Symptoms of Aerophagia Are Common in Patients on Continuous Positive Airway Pressure Therapy and Are Related to the Presence of Nighttime Gastroesophageal Reflux

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Study Objectives: Continuous positive airway pressure (CPAP), the mainstay treatment for obstructive sleep apnea (OSA), involves administration of air under pressure to the upper airway. A well-known but poorly understood side effect of positive airway pressure therapies is aerophagia, air entering the esophagus and stomach rather than the lungs. Gastric distension, a consequence of aerophagia, can increase gastroesophageal reflux (GER) by increasing transient lower esophageal sphincter relaxations, the most common cause of reflux. This study aimed to determine: (i) the prevalence of aerophagia symptoms in a group of OSA patients on CPAP therapy, and (ii) whether aerophagia symptoms are related to an increase in prevalence of GER symptoms.

Methods: Consecutive OSA patients undergoing polysomnography for the purpose of optimizing their CPAP therapy completed a validated questionnaire regarding GER symptoms and aerophagia symptoms. Complete datasets were collected for 259 individuals (203 males).

Results: The group with aerophagia symptoms ($n = 130$) had a greater prevalence of frequent ($\geq$ once a week) GER symp-

toms (29% vs. 10%, $p < 0.05$) and nighttime GER symptoms (9 vs. 2%, $p < 0.05$) than those without aerophagia ($n = 129$). The group with nighttime GER symptoms ($n = 27$) had a greater prevalence of aerophagia symptoms (63% vs. 23%, $p < 0.05$) than those without nighttime GER symptoms ($n = 232$).

Conclusions: In patients with OSA being treated with CPAP, the prevalence of GER and nighttime GER symptoms is greater in those with symptoms of aerophagia than those without. CPAP-induced aerophagia might precipitate GER, particularly nighttime GER, by exacerbating transient lower esophageal relaxations through gastric distension.

Keywords: Sleep apnea, continuous positive airway pressure, aerophagia, gastroesophageal reflux

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Continuous positive airway pressure (CPAP), the mainstay treatment for obstructive sleep apnea (OSA), involves administration of air under pressure to the upper airway via a nose or facemask. CPAP provides a pneumatic splint for the upper airway preventing narrowing or collapse of the airway lumen during sleep.¹ A well-recognized but poorly understood side effect of CPAP is ingestion of air into the esophagus and stomach, known as “aerophagia.” The consequences of aerophagia include diminished efficiency of the respiratory muscles, reduced cardiac output, uncomfortable distension of the stomach from gastric insufflation, and the potential for regurgitation and aspiration of stomach contents.²⁻⁴ Symptoms resulting from aerophagia include bloating, belching, decreased appetite, diarrhea, flatulence, and stomach noise.

During sleep, relaxation of the upper esophageal sphincter (UES) increases susceptibility to passage of pressurized air through it and into the esophagus.⁵ Once in the esophagus, air can enter the stomach via two main mechanisms. Firstly, esophageal distension causes reflex relaxation of the lower esophageal sphincter (LES), the main barrier between the stomach and the esophagus.^{6,7} Secondly, esophageal distension

BRIEF SUMMARY

Current Knowledge/Study Rationale: Aerophagia is a well-recognized side-effect of CPAP therapy. Gastric distension caused by aerophagia has the potential to precipitate gastroesophageal reflux events by way of an increase in transient relaxations of the lower esophageal sphincter. There has been very little research examining the potential link between GER and aerophagia, therefore the aim of the present study was to investigate this link in a large group of OSA patients being treated with CPAP therapy.

Study Impact: This is the first study to show that symptoms of aerophagia are extremely common in OSA patients on CPAP therapy. Symptoms of GER are significantly more common in individuals who report symptoms of aerophagia suggesting aerophagia may precipitate GER. This study suggests that individuals on CPAP should be monitored for symptoms of aerophagia and reflux to ensure that these common problems are detected and addressed.

activates the esophago-upper esophageal sphincter contractile reflex (EUCR/2P).^{8,9} This reflex results in increased UES pressure, presumably to protect the airways from refluxed material within the esophagus. However this increased UES pressure also acts to prevent air escaping into the pharynx, in which cir-

cumstance secondary peristalsis will propel the air down the esophagus, through the relaxed sphincter and into the stomach.

A consequence of air entering the stomach is gastric distension, which has been shown to increase the rate of transient lower esophageal sphincter relaxations (TLESR), the main mechanism underlying GER events.¹⁰⁻¹⁴ If such an increase in TLESR was combined with a reflex decrease in basal LES tone, as would be affected by air-induced esophageal distension, the propensity for GER events may be further increased. Despite this potential, several studies, including our own, have shown that CPAP can reduce GER events and symptoms in individuals with and without OSA, presumably by increasing intraesophageal pressure and LES tone.¹⁵⁻¹⁷ However these studies have not sought to identify individuals with aerophagia, in whom the positive effects of CPAP on GER might be mitigated by the degree to which CPAP causes aerophagia-induced gastric distension.

To date only one study has investigated the potential link between GER and aerophagia in OSA patients on CPAP therapy,¹⁸ and reported the presence of GER disease (GERD, defined by symptoms, medication or physician diagnosis) in 77% of patients on CPAP who report having aerophagia symptoms versus 36% of patients on CPAP who did not report aerophagia. While suggestive of an increased prevalence of sleep-related GER in patients on CPAP who experience aerophagia, the sample size of this study was relatively small, with 22 individuals in each group, and it did not specifically investigate GER symptoms *at night*, which is most relevant given that CPAP therapy for OSA is only applied during sleep.

The present study was undertaken to address these issues. Its aim was to determine the prevalence of aerophagia symptoms in a large group of OSA patients being treated with CPAP therapy and to determine whether the presence of aerophagia was related to an increased prevalence of GER symptoms.

METHODS

The study was approved by the Human Research Ethics Committee of Sir Charles Gairdner Hospital.

Study Population

Over an 18-month period, 477 consecutive patients undergoing in-laboratory polysomnography and CPAP titration were identified. These individuals had been prescribed CPAP previously, used it at home for a period of time (median time on CPAP was 1-6 months) and returned to the sleep laboratory for titration. Reasons for the titration study included: routine pressure check, problems with therapy tolerance/compliance, residual symptoms and weight gain/loss. These 477 individuals were asked to complete a questionnaire regarding aerophagia and GER symptoms prior to their titration study. Of this group, complete data sets of polysomnographic measurements and GER questionnaires were available on 259 individuals, in whom all subsequent data analyses were undertaken.

Polysomnography

All patients underwent in-laboratory polysomnography including monitoring of: electroencephalogram (C4-A1 and C3-A2); left and right electrooculograms; submental electro-

myogram; electrocardiogram; abdominal and thoracic motion; leg movements; nasal and oral airflow; nasal pressure; oxygen saturation; body position; and sound (E-Series, Compumedics, Melbourne, Australia). Categorization of sleep stage and respiratory events were performed according to standard criteria.^{19,20} The severity of sleep disordered breathing was defined by the apnea-hypopnea index (AHI), which is the average number of apneas and hypopneas per hour of sleep.

Questionnaire

The GER questionnaire (GERQ) was developed and validated against physician interview at the Mayo Clinic^{21,22} and designed to determine the presence of heartburn and acid regurgitation, chest pain, dysphagia, other gastroesophageal conditions, medication use and some lifestyle factors. For the purpose of the present study the GERQ was modified to investigate the effect of CPAP on GER symptoms. Specifically, the questionnaire asked about GER symptoms “since starting CPAP treatment” rather than “in the last 12 months” as was the case in the original questionnaire. Questions regarding the length of time they had been using therapy (i.e., months/years on CPAP) and their compliance with therapy (i.e., the number of hours per night and nights per week using CPAP) were also included. In addition, several questions were added regarding symptoms of aerophagia (see below). The questionnaire was also modified by replacing USA pharmaceutical names with Australian equivalents.

Characterizing GER Symptoms Using the GERQ

Heartburn or acid regurgitation experienced at least once in the last 12 months was defined as “any GER” and, if experienced at least once a week, was defined as “frequent GER.”^{21,23} The term “GER symptoms” refers to symptoms experienced at any time during the day or night, while “nighttime GER (nGER) symptoms” specifically refers to symptoms which woke the patient from sleep.

Characterizing Aerophagia Symptoms Using the GERQ

Patients were asked if they experienced any of the following after using CPAP: an increase in stomach noise/rumbles; bloating (particularly in the morning); reduction in morning appetite; belching; an increase in flatulence; or an increase in diarrhea. Aerophagia symptoms were analyzed as a binary variable, i.e., if a patient stated they had experienced one of the symptoms since being on CPAP therapy, they were classified as having aerophagia.

Statistical Analyses

Analyses were performed using SPSS (Version 15.0, SPSS Inc., Chicago, USA). Patients were categorized into an “aerophagia” group and a “no aerophagia” group, a “GER” and a “no GER” group, and a “nGER” and a “no nGER” group according to their questionnaire responses. Anthropometric data and prevalence data (i.e., prevalence of GER and aerophagia) were compared between these subgroups using unpaired t-tests and χ^2 tests or Mann-Whitney rank sum tests when data were not normally distributed. Univariate and multivariate logistic regressions were conducted to determine significant predictors of GER and aerophagia symptoms. Results are presented as mean

(standard deviation). Logistic regression results are presented as odds ratio (OR), 95% confidence interval (CI), and p-value. A p-value < 0.05 was considered significant for all statistical tests.

RESULTS

At the time of OSA diagnosis the group were 52 ± 13 years of age ($n = 234$), with a BMI of 35 ± 7 kg/m² ($n = 214$) and an AHI of 44 ± 35 events/h ($n = 225$). Mean prescribed CPAP pressure for the group was 11 ± 2 cmH₂O ($n = 159$). For the present analyses, complete questionnaire and polysomnographic data were available for 259 individuals (203 males). At the time of questionnaire completion, the group mean age was 54 ± 12 years ($n = 259$), BMI was 35 ± 8 kg/m² ($n = 259$), and AHI for the night of the CPAP titration was 14 ± 17 events/h ($n = 259$). Of these individuals, 130 (50.2%) reported aerophagia and 129 reported no aerophagia.

Effects of Aerophagia Symptoms

There were no differences between the groups with and without aerophagia in terms of gender (75 vs. 81% male, $p = 0.24$), age (54 ± 13 vs. 54 ± 12 years, $p = 0.89$), BMI (34 ± 7 vs. 35 ± 9 kg/m², $p = 0.19$), CPAP pressure (11 ± 2 vs. 11 ± 4 cmH₂O, $p = 0.90$), or residual AHI on CPAP (14 ± 20 vs. 15 ± 14 /h, $p = 0.70$), although there were more patients taking reflux medications in the aerophagia group (32% vs. 21%, $p < 0.05$). The prevalence of GER and nGER symptoms was significantly greater in the aerophagia group, regardless of whether symptoms occurred at least once in the last 12 months (“any”) or at least once a week (“frequent”) (Figure 1).

Univariate logistic regression analyses showed there were no significant effects of gender, age, BMI, self-reported CPAP compliance, or time on CPAP on the presence/absence of aerophagia symptoms. The use of GER medication, any or frequent GER symptoms or any or frequent nGER symptoms were all significant univariate predictors of “any aerophagia symptom.”

Individual multivariate logistic regression models to predict aerophagia were constructed for each measure of GER (any or frequent GER, any or frequent nGER). After accounting for gender, age, BMI, and use of GER medications, the only significant predictor of aerophagia symptoms in each model was GER symptoms whether considered as any GER (OR = 2.0, CI = 1.2-3.3, $p = 0.009$), frequent GER (OR = 3.3, CI = 1.6-6.7, $p = 0.001$), any nGER (OR = 5.2, CI = 1.9-14.5, $p = 0.001$), or frequent nGER (OR = 3.8, CI = 1.0-14.1, $p = 0.046$).

Effects of GER and nGER Symptoms

When the groups were compared in terms of those with and without GER or with and without nGER, there was a greater prevalence of aerophagia symptoms in those with GER than those without, and in those with nGER symptoms than those without (Table 1).

Univariate logistic regression analyses showed no significant effects of gender, age, BMI, or CPAP compliance on the presence of any or frequent GER or nGER symptoms; however, time on CPAP significantly predicted any nGER. Use of GER medication, and the presence of aerophagia symptoms (whether expressed as individual symptoms or as “any symptoms”) significantly predicted the presence of any or frequent GER or nGER symptoms in univariate analyses.

Figure 1—Prevalence of GER and nGER symptoms (any and frequent) in those with and without aerophagia symptoms

* $p < 0.05$ aerophagia vs. no aerophagia. GER, gastroesophageal reflux symptoms (heartburn or acid regurgitation); nGER, nighttime gastroesophageal reflux symptoms (heartburn or acid regurgitation during sleep).

The variables which significantly predicted any GER in the multivariate model were the use of GER medications (OR = 3.3, CI = 1.8-6.1, $p < 0.001$) and aerophagia symptoms (OR = 2.0, CI = 1.2-3.4, $p = 0.013$). Variables which significantly predicted frequent GER symptoms were the use of GER medications (OR = 2.6, CI = 1.3-5.0, $p = 0.006$) and aerophagia symptoms (OR = 3.3, CI = 1.6-6.7, $p = 0.001$).

The only significant multivariate predictor of any nGER was aerophagia symptoms (OR = 5.3, CI = 1.9-14.8, $p = 0.001$). Likewise, the only significant multivariate predictor of frequent nGER symptoms was also aerophagia symptoms (OR = 3.8, CI = 1.0-14.2, $p = 0.046$).

To test the directionality of the association between GER and aerophagia, we analyzed data from 127 individuals who had completed the reflux questionnaire both before commencing CPAP (as part of a related study²⁴) and after commencing CPAP (as described above). We did not find any difference in the occurrence of aerophagia symptoms on CPAP between those who had GER symptoms before commencing CPAP and those who did not. Furthermore, logistic regression analysis failed to demonstrate any relationship between GER/nGER symptoms before CPAP treatment and aerophagia symptoms after commencement of it.

DISCUSSION

The main findings of this study are that: (i) symptoms of aerophagia are common (reported by 52%) in OSA patients on CPAP therapy; (ii) the presence of GER and nGER symptoms is greater in individuals reporting aerophagia, being 57% vs. 37%

Table 1—Prevalence of aerophagia symptoms in those with and without GER symptoms

	GER	No GER	nGER	No nGER
N	113	146	27	232
Gender (% males)	73	83	74	79
Age (years)	53 (12)	54 (13)	54 (12)	53 (12)
BMI (kg/m ²)	35 (7)	34 (9)	36 (8)	34 (8)
AHI (events/h)	13 (19)	15 (16)	11 (10)	15 (18)
Reflux medications (%)	42	14 [†]	33	26
CPAP pressure	11 (3)	11 (3)	11 (3)	11 (3)
Increased stomach noise (%)	28	16 [†]	48	18 [†]
Morning bloating (%)	33	10 [†]	41	17 [†]
Decreased morning appetite (%)	18	8 [†]	22	11
Increased belching (%)	21	5 [†]	37	10 [†]
Increased flatulence (%)	43	26 [†]	59	31 [†]
Increased diarrhea (%)	18	5 [†]	18	10
Any aerophagia symptom (%)	65	38 [†]	81	47 [†]

Data are presented as mean (SD) or percent of population. [†]p < 0.05 GER vs. no GER. [†]p < 0.05 nGER vs. no nGER. GER, gastroesophageal reflux symptoms (heartburn or acid regurgitation); nGER, nighttime GER symptoms (heartburn or acid regurgitation during sleep); OSA, obstructive sleep apnea; BMI, body mass index; AHI, apnea hypopnea index.

for any GER, 29% vs. 10% for frequent GER, 17% vs. 4% for any nGER, and 9% vs. 2% for frequent nGER (**Figure 1**); and (iii) the presence of aerophagia symptoms is the strongest predictor of GER or nGER symptoms when using CPAP and vice versa. These data suggest that aerophagia induced by CPAP therapy may precipitate GER.

There has been very little research examining the potential link between aerophagia and GER in OSA patients using CPAP therapy. In the only study to date, Watson et al. reported GER disease (GERD, defined by symptoms, medication or physician diagnosis) to be more common in 22 patients who reported aerophagia than in 22 patients who did not (77% vs. 36%, respectively).¹⁸ These results are consistent with the findings of the present study, in which the presence of GER and nGER symptoms was far greater in individuals reporting aerophagia (n = 130) than those without (n = 129). Also consistent between the two studies is the finding that more patients who report aerophagia take GERD medications than controls, (in the case of the Watson et al. study), and that more patients were taking reflux medications in the aerophagia group in the current study. Taken together, these data support the suggestion of Watson et al. that aerophagia may indeed cause GER.

It is likely that increased TLESRs are involved in any aerophagia-induced GER. During CPAP therapy, movement of air from the upper airway into the esophagus is facilitated by a sleep-induced reduction in upper esophageal tone.⁵ The resultant increase in upper esophageal intraluminal pressure may trigger non-deglutitive esophageal peristalsis, moving the bolus of air towards the stomach.²⁵ In addition, the esophageal distension caused by the presence of air in the esophagus has been shown to trigger LES relaxation, further encouraging passage of air into the stomach. The resultant gastric distension can trigger vagally mediated TLESRs. It is well established that GER events primarily occur during TLESRs; therefore, it is likely that any increase in GER with aerophagia is precipitated by way of an increase in TLESRs.

Our data cannot directly answer the question of whether aerophagia precipitates GER or whether GER precipitates aerophagia.

However, a sub-analysis of 127 individuals who had completed the reflux questionnaire both before commencing CPAP (as part of a related study²⁴) and after commencing CPAP (this study) did not show any difference in the prevalence of aerophagia symptoms in individuals on CPAP between those who did and did not have GER symptoms before commencing it. Furthermore logistic regression failed to show any relationship between reported GER/nGER symptoms before CPAP treatment and occurrence of aerophagia symptoms after commencing it. These findings suggest that individuals with preexisting GER are not predisposed to aerophagia when on CPAP. Thus, it appears more likely that aerophagia precipitates GER than the reverse.

The results of the present study need to be reconciled with several previous studies, including our own, which have reported that CPAP reduces GER events and symptoms in those with and without OSA via a CPAP-induced increase in intraesophageal pressure and LES tone.^{15,16,24,27} It is important to note that none of these studies reported whether or not the patients had aerophagia. Hence they have not accounted for the possibility that beneficial effects of CPAP on GER could be offset, at least to some extent, by aerophagia, gastric distension, and TLESRs. In this regard, it is likely that upper esophageal sphincter tone, rather than lower esophageal sphincter tone, is a more important factor in individuals with aerophagia, as upper esophageal sphincter barrier pressure decreases markedly during sleep,⁵ making it particularly vulnerable to being breached by positive airway pressure, perhaps in a dose-dependent manner.

There are several limitations to the present study. Firstly, we did not have an objective measure of GER. However, a symptomatic diagnosis of GERD is accepted clinically. Secondly, a significant proportion of individuals did not complete the questionnaire and were therefore not included in the analysis. There was a significantly lower proportion of males among those who did not complete the questionnaire (69% vs. 79%), and those who did not complete the questionnaire tended to be older (54 ± 12 vs. 58 ± 12 years); however, there were no differences between BMI or AHI, therefore we do not believe these differences significantly influenced the results of the study. Thirdly,

CPAP pressures were not available for all patients; however, results were similar when only subjects with known CPAP pressures were analyzed. In addition, there was no relationship between CPAP pressure used and the presence of either GER or aerophagia symptoms, although the effect of changing pressure on symptoms was not examined; other work suggests reducing ventilator pressure may also reduce aerophagia.² Fourthly, symptoms such as belching and bloating are common among those with GER and may be a manifestation of GERD rather than aerophagia; however, by including questions regarding several different symptoms and asking about *changes* in symptoms “since beginning CPAP,” we have minimized this possibility. Finally, there are variables which may affect GER and/or aerophagia that were not included in the logistic regression analysis such as diet, meal size and timing of food intake. Due to the potentially variable effects of these factors on GER²⁸⁻³² and the lack of published effects of these factors on aerophagia, they were not included in our analyses.

In conclusion, the present study shows that the symptoms of aerophagia are extremely common in patients with OSA being treated with CPAP, and that aerophagia may, of itself, precipitate GER. These results suggest that individuals on CPAP should be monitored for symptoms of aerophagia and GER to ensure these frequent problems are detected and dealt with.

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