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SCIENTIFIC INVESTIGATIONS

Nasal Cytology: a Marker of Clinically Silent Inflammation in Patients with Obstructive Sleep Apnea and a Predictor of Noncompliance with Nasal CPAP Therapy

Farhad F. Shadan, M.D., Ph.D.[1]; Alfredo A. Jalowayski, Ph.D.[1]; John Fahrenholz, M.D.[2]; Lawrence E. Kline, D.O.[1]; Arthur Dawson, M.D.[1]

[1]Scripps Clinic Sleep Center and [2]Division of Allergy and Immunology, Scripps Clinic and the Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA

Study Objectives: Patients with obstructive sleep apnea treated with nasal continuous positive airway pressure (CPAP) often complain of nasal side effects. We studied patients before and after initiation of nasal CPAP to see how treatment affected nasal function and markers of nasal inflammation. We searched for pretreatment findings that might help to predict noncompliance.

Methods: Nasal symptom scores, nasal flow by anterior rhinomanometry, mediator levels (intercellular adhesion molecule-1, interleukin-6, interleukin-8 and interleukin-13), and nasal scrapes for cytology were obtained at baseline and monthly for up to 3 months of nasal CPAP therapy. Compliance was assessed from the patient's report and by recording hours of usage for up to 19 months of follow-up.

Results: Thirty-eight patients with newly diagnosed obstructive sleep apnea were classified as having no rhinitis (42%), allergic rhinitis (37%), or nonallergic rhinitis (21%). There was no significant difference in compliance in patients with and without rhinitis. Compliant and noncompliant patients showed no significant differences in their baseline nasal symptom scores, nasal flow, and mediator levels. Nasal neutrophil counts before treatment were greater in noncompliant than in compliant patients ($p = .004$) and greater in those discontinuing because of nasal symptoms than in patients who quit for other reasons ($p = .05$). There was a positive correlation between neutrophil counts and nasal bacterial scores, both before and after treatment with nasal CPAP.

Conclusions: Patients with increased neutrophil counts in the nasal scrape before beginning nasal CPAP are at increased risk of discontinuing therapy. They appear to have subclinical nasal inflammation that cannot be identified from clinical assessment, nasal symptom scores or rhinomanometry.

Keywords: Rhinitis, CPAP, compliance, adherence, inflammation, cytokines, rhinomanometry, cytology, neutrophils

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Obstructive sleep apnea (OSA) is a common condition that impairs the quality of life and is associated with an increased risk of hypertension, cardiovascular events, and motor vehicle accidents.[1-3] The most effective treatment is nasal continuous positive airway pressure (CPAP), but many patients cannot tolerate it. One large study found that patients with the greatest apnea-hypopnea indexes and those with more daytime sleepiness were more likely to continue on nasal CPAP after 3 years.[4] Other investigators have reported that there is no reliable way to predict which patients will continue with the therapy over the long term.[5,6] Those who discontinue treatment report a variety of problems, including lack of benefit and difficulty sleeping. Upper-airway symptoms like dryness, nasal stuffiness, and "sinusitis" are frequent complaints of those who drop out.[7,8]

It is reasonable to assume that patients suffering from chronic rhinitis would be at increased risk of being intolerant of nasal CPAP, but no prospective analysis of nasal function has been done in patients initiating therapy. Nor has there been any systematic investigation of how nasal function is affected by nasal CPAP. If there were some way of predicting which patients would be at risk of intolerance of nasal CPAP, then perhaps their compliance could be improved if they were started on topical nasal steroids or if they were prescribed humidified units when nasal CPAP was initiated.

We undertook this study to learn whether patients with rhinitis have more difficulties in tolerating nasal CPAP therapy than do patients without rhinitis and to see whether nasal CPAP produces or aggravates rhinitis. We tested whether assessment of nasal cytology, nasal inflammatory mediator levels, and nasal airflow would better predict noncompliance due to nasal side effects than the standard clinical evaluation. Nasal cytology was performed on nasal scrapes obtained from patients newly diagnosed with OSA to look for the presence of inflammatory cells and bacteria. We investigated, as markers of nasal inflammation, the intranasal levels of interleukins (ie, IL-6, IL-8, IL-13) and intercellular adhesion molecule-1 (ICAM-1) because these mediators have been implicated in the recruitment of nasal inflammatory cells.

METHODS

Subjects

We included patients newly diagnosed with OSA whose physi-

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Drs. Shadan, Jalowayski, Fahrenholz, Kline, and Dawson have indicated no financial conflicts of interest.

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Address correspondence to: Arthur Dawson, M.D., 10666 North Torrey Pines Road, Scripps Clinic, La Jolla, CA 92037-1027; Tel: (858) 554-8845; E-mail: adawson1@san.rr.com

cians had prescribed nasal CPAP and who were willing to return for 3 monthly follow-up visits. We did not exclude patients with chronic rhinitis or those using topical and systemic medications for rhinitis, wishing to see the whole spectrum of patients for whom nasal CPAP was prescribed.

In all patients, the diagnosis was established by in-laboratory polysomnography, in most cases a split-night study in which the latter half was used for "CPAP titration."

The study was approved by the Scripps Clinic Institutional Review Board.

Equipment

Most of our patients were under managed-care contracts and obtained their equipment through several home-care providers. However, the model of mask was selected in our CPAP clinic, and the choice was based on patient comfort. Patients were not routinely started on humidified CPAP units, which later proved necessary in only 2 patients. Decisions about changing mask type, CPAP pressure, and medications for nasal symptoms were made by the sleep specialist managing the patient and not by those conducting the study.

Diagnosis of Rhinitis

Subjects with newly diagnosed OSA were classified by history and physical examination as having rhinitis or no rhinitis. The diagnosis of rhinitis was based on history of 1 or more symptoms of stuffy, blocked, runny nose; sneezing; postnasal drip associated with the need to rub the nose or blow the nose; and evidence of rhinitis on the physical examination.

A complete list of medications was obtained to include the use of nasal corticosteroids, decongestants, antibiotics, and antihistamines.

Nasal Symptom Score

Patients completed the 28-item Rhinoconjunctivitis Quality of Life Questionnnaire[9] at each visit. This questionnaire includes questions about sleep quality, which would be expected to improve with nasal CPAP, and others that were more relevant to allergic rhinitis. Therefore we calculated a nasal symptom score using only the 4 questions pertaining to nasal symptoms. Each of the symptoms (stuffy/blocked nose, runny nose, sneezing, and itchy nose) was given a score from 0 to 6, so the nasal symptom score could range from 0 to 24.

Allergic Versus Nonallergic Rhinitis

All participants were evaluated by allergy skin testing. Those in the rhinitis group who tested positive were categorized as allergic rhinitis, and those who tested negative were designated nonallergic rhinitis. The allergic skin test included standardized subcutaneous injections of histamine (positive control), glycerine (negative control), and standard extracts of allergens from grasses, Bermuda, Johnson, dog, cat, dust mite, cockroach, aspergillus, weeds, trees, and mold. A positive skin test is defined as at least 1 area of wheal and flare greater in magnitude than that of the negative control. Allergy skin testing was not repeated if it had been done during the previous year. None of the patients was on systemic antihistamines or systemic glucocorticoids, which would invalidate allergy skin testing.

Nasal Cytology

Nasal scrapings were performed for cytology before the initiation of nasal CPAP therapy and at each follow-up visit to detect neutrophils, eosinophils, and basophils. Scrapings of the inferior turbinate were obtained from each nostril with a disposable curette. They were placed on a microscope slide, fixed at room temperature for at least 1 minute in 95% ethanol bath, and then were allowed to dry in air and stored. The slides were later stained and viewed under the microscope. The number of neutrophils, eosinophils, and basophils per high-power field (HPF) was averaged for 10 fields. If a field contained more than 100 cells, it was assigned a value of 100. The presence of bacteria in nasal smears was scored using the following semiquantitative scale: 0, none seen; 1, occasional clump; 2, moderate amount; 3, many easily seen; and 4, large amounts covering the entire field. The physicians, patients, and staff were blinded to the results of nasal cytology, and the nasal cytopathologist had no clinical information.

Nasal Airflow

Nasal flow was measured by 4-phase rhinomanometry, a method of anterior rhinomanometry first described by Vogt and colleagues.[10,11] We measured the flow at an inspiratory pressure of -150 Pascal during phase 1 of the breathing cycle, where flow was increasing at a constant rate. We report the sum of the flows from right and left nostrils, averaging the results of 3 runs.

Measurement of Cytokines

Nasal lavage was performed, and the aspirate used to measure IL-6, IL-8, IL-13, and ICAM-1 by enzyme-linked immunosorbent assay. Each nostril was lavaged with 5 mL of normal saline, and the samples were pooled for each patient at each visit. The pooled lavage aspirate was shaken in a test tube and then centrifuged, and aliquots of the supernatant were stored at -70°C for 3 to 6 months. Aliquots were then thawed and measured for IL-6, IL-8, IL-13, and ICAM-1 using enzyme-linked immunosorbent assay kits from BioSource International, Inc. (Camarillo, CA). The assays were performed in duplicate following the procedures recommended by BioSource, with the reported interassay variability and sensitivity of less than 5 pg/mL.

Assessment of Compliance With Nasal CPAP Therapy

Patients were seen in follow-up monthly for up to 3 months. Compliance was further assessed with telephone calls at 6 months and at approximately 19 months. Patients were considered compliant if they reported using nasal CPAP at least 50% of their time in bed. The patient's report was supplemented by calculating the number of hours of use per month, as recorded by the nasal CPAP machines at the 19th month of follow-up.

Statistical Analysis

Most of the data were not normally distributed, and so we used nonparametric statistical tests—Wilcoxon 2-sample rank test, Wilcoxon signed-rank test, and the Kruskal-Wallis test for comparisons and Kendall's τ test for correlation. We describe the distribution of the data by reporting the median and the interquartile range (IQR). We used the JMP IN 5.1 statistical software (SAS Institute, Inc., Cary, NC) with an α of .05 to reject the null hypothesis.

RESULTS

Thirty-eight patients with newly diagnosed OSA were included in the study (29 men, 9 woman; age range, 30 to 81 years; mean body mass index ± SD, 30.8 ± 7.7). Fourteen patients (37%) were noncompliant with nasal CPAP therapy. The median apnea-hypopnea index in the compliant patients was 39 (IQR 26 to 61), and, in the noncompliant, it was 52 (IQR 21 to 77, p = .63). Hour-meter readings an average of 19 months after the CPAP machines were issued showed that patients defined as "compliant" had a median of 122 hours per month (IQR 106 to 178) of CPAP use. The median duration of nasal CPAP use in the noncompliant group was 2 weeks.

Rhinitis and Nasal CPAP Usage

Twenty-two patients were diagnosed as having rhinitis (58%), and 16 of the subjects were classified as without rhinitis. Fourteen patients (36%) had allergic rhinitis, and 8 had nonallergic rhinitis. Of the 22 with rhinitis, 15 were found to be compliant with nasal CPAP therapy, and 7 were noncompliant. Of 16 patients without rhinitis, 9 were compliant and 7 were noncompliant. These differences were not statistically significant (χ^2, p = .51). Further subclassification of the patients into those without rhinitis and those with allergic rhinitis and nonallergic rhinitis by allergy skin testing did not improve the ability to predict noncompliance (p = .66).

Nasal Symptom Score

The nasal symptom scores are summarized in Table 1. The nasal symptom score was, as expected, greater in the allergic rhinitis and nonallergic rhinitis groups than in the patients with no rhinitis. The nasal symptom score was not significantly different in the compliant and noncompliant patients (p = .25). There was no significant correlation between nasal symptom score and apnea-hypopnea index (p = .47).

Nasal Cytology

We obtained technically satisfactory nasal scrapes on 34 of the 38 participants at baseline. The median baseline neutrophil count was significantly greater in the noncompliant (17.6/HPF, IQR = 0.9 to 27) than in the compliant (0.2/HPF, IQR = 0 to 10.7) patients (p = .004). The 8 noncompliant patients who discontinued nasal CPAP because of nasal symptoms had a median neutrophil count of 24.8/HPF (IQR = 14 to 82). This compared to a median neutrophil count of 0.40/HPF (range = 0.2 to 16.4) in the 3 patients who dropped out for reasons other than nasal symptoms (p = .05).

There was no significant correlation between hours per month of nasal CPAP use and nasal neutrophil count in the compliant patients (τ = -0.23, p = .26).

The median number of neutrophils in the nonallergic rhinitis group (10.7/HPF, IQR = 0 to 26) was not significantly different from that of the rhinitis group (0.3/hpf, IQR = 0 to 14.5) (p = .27). There was no significant correlation between nasal symptom score and the neutrophil counts (τ = -0.03, p = .80) or between neutrophil counts and apnea-hypopnea index (p = .77). The detection of basophils and eosinophils did not add any useful information to the neutrophil counts alone in predicting noncompliance with nasal CPAP.

Nasal Airflow

Baseline nasal airflow in the patients in the allergic rhinitis group (mean ± SD, 305 ± 157) did not differ significantly from those in the nonallergic rhinitis group (400 ± 178) (p = .16 by Wilcoxon 2-sample rank test). It was not significantly different in the patients in the compliant (347 ± 165) versus the noncompliant groups (344 ± 189) (p = .75).

Nasal Inflammatory Mediators

Nasal inflammatory-mediator levels are summarized in Table 2. There was a weak positive correlation between baseline IL-8 level and the neutrophil count (τ = 0.237, p = .061). If we confined the analysis to those patients who had neutrophils in their nasal smears, we found a positive correlation between baseline neutrophil count and nasal IL-6 level (τ = 0.40, p = .01) and between neutrophil count and nasal IL-8 level (τ = 0.52, p = .0008). Baseline levels of ICAM-1, IL-6, and IL-13 were not significantly different in patients with and without rhinitis or in compliant and noncompliant patients. The baseline IL-8 level was actually lower in the patients with than without rhinitis, though the difference was of borderline significance.

Table 1—Changes in Nasal Symptom Scores in Response to nCPAP Therapy

	Before nCPAP		On nCPAP	
	Median	IQR	Median	IQR
All	4.0	0.5-8.0	5.0	2.7-7.6
Allergic rhinitis	7.0	3.8-11.3	5.7	3.3-10.7
Nonallergic rhinitis	5.0	2.3-6.8	5.7	1.9-10.7
No rhinitis	1.0	0.0-3.0	3.3	0.0-6.3
Compliant	3.5	0.0-6.8	4.0	0.0-7.6
Noncompliant	6.0	2.0-9.5	5.7	3.0-8.2
Noncompliant nasal*	8.0	1.5-11.0	5.7	3.2-11.3

Nasal symptom scores did not change significantly with nasal continuous positive airway pressure (nCPAP) in the whole group (p =.90) and the changes were small in the subgroups. IQR refers to interquartile range.
*Noncompliant nasal refers to those patients reporting they discontinued because of nasal symptoms.

Table 2—Nasal Inflammatory Mediator Levels at Baseline in Patients With Newly Diagnosed Obstructive Sleep Apnea

	Rhinitis		No Rhinitis		
	Median	IQR	Median	IQR	p value
ICAM-1	1200	1068-1364	1128	1044-1223	0.31
IL-6	6.85	4.83-10.03	7.90	6.80-18.7	0.17
IL-8	49.2	27.8-92.7	92.3	61.1-276.5	0.05
IL-13	51.2	28.3-71.1	67.7	40.8-81.5	0.21
	Compliant		Noncompliant		
	Median	IQR	Median	IQR	p value
ICAM-1	1175	1047-1370	1144	1098-1276	0.92
IL-6	7.85	5.15-16.25	7.10	4.90-10.45	0.52
IL-8	81.6	40.4-148.2	60.1	28.3-84.7	0.20
IL-13	55.8	23.5-75.5	67.5	48.7-74.4	0.49

Levels, in pg/mL, are listed by group and interquartile range (IQR). ICAM-1 refers intercellular adhesion molecule-1; IL, interleukin.

Changes Following Nasal CPAP

The effect of nasal CPAP on nasal symptom score is summarized in Table 1. None of the changes was statistically significant. The nasal symptom score showed little change in the noncompliant patients, even in those who discontinued because of nasal symptoms. This apparent paradox is explained by the fact that the nasal symptoms leading to discontinuation included "dryness" and "postnasal drip," neither of which was included in the nasal symptom score.

There were no significant changes in ICAM-1, IL-6, IL-8, and IL-13. For the 25 subjects with pretreatment and posttreatment data, the median neutrophil count rose from 1.1 (IQR = 0 to 17.1) to 15.9 (IQR = 2.2 to 41), and the median increase was 6.6 (IQR = -0.25 to 37.4, p = .021 by Wilcoxon signed-rank test). The median change in the neutrophil count was 15.4 (IQR = 0.4 to 39.6) in the compliant patients, and it was -11.7 (IQR = -36.5 to 19.5) in the noncompliant patients (p = .045).

In 26 subjects, the mean nasal flow increased from 344 to 407 following nasal CPAP, but the change did not reach statistical significance by Wilcoxon signed-rank test (p = .052).

Nasal Bacterial Score

Bacteria were detected in the baseline nasal smears of 11 out of 36 subjects. They were seen in the follow-up smears of 13 out of 29. The nasal bacterial score increased in 9 of 33 subjects on at least 1 of the follow up-visits and decreased in 2. There was a significant increase from the baseline to the first follow-up visit (p = .032 by Wilcoxon signed-rank test).

There was a significant positive correlation between the baseline neutrophil count and the baseline nasal bacterial score (τ = 0.314, p = .028) and between the posttreatment neutrophil count and nasal bacterial score (τ = 0.455, p = .0031). There was also a significant correlation between the increase in neutrophil count (averaged over up to 3 follow-up visits) and the greatest increase in nasal bacterial score after treatment (τ = 0.39, p = .013).

The nasal bacterial score of patients with rhinitis was significantly less than that of those without rhinitis (p = .033). There was no significant difference between the nasal bacterial score of compliant and noncompliant patients (p = .33). The nasal bacterial score showed a weak negative correlation with nasal symptom scores (p = .098) and a weak positive correlation with the baseline IL-8 level (τ = 0.272, p = .052). There were no significant correlations with the other 3 mediators or with any of the posttreatment mediator levels.

The Effect of Medications

At baseline, 6 of the 38 patients were on some type of treatment for rhinitis (6 on topical nasal steroids, 1 on decongestants, and 1 on cromolyn). Of these 6 patients, 1 was noncompliant, and 5 were compliant. Medications were added during follow-up visits in 8 patients (systemic corticoids 1, nasal corticoids 1, antihistamines 4, decongestants 2). Of the patients whose medications were changed, 2 were noncompliant and 6 were compliant.

The baseline nasal neutrophil count was lower in the patients on nasal corticoids (n = 5, median 0.2) than in those not on steroids (n = 29, median 7.2, p = .077). Had there been more subjects, it is likely that this difference would have been significant. When patients receiving anti-inflammatory medications were excluded, the baseline neutrophil count still was slightly lower in those with (median 1.7, IQR 0.15 to 17.1) than in those without rhinitis (median 10.7, IQR 0 to 26.1, p = .64). When those receiving medications at baseline were excluded, there was still a significant difference in the neutrophil count between compliant (median 0.75, IQR 0 to 14.9) and noncompliant patients (median 17.6, IQR 0.9 to 27.0) patients (p = .016).

The Effect of Mask Type

Twenty-one subjects had intranasal interfaces for their CPAP, and the rest had various over-the-nose types. Compliance did not differ significantly with the mask type (p = .92)

DISCUSSION

A high prevalence of chronic rhinitis has been reported in patients with OSA.[12,13] One might expect that a person with symptoms of rhinitis before nasal CPAP is initiated would be at a higher risk for noncompliance, but we did not find this to be the case. Nor did we find that nasal symptom scores increased with nasal CPAP in either the compliant or the noncompliant patients. Nasal flow actually increased slightly after treatment, though the change did not reach statistical significance.

We did find that patients with OSA who have a high neutrophil count in their nasal smear at baseline are at increased risk of discontinuing nasal CPAP because of nasal symptoms. However, most of these patients had no clinical evidence of rhinitis.

Our results suggest that some patients with OSA may have low-grade subclinical nasal inflammation, which can be aggravated by nasal CPAP to the point where they cannot tolerate the therapy. The greater increase in the neutrophil count after treatment in the compliant than in the noncompliant patients may be explained by the lower exposure to nasal CPAP of the latter group.

Although the difference was not statistically significant, it was an unexpected finding that patients with rhinitis had fewer neutrophils in their baseline nasal scrapes than those patients without rhinitis. Patients with rhinitis were more likely to be using anti-inflammatory medications but when we excluded those on medications we had the same result. If the patients with rhinitis had an increased volume of nasal secretions, simple dilution might partially explain their reduced neutrophil counts and also their lower nasal bacterial scores. The neutrophilia is presumably a manifestation of nasal inflammation, but in most cases the associated rhinitis appears to be subclinical.

Rubinstein reported that patients with OSA without nasal symptoms have increased polymorphonuclear leukocytes in their nasal washings compared with normal controls.[14] He suggested that neutrophils might compromise nasal patency and increase the tendency for upper-airway collapse. However, neither the history nor rhinomanometry suggested that our patients with high neutrophil counts were more likely to have nasal obstruction.

Salerno and associates found increased numbers of neutrophils in the induced sputum of patients with OSA compared with normal volunteers.[15] They noted Rubinstein's study and also the report by Sekosan et al[16] that there are increased numbers of leukocytes in the lamina propria of surgically removed uvulas of patients with OSA. They suggested that the pressure gradient during intermittent obstruction causes a mechanical stress in the respiratory mucosa that may produce inflammation of the whole respiratory system.

Our finding of a significant positive correlation between the nasal bacterial score and the neutrophil count and the rise after treatment in both neutrophil count and bacterial score leads us to speculate that nasal CPAP aggravates a subclinical nasal infectious process. Some 20% of the normal population are asymptomatic carriers of *Staphylococcus aureus*,[17] and this figure is even greater in patients with chronic rhinitis.[18] Levels of bradykinin and vasoactive intestinal peptide are increased in the nasal lavage fluid of patients with OSA.[14] *Staphylococcus aureus* has been shown to increase the release of bradykinin, both in the plasma[19] and in infected tissues.[20] However, the fact that the bacterial counts in our study were not significantly different in compliant and noncompliant patients argues against the hypothesis that intolerance to nasal CPAP was due to exacerbation of an asymptomatic bacterial infection.

Our findings must be interpreted with caution because most of the statistically significant results were based on posthoc analysis of the data. One weakness of our study is that we relied on the patients' report of their hours of use of the nasal CPAP equipment, supplemented by hour-meter recordings, rather than measuring hours-at-pressure, the "gold standard" for determining compliance. However, it is not likely that the noncompliant patients underestimated their use of the equipment, while the "compliant" patients probably overestimated it. Therefore, any discrepancy between the reported and the actual use of the equipment would have tended to obscure rather than exaggerate the differences between the groups.

A nasal scrape for neutrophils is a simple examination, the results of which can be available almost immediately. If a prospective study confirmed our findings, it would show us how to identify a group of patients at increased risk of discontinuing nasal CPAP because of nasal symptoms and who might be targeted for extra measures to prevent aggravation of their subclinical nasal inflammation.

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SCIENTIFIC INVESTIGATIONS

Effects of Oxygen Therapy on Left Ventricular Function in Patients with Cheyne-Stokes Respiration and Congestive Heart Failure

Samuel L. Krachman, D.O.; Thomas Nugent, M.D.; Joseph Crocetti, D.O.; Gilbert E. D'Alonzo, D.O.; Wissam Chatila, M.D.

Division of Pulmonary and Critical Care, Temple University School of Medicine, Philadelphia PA

Study Objectives: Whereas both oxygen therapy and nasal continuous positive airway pressure (CPAP) decrease the apnea-hypopnea index (AHI) in patients with Cheyne-Stokes respiration (CSR) and congestive heart failure (CHF), only nasal CPAP is known to affect the left ventricular ejection fraction (LVEF). We therefore evaluated the effects of 1 month of nocturnal oxygen therapy on LVEF.

Methods: Ten patients (52 ± 12 years) with CHF (LVEF of 12% ± 5%) and CSR (AHI 57 ± 61 events/hour) were studied. Polysomnograms identified CSR and were repeated on oxygen initially (oxygen night 1 [2 L/min]) and after 30 nights (oxygen night 2). LVEF was measured by radionuclide ventriculography.

Results: Oxygen therapy decreased the AHI from a baseline of 57 ± 61 to 9 ± 11 and 12 ± 17 events per hour during oxygen nights 1 and 2, respectively ($p < .05$), with no difference between treatment nights. The lowest oxygen saturation increased during oxygen nights 1 and 2, from a baseline of 87% ± 7% to 94% ± 4% and 91% ± 7%, respectively ($p < .05$), with no difference between treatment nights. The LVEF did not significantly change from a baseline of 22% ± 11% to 19% ± 9% after 1 month of nocturnal oxygen ($p = .05$). Compared to baseline, there was no change in circulation time during oxygen nights 1 and 2, from 24 ± 8 seconds to 30 ± 15 seconds and 23 ± 6 seconds, respectively ($p = .2$). Total sleep time, sleep efficiency, and sleep architecture, when compared with baseline, remained unchanged during both oxygen therapy nights.

Conclusions: Although 1 month of nocturnal oxygen therapy decreases the AHI in patients with CSR and CHF, there is no improvement in left ventricular function.

Keywords: Cheyne-Stokes respiration, congestive heart failure, apnea-hypopnea index, oxygen therapy, left ventricular ejection fraction, circulation time

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Cheyne-Stokes respiration (CSR) is a form of sleep-disordered breathing characterized by a crescendo-decrescendo alteration in tidal volume, separated by periods of apnea or hypopnea. Present in approximately 45% to 56% of patients with congestive heart failure (CHF) and a left ventricular ejection fraction (LVEF) < 40%,[1-4] CSR has been associated with an increased mortality.[5] Both oxygen therapy[4,6-12] and nasal continuous positive airway pressure (CPAP)[4,13-16] have been shown to be effective therapies for CSR, specifically in regard to decreasing the apnea-hypopnea index (AHI). We have previously demonstrated that oxygen therapy and nasal CPAP are equally effective at decreasing the AHI in patients with CSR and CHF.[4]

In addition to being studied for the treatment of sleep-disordered breathing, nasal CPAP has been studied in regard to its effects on left ventricular function.[13-17] Some studies have shown nasal CPAP to improve left ventricular function in patients with CHF and CSR.[13-16] By increasing intrathoracic pressure and decreasing the transmural pressure across the left ventricle, nasal CPAP can decrease left ventricular afterload.[18,19] In addition, nasal CPAP has been shown to significantly decrease sympathetic nerve activity in patients with CSR and CHF, as measured by a decrease in urine and plasma catecholamine levels.[20,21] Both mechanisms may result in an increase in LVEF. However, other studies have not demonstrated such beneficial effects with nasal CPAP, in regard to cardiac function,[17] as well as sympathetic nerve activity.[22] Whereas oxygen therapy has been shown to decrease urinary catecholamine levels[12] and increase exercise tolerance,[9] its effect on left ventricular function has not been studied. We therefore prospectively studied a group of patients with severe CHF (LVEF < 40%) and CSR. Our primary endpoint was to evaluate the effects of 1 month of nocturnal oxygen therapy on LVEF. Secondary endpoints included evaluating the effects of therapy on sleep-disordered breathing, sleep quality, and sleep architecture.

Disclosure Statement
Drs. Krachman, Nugent, Crocetti, D'Alonzo, and Chatila have indicated no financial conflicts of interest.

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Address correspondence to: Samuel L. Krachman, D.O., Temple University School of Medicine 767 Parkinson Pavilion, Broad and Tioga Sts., Philadelphia, Pa. 19140; Tel: 215 707 4678; Fax: 215 707 6867; E-mail: Krachms@tuhs.temple.edu

MATERIALS AND METHODS

Patient Selection

Ten patients with severe CHF (New York Heart Association class IV, LVEF < 40%) were studied. All patients were recruited from a special inpatient heart failure unit where they were evaluated and listed for heart transplantation, as previously described.[4,23] Patients were medically stable for a minimum of 4 weeks prior to the start of the study, with no change in their treatment regimen during the study period. All patients were ambulatory and active-

ly participating in physical-conditioning classes at the time of the study. Patients were identified as having CSR during a baseline polysomnographic study.

Our institutional review board approved the protocol, and informed consent was obtained from each patient prior to the study. Patients were excluded from the study if they (1) had an episode of acute pulmonary edema within 4 weeks of the study or during the study period, (2) had a prior cerebrovascular accident, (3) underwent transplantation prior to the completion of the study, or (4) refused to sign an informed consent or complete the study protocol.

Protocol

All patients underwent a baseline polysomnographic study that identified the presence of CSR. Patients then had a radionuclide ventriculography to determine the LVEF. A repeat polysomnogram while on oxygen at 2 L per minute (oxygen therapy night 1) was then completed. Patients were then placed on nocturnal oxygen therapy at 2 L per minute for 1 month. At the end of that time, a repeat polysomnogram on oxygen at 2 L per minute was performed (oxygen therapy night 2), followed by a repeat radionuclide ventriculography.

Cardiac Hemodynamics, Echocardiogram, and Radionuclide Ventriculography

Within 1 month of the study (23 ± 12 days), all patients underwent a right-heart catheterization, and medical therapy was optimized. Measurements were recorded just prior to removal of the catheter and included right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure. Cardiac output was measured as the mean of 3 recordings using thermodilution technique. LVEF was determined by echocardiogram prior to the study and by radionuclide ventriculography during the study period.

Sleep Studies

The polysomnographic recording consisted of rib-cage and abdominal motion (Resp-EZ; EPM Systems; Midlothian, Calif), oral and nasal thermistors, electrocardiogram, electrooculogram, digastric electromyogram, electroencephalogram, and finger pulse oximetry (model N-100; Nellcor Puritan Bennett; Pleasanton, Calif). All variables were continuously recorded and stored in a computerized system (Alice 3; Healthdyne Information Enterprises; Marietta, GA). Sleep was staged using the standard criteria of Rechtschaffen and Kales.[24] Arousals were defined by an abrupt shift in electroencephalographic frequency lasting at least 3 seconds.[25] Total sleep time (TST) and sleep efficiency (defined as TST divided by the time in bed) were determined. Central apneas were defined by a lack of airflow for more than 10 seconds, associated with the absence of rib-cage and abdominal movement.[23] Central hypopneas were defined by a 50% decrease in airflow for more than 10 seconds, associated with a decrease in rib-cage and abdominal excursion and lack of abdominal–rib cage paradox.[23] The central AHI was expressed as the number of apneas and hypopneas per hour of sleep. CSR was determined to be present when the central AHI was 10 or more events per hour,[26] with events associated with a crescendo-decrescendo alteration in breathing pattern characteristic of CSR. Circulation time was measured as the time from the end of a central apnea to the nadir in oxygen saturation.[4]

Oxygen Therapy

During the study, oxygen was administered at night by nasal cannula at 2 L per minute. Compliance was documented by the nursing staff and marked on a calendar that was placed in the patient's room.

Statistical Analysis

Data are represented as the mean ± SD. One-way repeated analysis of variance was used to compare variables at baseline and during the 2 oxygen-therapy nights. When significant, pairwise multiple comparisons were made using the Student-Newman-Keuls method. Radionuclide ventriculography data were analyzed using a paired student t test. All statistical analyses were performed using a commercially available computer software program (Sigmastat, version 2.0; Jandel, San Rafael, CA). A p value $< .05$ was considered significant.

RESULTS

Patient Characteristics

Ten patients (9 men; mean age 52 ± 12 years; body mass index 26 ± 5 kg/m^2) were studied (Table 1). All patients had their medications maximized prior to the study, including the use of a continuous inotropic infusion (Table 1). The mean baseline LVEF by echocardiogram was 12% ± 4%. Baseline cardiac hemodynamic measurements revealed a cardiac index of 2.3 ± 0.3 L• min^{-1}• m^{-2}, pulmonary capillary wedge pressure of 21 ± 8 mm Hg, mean pulmonary artery pressure of 30 ± 10 mm Hg, and heart rate of 96 ±

Table 1—Patient Characteristics*

Characteristic	Values
Age, y	52 ± 12
Men, no.	9
BMI, kg/m^2	26 ± 5
NYHA class IV (ischemic:idiopathic)	4:6
LVEF, %	12
Cardiac output, L/min	4.4 ± 0.8
Cardiac index, L• min^{-1}• m^{-2}	2.3 ± 0.3
PCWP, mm Hg	21 ± 8
Mean pulmonary artery pressure, mm Hg	30 ± 10
Heart rate, beats/min	96 ± 12
Inotropic infusion, µg• kg^{-1}• min^{-1}	
Dobutamine, n = 4	6.3 ± 2.5
Milrinone, n = 5	0.3 ± 0.1
Oral medications, no.	
B-Blocker	3
ACE inhibitor	8
Diuretic	7
Digoxin	5
Nitrates	5
Hydralazine	3
Losartan	5

*Data from 10 patients are presented as mean ± SD or number of patients unless otherwise specified. BMI refers to body mass index; NYHA, New York Heart Association; LVEF, left ventriculography ejection fraction; PCWP, pulmonary capillary wedge pressure; ACE, angiotensin-converting enzyme.

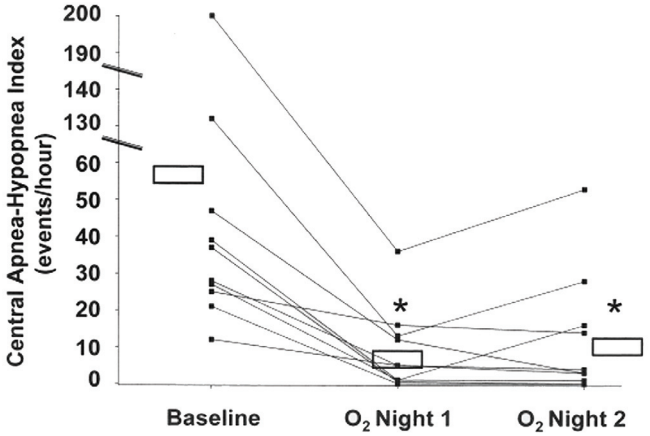

Figure 1—Effects of oxygen therapy on the central apnea-hypopnea index. When compared with baseline, oxygen therapy significantly decreased the apnea-hypopnea index, both acutely during the first night of use (oxygen night 1), as well as after 1 month of use (oxygen night 2) (*p < .05), with no difference between the 2 treatment nights.

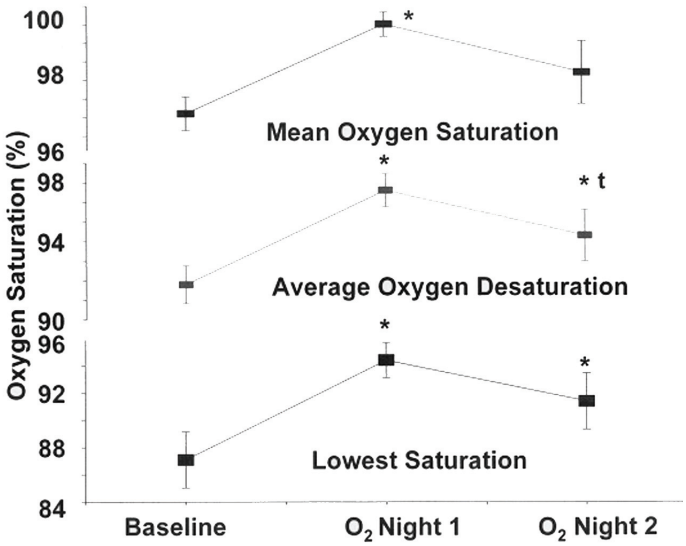

Figure 2—Effects of oxygen therapy on oxygen saturation during the night. When compared with baseline, the average oxygen desaturation and lowest oxygen saturation during the night significantly increased during both oxygen nights 1 and 2 (*p < .05), with only the average oxygen desaturation demonstrating a significant difference between the 2 treatment nights (†p < .05). The mean oxygen saturation, when compared with baseline, only significantly increased during oxygen night 1 (*p < .05), with no difference between the 2 oxygen therapy nights.

12 beats per minute. The mean baseline AHI was 57 ± 61 events per hour, with a TST of 273 ± 90 minutes and a sleep efficiency of 64% ± 18%. The arousal index was 11 ± 9 arousals per hour.

Effects of Oxygen Therapy

When compared with baseline, both oxygen therapy nights 1 and 2 significantly decreased the AHI, from 57 ± 61 to 9 ± 11 and 12 ± 17 events per hour, respectively (p < .05), with no difference between the 2 treatment nights (Figure 1). The mean oxygen saturation, when compared with baseline, significantly increased during oxygen therapy night 1 but not during oxygen therapy night 2, from 97% ± 1% to 99% ± 1% and 98% ± 3%, respectively, (p < .05 as compared with baseline and oxygen night 1), with no difference between the 2 oxygen nights (Figure 2). The average oxygen desaturation during a central apnea significantly decreased during oxygen therapy nights 1 and 2, from a baseline of 92% ± 3% to 97% ± 3% and 94% ± 4%, respectively (p < .05), with a significant difference between the 2 oxygen nights (p < .05) (Figure 2). Similarly, the lowest oxygen saturation, when compared with baseline, significantly increased during both oxygen therapy nights 1 and 2, from 87% ± 7% to 94% ± 4% and 91% ± 7%, respectively (p < .05), but with no difference between the 2 oxygen nights (Figure 2).

The LVEF, as measured by radionuclide ventriculography, did not significantly change after 1 month of nocturnal oxygen therapy, from a baseline of 22% ± 11% to 19% ± 9% (p = .05) (Figure 3). In addition, the circulation time could be determined in all 3 polysomnogram studies in 6 patients due to the continued presence of CSR. Compared with baseline, there was no significant change in the circulation time, from a baseline of 24 ± 8 seconds to 30 ± 15 seconds and 23 ± 6 seconds during oxygen therapy nights 1 and 2, respectively (p = .2).

TST, as compared with baseline, remained unchanged during oxygen therapy nights 1 and 2, from 273 ± 90 minutes to 319 ± 44 minutes and 274 ± 57 minutes, respectively (p = .2). Similarly, sleep efficiency did not change with oxygen therapy, from a baseline of 64% ± 18% to 75% ± 9% and 70% ± 9% during oxygen therapy nights 1 and 2, respectively (p = .2). The arousal index, as compared with baseline, also did not change on oxygen therapy nights 1 and 2, from 11 ± 9 arousals per hours to 10 ± 7 arousals per hour and 10 ± 3 arousals per hour, respectively (p = .7). Sleep architecture, as a percentage of TST, was not different when compared with baseline on either of the 2 oxygen therapy nights (Table 2).

DISCUSSION

Nocturnal oxygen therapy has been shown to be effective in treating patients with CSR due to CHF.[6-12] While oxygen therapy may improve sleep-disordered breathing in patients with CSR due to CHF, its effect on left ventricular function has not been previously evaluated. There are 3 major findings in this study: (1) oxygen therapy acutely decreases the AHI in patients with CSR and CHF, (2) the decrease in AHI with oxygen therapy is maintained after 1 month of therapy, and (3) 1 month of nocturnal oxygen therapy is not associated with an improvement in the LVEF.

Nocturnal oxygen therapy has been shown to significantly decrease the AHI, both acutely,[4,6,7] as well as after more-prolonged therapy,[9,11,12] in patients with CSR due to CHF. Hanly et al[6] observed a decrease in the central AHI from 30 ± 5 to 14 ± 2 events per hour with 1 night of oxygen therapy in 9 patients with CSR and CHF. We previously demonstrated a similar decrease in the central AHI in 9 patients with CSR and CHF, from 44 ± 9 to 18 ± 5 events per hour, when oxygen was used overnight at 2 L per minute.[4] Franklin et al[7] titrated oxygen from 1 to 5 L per minute overnight in 20 patients with central sleep apnea due to CHF or a prior stroke. They noted a similar decrease in the central AHI, from a baseline of 34 to 5 events per hour while on oxygen. Al-