodes, but a direct association between GER events and obstructive apneas was not identified. In a study by Graf et al,[12] 8 patients with mild OSA (apnea-hypopnea index between 5 and 15) were compared with 9 patients with severe OSA (apnea-hypopnea index >15) during 24-hour esophageal pH monitoring and simultaneous apnea monitoring during the night. Although nearly all patients had GER, there was no significant difference in reflux times between the groups, nor were reflux episodes and apnea periods correlated in time. Ing et al[7] found that 40% to 50% of arousals and apneas were temporally related to esophageal acid reflux in 63 patients.

We found a correlation between the severity of OSA (measured by RDI) and the severity of nGER. This could be explained by either OSA worsening nGER, by the previously mentioned mechanisms, or by GER precipitating apneic events through microaspiration producing laryngeal inflammation and edema or by a vagal-mediated reflex. Ing et al[7] found that patients with OSA receiving nizatidine had a significantly lower mean RDI than patients receiving placebo, supporting the theory that GERD worsens OSA. Although our study supports a strong association between nGER and OSA, it does not examine the pathophysiologic mechanisms behind this association.

We found that nasal CPAP decreased the frequency of nGER by 48% in the treatment group. This is consistent with previous smaller studies.[3,6-9] Although 75% of the patients using CPAP had an improvement in their nGER score, only 31% of the control group did. In previous studies CPAP has reduced GER in patients with and without OSA, supporting the theory that the antireflux effect of CPAP is nonspecific and likely due to increases in intraesophageal pressure or reflex increases in LES tone.[7-9] Fournier et al[13] studied esophageal function in 16 healthy control subjects with nasal CPAP at 4 and 8 cm H_2O. They found that mean esophageal pressure rose by 1.9 cm H_2O and 2.6 cm H_2O, respectively. In contrast to the study by Kerr et al,[6] this increase in LES pressure was not significant. It was concluded that CPAP reduced GER by increasing mean esophageal pressure through a direct transmission of pressure. This is supported by the finding in our study of a strong correlation between the CPAP pressure and the improvement in nGER. We found that the mean CPAP pressure of patients whose nGER responded to treatment was 31% greater than that of nonresponders (9.64 vs 7.38 cm H_2O). Responders also had a higher RDI than nonresponders; however, this likely represents a confounding variable, as patients with higher RDI generally receive higher levels of CPAP. The finding of responders having higher pretreatment nGER scores is more difficult to explain. It is likely due to the fact that severe OSA is associated with worse nGER (shown in our study). Patients with more severe OSA are treated with higher CPAP pressures, which in turn decreases nGER more effectively.

Our study offers important new information to elucidate the relationship between nGER symptoms, OSA, and a major reduction in nocturnal reflux by nasal CPAP. It does, however, have some limitations. There was a potential for bias when the interviewer obtained follow-up. The patients may have minimized their symptoms in an effort to please the interviewer, possibly inflating the benefit of CPAP on nGER. This is unlikely, however, because patients were unaware of the intention of the study. Other limitations are the self-reported nature of patient responses to the questions about nGER, medication use, CPAP use, CPAP pressure setting, and surgery. Our control group consisted of patients who did not use CPAP. However, patients were self-assigned to the control group rather than being randomized. Nonetheless, the reasons for assignment to the control group were intolerance of the CPAP apparatus, unrelated to reflux. The reliability and validity of our single nighttime reflux question has not been formally established. However, it has strong face validity. In a recent national telephone survey about GERD,[2] the following symptoms were chosen, by expert clinical consensus, to represent nGER: " . . . awakened at night by coughing or choking because of fluid, an acid or bitter taste or food in the throat. . . ." The key elements of this expert consensus are very similar to those in our question. Although our study lacks the objective measure of esophageal pH, the symptoms of GERD are generally accepted for use in population research.[10,11,14] Despite these limitations, we believe that the large number of patients, long duration of follow-up, and new information make our study important.

In conclusion, we found that nGER is common in patients with OSA, and that treatment with nasal CPAP decreases the frequency of nGER symptoms by 48%. Higher nasal CPAP pressures are associated with greater improvement in nGER, supporting the hypothesis that nasal CPAP works by increasing mean esophageal pressure via a direct transmission of pressure to the esophagus.

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