

Inspiratory Airflow Dynamics During Sleep in Women with Fibromyalgia

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Study Objectives: To determine whether women with fibromyalgia have inspiratory airflow dynamics during sleep similar to those of women with upper-airway resistance syndrome (UARS).

Design: A descriptive study of consecutive female patients with fibromyalgia.

Setting: An academic sleep disorders center.

Patients or Participants: Twenty-eight women with fibromyalgia diagnosed by rheumatologists using established criteria. Fourteen of the women gave a history of snoring, while 4 claimed to snore 'occasionally' and 10 denied snoring. The comparison group comprised 11 women with UARS matched for age and obesity.

Interventions: Eighteen of the 28 women with fibromyalgia and all of the women with UARS had a full-night polysomnogram. All participants had a nasal continuous positive airway pressure (CPAP) study with quantitative monitoring of inspiratory airflow and effort between atmospheric pressure and therapeutic CPAP. Fourteen patients with fibromyalgia and all patients with UARS had a successful determination of pharyngeal critical pressure.

Measurements and Results: Twenty-seven of 28 women with fibromyalgia had sleep-disordered breathing. One of the 27 had obstructive sleep apnea hypopnea while 26 had milder inspiratory airflow limitation with

arousals. One patient had no apnea or hypopnea or inspiratory airflow limitation during sleep. While the patients were sleeping at atmospheric pressure, apnea-hypopnea index, arousal index, the prevalence of flow-limited breaths, and maximal inspiratory flow were similar between groups. The pharyngeal critical pressure of the patients with fibromyalgia was -6.5 ± 3.5 cmH₂O (mean $\pm$ SD) compared to -5.8 ± 3.5 cmH₂O for patients with UARS ($P = .62$). Treatment of 14 consecutive patients with nasal CPAP resulted in an improvement in functional symptoms ranging from 23% to 47%, assessed by a validated questionnaire.

Conclusion: Inspiratory airflow limitation is a common inspiratory airflow pattern during sleep in women with fibromyalgia. Our findings are compatible with the hypothesis that inspiratory flow limitation during sleep plays a role in the development of the functional somatic syndromes.

Key Words: Fibromyalgia, functional somatic syndromes, obstructive sleep apnea, pharyngeal critical pressure, upper-airway resistance syndrome, inspiratory airflow limitation

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INTRODUCTION

FIBROMYALGIA, ONE OF THE FUNCTIONAL SOMATIC SYNDROMES, IS A DISORDER OF UNKNOWN ETIOLOGY AFFECTING APPROXIMATELY 6 MILLION AMERICANS (2% OF THE POPULATION¹). Fibromyalgia patients may present with the symptoms of fatigue, widespread body pain and tenderness, headache, heartburn, abdominal pain, bloating and diarrhea, cognitive deficits, depression, and sleep-onset and sleep-maintenance insomnia.² These subjective complaints of fibromyalgia patients are associated with the objective findings of alpha-wave intrusion into stages 1 and 2 non-rapid eye movement (NREM) sleep and alpha-delta sleep.³ Because the etiology of fibromyalgia is unknown, its treatment is symptomatic. Patients with fibromyalgia often receive a combination of psychotherapy, physical therapy, psychotropic medications, and analgesics. The efficacy of fibromyalgia treatment is limited, and people with fibromyalgia often live with chronic insomnia, fatigue, and pain.²

Previous investigators have demonstrated an association between sleep-disordered breathing and fibromyalgia.⁴⁻⁶ May and associates⁶ evaluated 92 women and 25 men with a new diagnosis of fibromyalgia for the presence of obstructive sleep apnea-hypopnea (OSAH). While 44% of the men with fibromyalgia had OSAH, only 2% of the women with fibromyalgia had OSAH. They concluded that although an association appears to exist between fibromyalgia and OSAH in men, no such relationship exists in women.

Disclosure Statement

No significant financial interest/other relationship to disclose.

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Over the past decade, it has become evident that mild inspiratory flow limitation during sleep may cause sleep fragmentation and daytime sleepiness and fatigue. This form of sleep-disordered breathing, the upper-airway resistance syndrome (UARS),⁷ is caused by increased airway collapsibility during sleep that is intermediate between that of normal subjects and patients with mild to moderate OSAH.⁸ In a recent study,⁹ we demonstrated that, with the exception of widespread body pain and tenderness, the symptoms of patients with UARS are very similar to those of patients with fibromyalgia. In addition, we demonstrated that 24% of UARS patients have electroencephalographic evidence of alpha-delta sleep. The similarity of the clinical findings of UARS and fibromyalgia suggests that the 2 disorders may share a common pathophysiology.

Although OSAH is an uncommon finding in women with fibromyalgia,⁶ the relationship between milder inspiratory flow limitation during sleep and fibromyalgia in women is unexplored. We hypothesize that the common pathophysiology shared between UARS patients and fibromyalgia patients is inspiratory flow limitation during sleep. The inspiratory flow limitation of fibromyalgia patients, like that of UARS patients, results from increased upper-airway collapsibility during sleep. Furthermore, we hypothesize that splinting of the upper airway during sleep, preventing inspiratory flow limitation, will improve the functional symptoms of fibromyalgia patients. To begin examining the relationship between inspiratory airflow dynamics during sleep and fibromyalgia in women, we have examined consecutive female fibromyalgia patients for the presence of inspiratory flow limitation during sleep. We compared inspiratory airflow dynamics between the women with fibromyalgia and a matched group of women with UARS. We compared upper-airway collapsibility during sleep between the fibromyalgia patients and the UARS patients by comparing their values of pharyngeal critical pressure (Pcrit). In addition, we examined the effects of splinting the upper airway during sleep with nasal continuous positive airway pressure on the functional symptoms of women with fibromyalgia.

METHODS

Study Population

Fibromyalgia

The study sample included 28 women with fibromyalgia (Figure 1a). The first 16 patients were consecutive female patients with fibromyalgia referred to the Stony Brook University Sleep Disorders Center between February 1999 and August 2000 with complaints of disturbed sleep and fatigue or sleepiness. The Stony Brook University Sleep Disorders Center is an academic center that is not typical of pulmonary-administered sleep disorders centers. Because we have had a strong clinical and research interest in UARS for the past 5 years,^{8,9} women constitute nearly half the referrals to our center. This has resulted from our referring physicians learning that complaints of sleep-onset insomnia and fatigue or tiredness, even in the absence of snoring, are reasons to evaluate a patient for sleep-disordered breathing.⁹ For this reason, we came to evaluate 16 women with fibromyalgia over this 1.5-year period.

The remaining participants were 12 consecutive women with fibromyalgia who volunteered to participate in a treatment study administered by 1 of the authors (JB). The treatment study began after our consecutive patient series was complete (October 2000) and included in its protocol, a screening study for inspiratory flow limitation during sleep. For every patient in both groups, the diagnosis of fibromyalgia was established by a board-certified rheumatologist using American College of Rheumatology criteria.¹⁰

Upper-Airway Resistance Syndrome

In order to compare the inspiratory airflow-dynamics data and Pcrit values of the women with fibromyalgia to those of a sample of women with UARS, we examined the data obtained in our previous study of inspiratory airflow dynamics during sleep and Pcrit in UARS patients (Figure 1b).⁸ Because our UARS patient sample in that study (17 men and 5 women) did not provide a large enough sample of women with UARS, we extracted the data from the 5 women with UARS who had participated in our previous study and added data on inspiratory airflow dynamics from the next 6 consecutively studied women with UARS in whom Pcrit values were obtained. This provided a dataset from a sample of 11 women with UARS with which to compare our data from the women with fibromyalgia. As in our previous studies of UARS patients,^{8,9} we diagnosed UARS in patients with a complaint of daytime fatigue or sleepiness who did not meet diagnostic criteria for OSAH, narcolepsy, or periodic limb movement disorder and whose complaint of fatigue or sleepiness was associated with inspiratory flow limitation while breathing at atmospheric pressure during a nasal CPAP titration study (described below).

Publication of the consecutive female fibromyalgia patient data, the female UARS patient data, and the fibromyalgia treatment study protocol were approved by the Institutional Review Board of Stony Brook University. Informed consent was obtained from each of the treatment study patients.

Initial Evaluation

All of the patients completed a detailed medical and sleep-related questionnaire before being evaluated by a physician board-certified in both internal medicine and sleep medicine. The physician performed a general medical and sleep-related history and physical examination.

Full-Night Polysomnography

The 16 consecutive patients with fibromyalgia and 2 of the 12 treatment-study participants (the 2 were recruited after evaluation at the Stony Brook University Sleep Disorders Center) had full-night polysomnography (Figure 1a, Table 1). The 10 remaining treatment-study patients did not have full-night polysomnography before their

nasal CPAP studies. The 11 patients with UARS all had full-night polysomnography (Figure 1b, Table 1).

Full-night polysomnography was performed using standard methodology. Airflow at the nose and mouth was monitored with a thermocouple. Thoracoabdominal movement was monitored with piezoelectric belts. Oxyhemoglobin saturation was monitored at the finger using a pulse oximeter.

Sleep was staged using the scoring system of Rechtschaffen and Kales¹¹ with the modifications of Flagg and Coburn¹² for sleep-disordered breathing. The presence of alpha-delta sleep was identified by the characteristic low-frequency (< 2 cycles per second) high-amplitude (> 75 μ V peak to trough) delta waves with superimposed 7 to 11 cycle per second alpha waves. Electroencephalographic arousals not associated with hypopnea or apnea were identified using the American Sleep Disorders Association Atlas Task Force criteria.¹³ For each patient, the total of arousals not associated with hypopnea or apnea was divided by the total sleep time to derive an arousal index (arousals per hour).

We quantified an apnea-hypopnea index (AHI) for each patient. The diagnosis of OSAH was established by an AHI of at least 10 events per hour of sleep.

Nasal CPAP Study

All 28 of our patients with fibromyalgia and our 11 patients with UARS had a nasal CPAP study (Figures 1a, 1b; Table 1). The study was performed to identify the presence of inspiratory flow limitation at atmospheric pressure and to determine the appropriate CPAP level to overcome the inspiratory flow limitation. Each patient slept wearing a nasal CPAP mask connected to a source of pressure varying between +20 cmH₂O and -20 cmH₂O. Nasal airflow was measured with a heated pneumotachograph. Inspiratory effort was measured as a change in esophageal pressure (Pesoph) using a balloon-tipped catheter.

Inspiratory flow limitation during sleep at atmospheric pressure (between +1 cmH₂O and -1 cmH₂O) was considered to occur when inspiratory flow reached a plateau despite a Pesoph that continued to decrease. When inspiratory flow limitation was demonstrated at atmospheric mask pressure (Pmask), we characterized the airflow dynamics by measuring both the maximal inspiratory flow ($\dot{V}_{imax}$) and the inspiratory change in Pesoph (Δ Pesoph) for 5 to 8 consecutive breaths during continuous NREM sleep. To determine each patient's prevalence of flow-limited breaths at atmospheric pressure, we sampled a continuous period of approximately 4 minutes of continuous sleep (no epochs of wakefulness during the period but arousals were permitted). Each breath during the period (including breaths during arousals) was evaluated by our criteria for flow limitation and categorized as flow limited or non-flow limited. The prevalence of flow-limited breaths was determined by dividing the total of flow-limited breaths by the total of breaths during the period. Pmask was then raised in 1-cmH₂O increments while inspiratory flow and effort were monitored until inspiratory airflow limitation was abolished and Δ Pesoph was minimized. This level of Pmask was termed the therapeutic CPAP (Ptherapeutic).

For each fibromyalgia patient, we attempted to determine the pharyngeal Pcrit (the nasal mask pressure at which the upper airway occludes during NREM sleep and an index of upper-airway collapsibility) using the same steady-state method that we have detailed in our previous study of upper-airway collapsibility in UARS. In addition, we calculated resistance upstream to the site of flow limitation (Rus) using the equation: $Rus = -Pcrit/\dot{V}_{imax}$, as previously described.⁸ Each of our 11 UARS patients had a determination of pharyngeal Pcrit and Rus (only patients in whom we accomplished a Pcrit determination were included in the sample.)

Evaluating Functional Symptoms

All clinical fibromyalgia patients who elected to undergo nasal CPAP treatment of inspiratory flow limitation during sleep completed a self-report functional-symptom questionnaire before and after 3 weeks of

nasal CPAP treatment during which at least 5 hours of use per night was requested. Compliance with treatment was assessed by patient report.

Functional symptoms were evaluated with the Clinical Health Assessment Questionnaire^{14,15} (CLINHAQ). The CLINHAQ contains self reports from the Health Assessment Questionnaire Functional Disability Index¹⁶; the Arthritis Impact Measurement Scales Anxiety Index and Depression Index¹⁷; and double-anchored visual analogue scales (VAS) for pain, gastrointestinal symptoms, sleep problems, fatigue and global severity, satisfaction with health, patient estimate of health status, and work ability.

In addition to the functional parameters directly assessed by the CLINHAQ, we calculated a derived parameter, the rheumatology distress index. The rheumatology distress index is an index of distress that has been validated in a large sample of rheumatology patients.¹⁴ It is derived by normalizing the CLINHAQ anxiety index and depression index and the VAS for global severity, sleep problems, and fatigue to a 0 to 100 scale. The 5 parameters are then averaged to obtain the rheumatology distress index.

Statistical Analysis

Differences in parameters between the 2 groups of patients were analyzed statistically using unpaired *t* tests. The changes between pre-CPAP

and post-CPAP CLINHAQ parameters were analyzed statistically using paired *t* tests. Correlations between changes in CLINHAQ parameters with treatment were determined using the Pearson correlation coefficient.

RESULTS

Our fibromyalgia patients were 44 ± 11 years of age (mean $\pm$ SD; range, 18 – 63 years) with a body mass index (BMI) of 29 ± 8 kg/m² (range, 18 – 45). The 18 patients who had full-night polysomnography were matched for age with the 10 patients who did not have polysomnography (43 ± 12 years and 47 ± 8 years, respectively; $P = .39$) but tended to have a greater BMI (31.7 ± 7.7 kg/m² and 25.8 ± 6.8 kg/m², respectively; $P = .054$). Eleven of the 28 patients with fibromyalgia (39%) had the polysomnographic finding of alpha-delta sleep (For patients without full-night polysomnography, alpha-delta sleep was observed in the CPAP study.). Of the 28 patients with fibromyalgia, 12 claimed to snore loudly or heavily, 2 snored mildly, 4 snored occasionally, and 10 denied snoring. The 14 patients who denied snoring or snored occasionally were equally distributed between the referral group and the treatment-study group. Our patients with UARS were well matched for both age and BMI with our patients with fibromyalgia (Table 2).

Two classes of medication used to treat fibromyalgia are known to affect upper-airway collapse during sleep. The opiates are respiratory depressants and may promote upper-airway collapse during sleep,¹⁸ while the selective serotonin reuptake inhibitors tend to prevent upper-airway collapse by activating the upper-airway musculature.^{19,20} Six of our 28 patients were using hydrocodone on an as-needed basis. Three of these 6 patients listed hydrocodone among the medications taken on the day preceding the CPAP study. Three of our 28 patients were taking selective serotonin reuptake inhibitors (paroxetine, citalopram, and fluvoxamine). None of the patients took drugs from both classes.

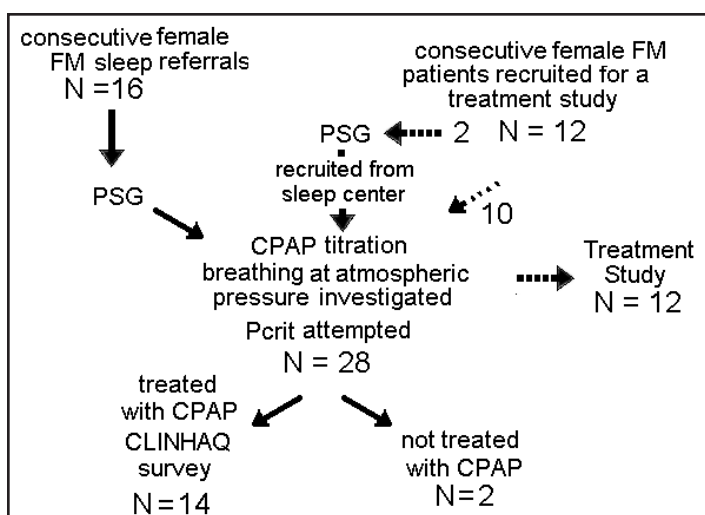


Figure 1a—This figure illustrates the sources of our 28 female patients with fibromyalgia (FM) and the studies they underwent. The figure demonstrates a consecutive series of 16 clinical referrals and a group of 12 volunteers for a treatment study that had an evaluation of their inspiratory airflow dynamics during sleep as part of the study protocol. See the Methods for a description of the sleep studies performed. PSG refers to polysomnography; CPAP, continuous positive airway pressure; Pcrit, pharyngeal critical pressure; CLINHAQ, Clinical Health Assessment Questionnaire.

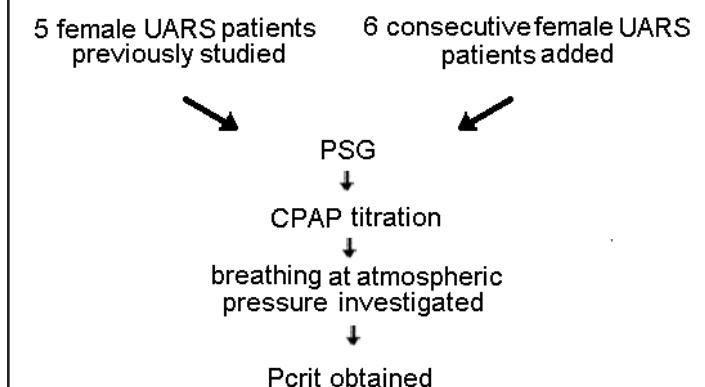


Figure 1b—This figure illustrates the sources of our 11 female patients with upper-airway resistance syndrome (UARS) and the studies they underwent. The figure demonstrates 5 patients in whom complete evaluations of inspiratory airflow dynamics during sleep were obtained as part of a previous protocol⁸ and 6 patients with complete evaluations of inspiratory airflow dynamics added for this study. See the Methods for a description of the studies performed. PSG refers to polysomnography; CPAP, continuous positive airway pressure; Pcrit, pharyngeal critical pressure.

Table 1—Procedures performed in our patient samples

	Procedure Subjects, no.	
	Fibromyalgia	UARS
Full-night polysomnography	18	11
Nasal CPAP study	28	11
Nasal CPAP with CLINHAQ assessment	14	
Pcrit determination attempted	28	11
Pcrit determined	14	11

UARS refers to upper-airway resistance syndrome; CPAP, continuous positive airway pressure; CLINHAQ, Clinical Health Assessment Questionnaire; Pcrit, pharyngeal critical pressure.

Table 2—Anthropometric, Polysomnographic, and Airflow-Dynamics Data from 28 Women with Fibromyalgia and 11 Women with Upper-Airway Resistance Syndrome*

Parameter	Subjects		<i>P</i> value
	Fibromyalgia	UARS	
Age, y	44 (11)	46 (8)	.74
BMI, kg/m ²	29 (8)	29 (7)	.91
AHI, events/h	2.4 (4.5)	2.0 (2.1)	.80
Arousal Index, 1/h	30.0 (13.7)	27.1 (11.2)	.57
$\dot{V}$ imax, mL/s	169 (90)	198 (95)	.44
Δ Pesoph, cm H ₂ O	13 (9)	20 (9)	.07
Pcrit, cm H ₂ O	-6.5 (3.5)	-5.8 (3.5)	.62
Rus, cm H ₂ O/L ⁻¹ /s ⁻¹	31.6 (14.7)	23.4 (7.5)	.10
Ptherapeutic, cm H ₂ O	7(2)	7(1)	.87

*Data are presented as mean (SD) with *P* values determined by *t* test.

UARS refers to upper-airway resistance syndrome; BMI, body mass index; AHI, apnea-hypopnea index; $\dot{V}$ imax, maximal inspiratory flow under conditions of inspiratory flow limitation during non-rapid eye movement sleep at atmospheric pressure; Δ Pesoph, the inspiratory effort measured as the decrease in esophageal pressure during inspiration under the flow-limited conditions described above; Rus, resistance upstream to the site of flow limitation; Ptherapeutic, therapeutic continuous positive airway pressure level.

The 18 patients with fibromyalgia who were evaluated with full-night polysomnography had an AHI of 2.4 ± 4.5 events per hour and an arousal index (arousals unrelated to apneas and hypopneas) of 30.0 ± 13.7 arousals per hour. Only 1 of the patients qualified for a diagnosis of OSAH, with an AHI of 17.7 events per hour. Ninety percent of this patient's disordered breathing time was hypopnea.

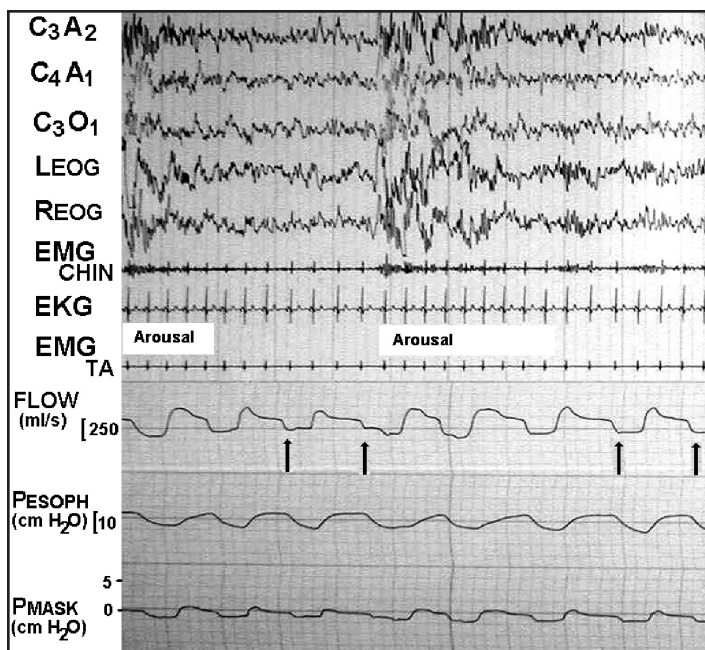


Figure 2a—This figure (from a nasal continuous positive airway pressure study) illustrates a 30-second epoch of non-rapid eye movement sleep in a 56-year-old nonsnoring woman with fibromyalgia (body mass index = 33.5 kg/m^2). Two periods of arousal are visible (labeled) during which inspiration is not flow limited (the down-going inspiratory flow signal has a rounded contour). Each arousal is followed by a return to sleep and a dissociation between inspiratory airflow and the pressure gradient driving airflow evident in esophageal pressure (Pesoph). The resulting plateau in inspiratory airflow (small arrows) is characteristic of inspiratory flow limitation. C3A2, C4A1, C3O1 refer to electroencephalogram channels; LEOG and REOG, left and right electrooculogram, respectively; EMGCHIN, superficially monitored electromyogram of the chin; EKG, electrocardiogram; EMGTA, superficially monitored electromyogram of the tibialis anterior muscle; Flow, airflow measured with a pneumotachograph; Pmask is nasal mask pressure.

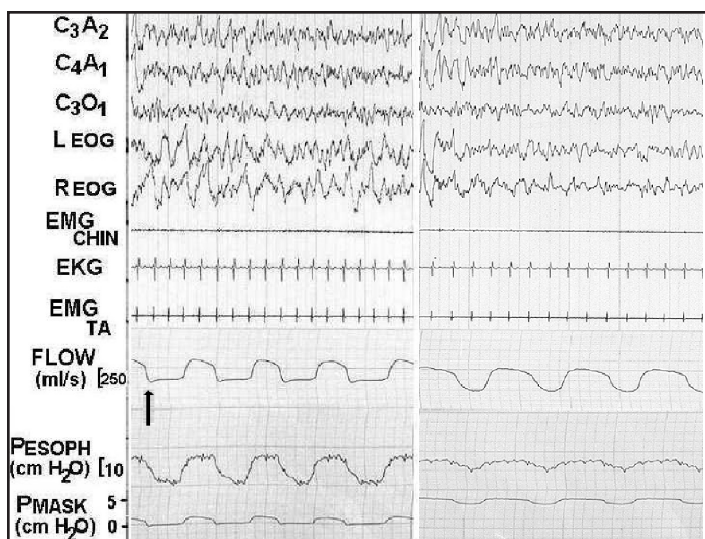


Figure 2b—This figure (from a nasal continuous positive airway pressure [CPAP] study) illustrates non-rapid eye movement sleep in a 33-year-old, nonsnoring woman with fibromyalgia (body mass index = 19.0 kg/m^2). The left panel demonstrates inspiratory flow limitation during sleep at atmospheric pressure (4 breaths). The arrow demonstrates the characteristic plateau in inspiratory flow (down going). The right panel demonstrates the resolution of inspiratory flow limitation during sleep at a mask pressure of 6 cmH₂O (therapeutic CPAP). In the right panel, the inspiratory airflow contour is rounded and follows the esophageal pressure contour. Note the decrease in inspiratory effort (esophageal pressure gradient) from 14 cmH₂O to 5 cmH₂O between atmospheric pressure and therapeutic CPAP. Labels are defined in the legend to Figure 2a.

While breathing at atmospheric pressure during the nasal CPAP study, 26 of the 27 fibromyalgia patients without OSAH experienced inspiratory flow limitation during NREM sleep (Figure 2a + 2b). We sampled 61 ± 17 consecutive breaths at atmospheric pressure per patient and found a prevalence of flow-limited breaths of $90\% \pm 13\%$. Therefore, inspiratory flow limitation was the prevalent breathing pattern during sleep among the fibromyalgia patients. The mean $\dot{V}_{\text{imax}}$ for the fibromyalgia patients with inspiratory flow limitation was $169 \pm 90 \text{ mL per second}$ and the mean inspiratory ΔPesoph was $13 \pm 9 \text{ cmH}_2\text{O}$. The Ptherapeutic was $7 \pm 2 \text{ cmH}_2\text{O}$. At Ptherapeutic, the mean inspiratory ΔPesoph for the group was $6 \pm 5 \text{ cmH}_2\text{O}$, representing a 7-cmH₂O decrease in inspiratory effort from a Pmask of atmospheric pressure. The nasal CPAP findings confirm that the 30.0 ± 13.7 arousals per hour that were experienced by the 18 fibromyalgia patients who underwent full-night polysomnography were respiratory-event-related arousals.

One patient had no evidence of inspiratory flow limitation (Figure 2c). This patient was not using selective serotonin reuptake inhibitors. Of 301 breaths recorded at atmospheric pressure, all had a rounded contour and nearly all had cardiac artifact in the inspiratory limb (changes in airflow associated with cardiac filling and emptying that demonstrate a non-flow-limited state). Inspiratory effort was between 2 cmH₂O and 5 cmH₂O and was difficult to measure precisely because the cardiac artifact in the esophageal-catheter tracing was nearly as large as the respiratory effort (Figure 2c). Because this patient did not have a full-night polysomnogram, we do not know how the absence of inspiratory flow limitation during NREM sleep relates to this patient's arousal index. When nasal mask pressure was decreased to determine upper-airway Pcrit, the inspiratory airflow plateau, characteristic of inspiratory flow limitation, was observed consistently at a mask pressure of $-3 \text{ cmH}_2\text{O}$ (Figure 2c).

The upper-airway airflow dynamics during sleep of the UARS patients were comparable to those of the fibromyalgia patients (Table 2). Compared to the fibromyalgia patients, the UARS patients had similar values of AHI and arousal index. Their values of $\dot{V}_{\text{imax}}$ under conditions of inspiratory flow limitation during NREM sleep were similar. Their values of Ptherapeutic were similar. There were statistically non-significant trends toward a lower ΔPesoph and a higher R_{us} in the

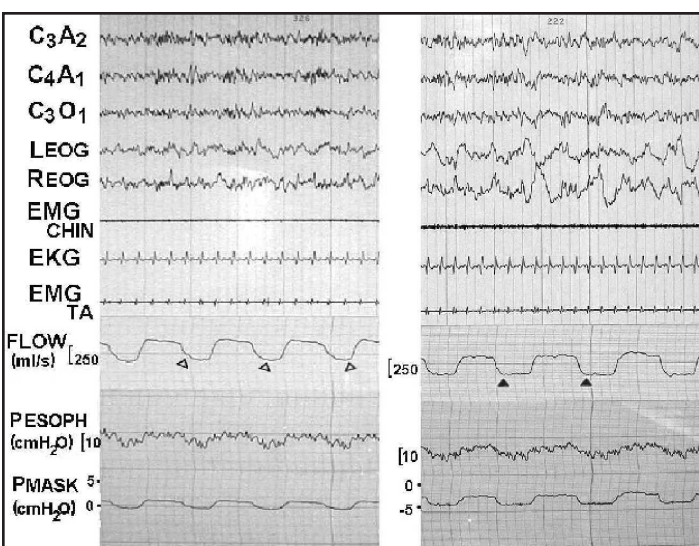


Figure 2c—This figure (from a nasal continuous positive airway pressure study) illustrates non-rapid eye movement sleep in a 52-year-old, occasionally snoring woman with fibromyalgia (body mass index = 24.2 kg/m^2). The left panel demonstrates sleep at atmospheric pressure without inspiratory flow limitation. Notice the rounded contour of the inspiratory airflow tracing that parallels the esophageal pressure trace (the driving pressure for airflow). Cardiac artifact (open arrowheads) related to ventricular volume changes is seen in the inspiratory flow tracing, consistent with a non-flow-limited state. Inspiratory effort (esophageal pressure gradient) is comparable to waking levels at 2 to $-5 \text{ cmH}_2\text{O}$. The right panel demonstrates sleep at a mask pressure of $-3 \text{ cmH}_2\text{O}$. The inspiratory airflow tracing demonstrates the plateau characteristic of inspiratory flow limitation (solid arrowheads). Labels are defined in the legend to Figure 2a.

fibromyalgia patients compared to the UARS patients. We sampled 58 ± 18 consecutive breaths at atmospheric pressure per UARS patient and found a prevalence of flow-limited breaths of $91\% \pm 12\%$ (a prevalence nearly identical to that of the fibromyalgia patients).

The Pcrit values for our fibromyalgia patients (-6.5 ± 3.5 cmH₂O) and UARS patients (-5.8 ± 3.5 cmH₂O) are illustrated in Figure 3 alongside the values for normals (-15.4 ± 6.8 cmH₂O), male patients with UARS (-3.4 ± 1.4 cmH₂O), patients with mild to /moderate OSAH (-1.6 ± 2.6 cmH₂O), and patients with moderate to severe OSAH (2.4 ± 2.8 cmH₂O), upon whom we have reported previously.⁸ The Pcrit of our female patients with UARS was significantly lower than that of male patients with UARS ($P = .02$; this difference was not appreciated during our previous study⁸). We successfully obtained Pcrit values for 14 of our 28 patients with fibromyalgia (Table 1). The remaining 14 patients with fibromyalgia did not sleep continuously enough at subatmospheric Pmask to allow for a Pcrit determination. One of the 14 patients demonstrated 2 distinct patterns of airflow dynamics that were accompanied by 2 different amplitudes of the superficial chin electromyogram (Figure 4). For this patient, we obtained 2 values of Pcrit that are connected with a line in Figure 3. The 2 Pcrit values of this patient were averaged to provide a single value for determining a mean Pcrit for the fibromyalgia patients.

The effect of nasal CPAP treatment upon functional symptoms in our 16 consecutive patients with fibromyalgia is illustrated in Figure 5. Table 3 presents questions and anchors for the VAS data presented in Figure 5. Of our 16 patients, 14 chose to try nasal CPAP treatment, 1 chose a mandibular advancement appliance, and 1 declined treatment of inspiratory flow limitation during sleep. Figure 5 demonstrates a 46%

improvement in fatigue, a 38% improvement in pain, a 39% improvement in sleep problems, and a 47% improvement in gastrointestinal symptoms after 3 weeks of nasal CPAP treatment. Changes in fatigue after 3 weeks of nasal CPAP treatment correlated with changes in sleep problems ($R = 0.66$, $P = .0135$). Changes in fatigue also tended to correlate with changes in pain ($R = 0.53$, $P = .0754$) and gastrointestinal problems ($R = 0.50$, $P = .0828$).

Three weeks of nasal CPAP treatment also decreased the level of functional disability and distress experienced by the patients. Functional disability, represented by the Health Assessment Questionnaire disability index, decreased by 23% (Figure 5). Distress, represented by the rheumatology distress index, decreased by 33% from 62.8 ± 17.7 (comparable to a previously published value for fibromyalgia patients¹⁴) to 42.2 ± 23.3 (comparable to a previously published value for patients with osteoarthritis and rheumatoid arthritis¹⁴, (Figure 5)). Of the 14 fibromyalgia patients who tried nasal CPAP treatment, 5 (36%) remained on nasal CPAP 9 months to 21 months after the trial. One of the latter patients, an unemployed nurse (because of symptoms), returned to full employment.

DISCUSSION

In this study, we compared upper-airway inspiratory airflow dynamics during sleep between women with fibromyalgia and women with UARS. We observed inspiratory flow limitation during sleep in 96% of the fibromyalgia patients. As in a previous study,⁶ only 4% of women with fibromyalgia patients had OSAH. The remaining 92% had higher levels of maximal inspiratory airflow during sleep, characteristic of women with UARS. Parameters describing sleep-disordered breathing and inspiratory airflow dynamics, such as AHI, arousal index, prevalence of flow-limited breaths during sleep, $\dot{V}_{\text{imax}}$, Pcrit, and Ptherapeutic were comparable between women with fibromyalgia and women with UARS. Treatment of our fibromyalgia patients' inspiratory flow limitation during sleep with nasal CPAP resulted in an improvement in their functional symptoms. Our findings demonstrate that inspiratory flow limitation during sleep is commonly observed in women

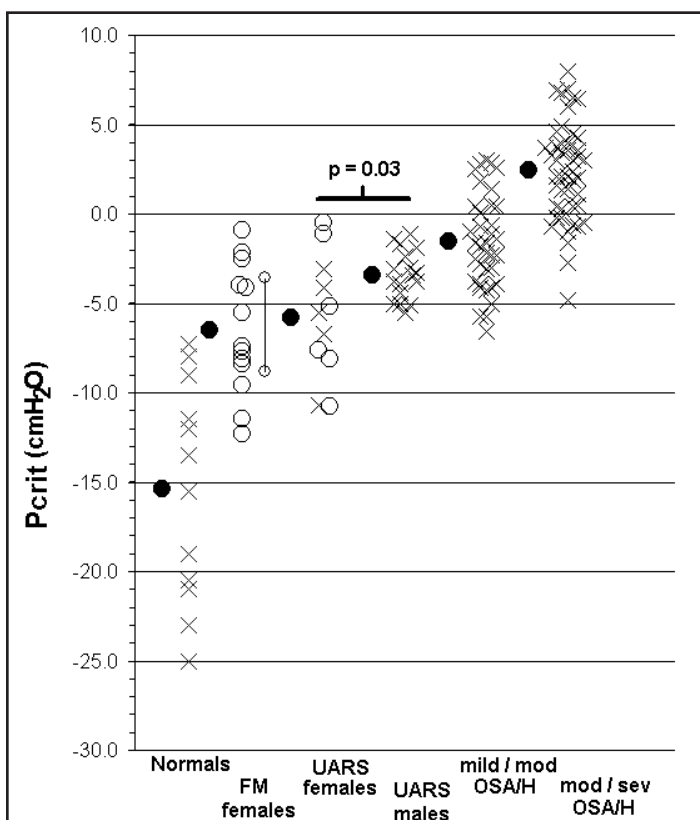


Figure 3—This figure compares the pharyngeal critical pressure (Pcrit) values of our female patients with fibromyalgia to those of normal controls, female patients with upper-airway resistance syndrome (UARS), male patients with UARS, patients with mild to moderate obstructive sleep apnea-hypopnea (OSA/H), and patients with moderate to severe OSA/H. Data represented by $\times$ were taken from previously published data.⁸ Data presented for the first time are represented as $\circ$. The mean values for each group are represented as $\bullet$ to the left of the data. The figure demonstrates that the Pcrit values of female fibromyalgia patients are similar to those of female UARS patients. The Pcrit values of female UARS patients are lower than those of male UARS patients. The connected Pcrit values in the fibromyalgia group are those of 1 patient with differing Pcrit values at differing superficial chin electromyogram activities (Figure 4).



Figure 4—This figure (from a nasal continuous positive airway pressure study) illustrates non-rapid eye movement sleep in a 38-year-old, nonsnoring woman with fibromyalgia (body mass index = 17.5 kg/m^2). The left panel demonstrates inspiratory airflow limitation during sleep at atmospheric pressure at a lower superficial chin electromyogram (EMG) activity. The arrow demonstrates the characteristic plateau in inspiratory airflow (down going). The right panel demonstrates inspiratory airflow limitation at a higher superficial chin EMG activity. Notice the higher maximal inspiratory airflow at the higher EMG activity. The higher EMG activity corresponds to a lower pharyngeal critical pressure (Pcrit) value (Figure 3, connected points). Notice the relative absence of esophageal pressure (Pesoph) swings in both panels. This patient had no evidence of diaphragmatic inspiratory activity during waking supine breathing (abdomen did not move outward on inspiration). Labels are defined in the legend to Figure 2a.

with fibromyalgia, a group previously thought to be without sleep-disordered breathing.⁶ The similar inspiratory airflow dynamics during sleep of women with fibromyalgia and women with UARS, together with their similar symptoms (previously demonstrated⁹), suggest that these 2 syndromes have a similar pathophysiology.

We believe that the female patients with fibromyalgia in this study are similar to female patients with fibromyalgia reported in the literature. The American College of Rheumatology¹⁰ has proposed criteria for the diagnosis of fibromyalgia that include (1) widespread pain in combination with (2) tenderness at 11 of 18 specific tender point sites. Although widely accepted diagnostic criteria for fibromyalgia have been established, the diagnostic criteria are based upon subjective findings. The only readily obtainable objective finding of fibromyalgia patients is alpha-delta sleep. Alpha-delta sleep is not specific for fibromyalgia, however, and has been described in individuals with other functional somatic syndromes.^{21,22} To increase the probability that our female patients with fibromyalgia truly had the syndrome, we studied patients only if their diagnosis of fibromyalgia was established by a rheumatologist using American College of Rheumatology criteria.¹⁰ Our resulting group of female patients with fibromyalgia was comparable in age to

previously published patient samples.^{3,6} Our patients had a prevalence of alpha-delta sleep of 39%, similar to the 50% observed by Roizenblatt and associates³ in a group of 40 female patients with fibromyalgia. Our patients had a prevalence of OSAH of 4%, similar to the 2.2% prevalence observed by May and associates⁶ in 92 female patients with fibromyalgia. Our patients had a rheumatology distress index of 62.8 ± 17.7 , comparable to the value of 58.3 ± 17.0 published for fibromyalgia patients by Wolfe and Skevington.¹⁴ The comparability of findings between our patient sample and previously described samples of female patients with fibromyalgia suggests to us that our patients are representative of female patients with fibromyalgia.

Although our sample of women with fibromyalgia appears to be similar to other groups of fibromyalgia patients in the literature, can we be certain that they are representative of the population of women with fibromyalgia with respect to the prevalence of inspiratory flow limitation during sleep? Could our sample be strongly biased in favor of women with fibromyalgia who have concomitant inspiratory flow limitation? In this preliminary study, we took patients from 2 sources. Our group referred for sleep evaluation could have been biased in favor of having sleep-disordered breathing. It is less likely that our group participating in a treatment study was biased toward having sleep-disordered breathing. Examining the tendency to snore within our sample, however, provides some perspective on our findings. While 50% of our fibromyalgia patients did not snore regularly, 96% of our patients had inspiratory flow limitation during sleep. Moreover, all 10 of the patients who denied snoring had inspiratory flow limitation. Therefore, it is not likely that a strong bias toward sleep-disordered breathing patients in our sample accounts for our results. Nevertheless, the question of bias is an empirical question that will only be resolved in subsequent studies. It will be necessary to directly recruit a representative sample of fibromyalgia patients from a large base of clinical patients (eg, a large rheumatology practice). Recruitment should be based solely on the diagnosis of fibromyalgia and not on physician referral or on symptoms suggestive of a sleep disorder.

Although the presence of inspiratory flow limitation during sleep in 27 of 28 female fibromyalgia patients allows us to hypothesize an association between the 2, in order to assess the strength of that association, we must know the odds of having inspiratory flow limitation if a woman does not have fibromyalgia (which would allow us to calculate an odds ratio). In our study, we do not present data on inspiratory airflow dynamics during sleep at atmospheric pressure for women without fibromyalgia. Although we do not have airflow-dynamics data for normal women sleeping at atmospheric pressure, our previous work on the airflow dynamics of patients with sleep-disordered breathing suggests that inspiratory flow limitation during sleep is uncommon in normal subjects. In our previously published study of upper-airway collapsibility in UARS patients,⁸ we demonstrated a difference of approximately 12 cmH₂O

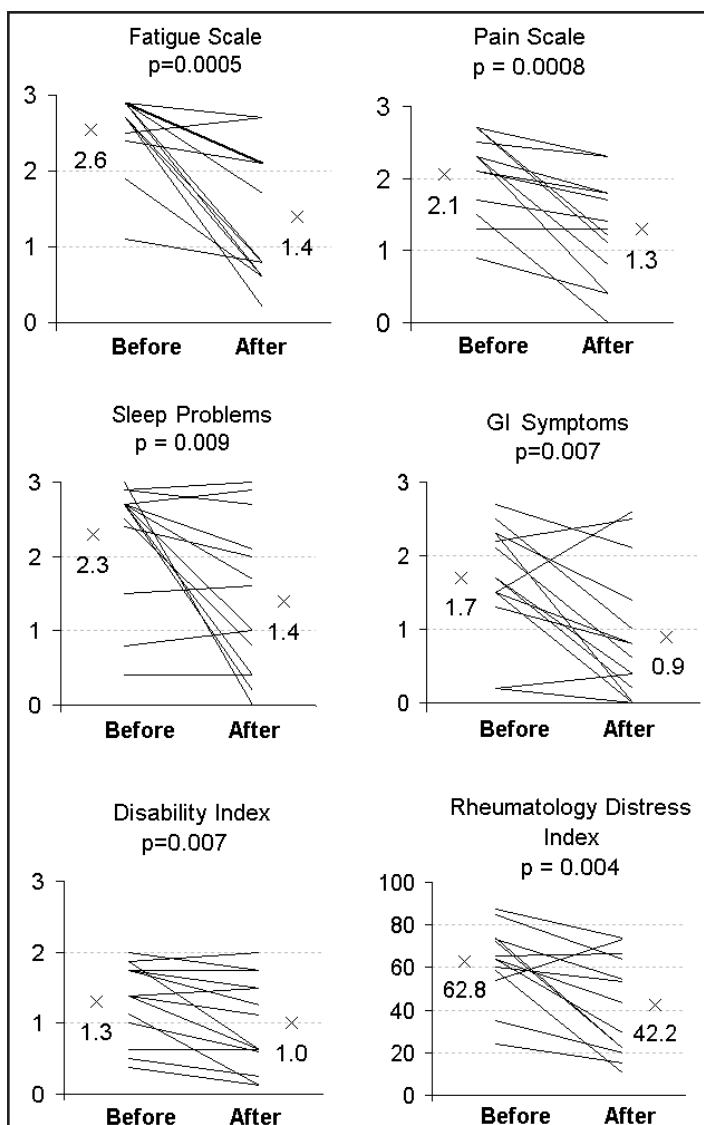


Figure 5—This figure illustrates the effect of 3 weeks of nasal continuous positive airway pressure (CPAP) treatment upon fatigue, pain, sleep problems, and gastrointestinal (GI) symptoms. The functional symptoms were assessed by visual analogue scales whose questions and anchors are demonstrated in Table 3. The effect of nasal CPAP treatment upon the disability index and the rheumatology distress index, an index of distress in rheumatology patients (see Methods for derivation), is also demonstrated. Nasal CPAP treatment for 3 weeks produced improvements in all the functional parameters that were both statistically and clinically significant.

Table 3—The Questions and Anchors for the Visual Analogue Scale Data Presented in Figure 5.

Specific Assessment	Question	Anchors
Fatigue	How much of a problem has fatigue or tiredness been for you IN THE PAST WEEK?	0: Fatigue is no problem 3: Fatigue is a major problem
Pain	How much pain have you had because of your illness in the past week?	0: No pain 3: Severe pain
Sleep Problems	How much problem has sleep (ie, resting at night) been for you in the past week?	0: Sleep is no problem 3: Sleep is a major problem
Gastrointestinal Symptoms	How much trouble have you had with your stomachs (ie, nausea, heartburn, bloating, pain, etc.) in the past week?	0: No stomach problem 3: A lot of stomach problems

between P_{crit} and therapeutic CPAP pressure (the pressure that eliminates inspiratory flow limitation) for UARS patients. In the same study, our 12 normal subjects (8 women and 4 men) had a P_{crit} of -15.4 cmH_2O , which is 15.4 cmH_2O below the nasal pressure at which they sleep. Only 3 normal subjects, all women, had a P_{crit} above -12 cmH_2O (Figure 3). If the relationship between P_{crit} and nasal pressure for normal female subjects is similar to that for patients with UARS, then we would anticipate a much lower prevalence of inspiratory flow limitation during sleep among normal female subjects than among women with fibromyalgia. To verify this assumption, future investigations of inspiratory airflow dynamics during sleep in patients with fibromyalgia will require a control group matched for sex, age (menopausal status), and body mass index. All control subjects should be without fatigue or sleepiness (the chief symptom) and should also be without key symptoms of the functional somatic syndromes.⁹ In this way, the strength of the association between inspiratory flow limitation during sleep and fibromyalgia can best be determined.

Another issue to be considered in future studies is the definition of inspiratory flow limitation during sleep. In this study, as in previously published research,^{7,8} we considered flow limitation to occur when inspiratory flow reached a plateau despite a P_{esoph} that continued to decrease. A more-precise definition of inspiratory flow limitation has been used by Rowley and associates²³ in their study of the influence of sex upon inspiratory airflow dynamics during sleep. For each inspiration during sleep, Rowley and associates plotted flow against pressure and recognized inspiratory flow limitation as a plateau in inspiratory flow despite an increase in driving pressure of 1 cmH_2O . This latter definition makes flow limitation dependent upon not only a plateau in airflow, but also a minimum increase in driving pressure beyond the plateau. Because it is possible that fibromyalgia patients differ from normal subjects not only in the prevalence of an inspiratory airflow plateau during sleep, but also in the increase in effort that is associated, the latter definition of flow limitation may be better suited for comparing the 2 groups in future studies.

The demonstration of inspiratory flow limitation during sleep in women with fibromyalgia raises an interesting therapeutic question. Does splinting the upper airway of women with fibromyalgia during sleep ameliorate their symptoms of fibromyalgia? The 2 principal symptoms of fibromyalgia are pain and fatigue or sleepiness. In patients with UARS treated with nasal CPAP, Guilleminault has demonstrated a resolution of subjective sleepiness associated with a significant increase in sleep latency from 5.3 minutes to 13.5 minutes by sleep-latency testing.⁷ While similar changes in fatigue or sleepiness might be predicted in fibromyalgia, no data supporting this hypothesis have been published. May and associates⁶ mention some improvement of fibromyalgia symptoms in those patients with OSAH treated with nasal CPAP. Their paper, however, does not specify which symptoms improved and does not quantify the improvement. In this study, we have demonstrated a 23% to 47% improvement in parameters reflecting functional symptoms in fibromyalgia patients after upper-airway splinting during sleep with nasal CPAP. In the absence of a placebo control, however, we cannot rule out some degree of placebo response. With the recent development of placebo CPAP breathing circuits, and their use to test the efficacy of nasal CPAP in OSAH,²⁴ it should be possible to include a placebo control in future studies of the effects of nasal CPAP on the functional symptoms of fibromyalgia.

As has been observed among patients with OSAH, patient compliance and tolerance of nasal CPAP emerged as an issue in our patients with fibromyalgia. Despite reports of marked improvements in functional symptoms, only 36% of our patients remained on nasal CPAP beyond 9 months. This compliance rate contrasts with the rate of approximately 67% published for OSAH patients.^{25,26} There are several differences between our patients and OSAH patients, however, that may contribute to the different rates of compliance. First, unlike the predominantly male population that has been evaluated in studies of OSAH compliance, our patients were women. There may be sex-related differences in CPAP

compliance. Second, 67% of our patients had rhinitis (at least 2 of the following symptoms: chronic nasal stuffiness, post nasal drip, or nasal allergies⁹). Rhinitis is a common complaint among patients with functional somatic syndromes.^{27,28} In our study of the symptoms of UARS,⁹ rhinitis was found in approximately 45% of our 50 patients with OSAH. Because rhinitis can increase nasal resistance (Table 2) and affect one's ability to breathe nasally, a higher prevalence of rhinitis in our fibromyalgia patients may have decreased their compliance with nasal CPAP. In addition, many of our fibromyalgia patients reported difficulty tolerating the nasal mask. Their problems included skin rashes, erythema, and discomfort breathing against positive pressure. This may be consistent with the emerging data that fibromyalgia patients evidence lower discomfort thresholds for various sensory stimuli.²⁹ We expect that nasal CPAP treatment of fibromyalgia patients will require a high degree of initial support to enhance patient tolerance of the device. When patients with fibromyalgia do not tolerate nasal CPAP, oral mandibular advancement appliances may adequately splint their upper airways³⁰ and may be better tolerated.

In this study, we have presented evidence of a high prevalence of inspiratory flow limitation during sleep in women with fibromyalgia. This observation extends the observations already made concerning the relationship between mild inspiratory flow limitation during sleep and human illness. Guilleminault and associates⁷ recognized the relationship between mild inspiratory flow limitation during sleep and excessive daytime sleepiness in adults. He termed the syndrome *UARS*. Subsequently,⁹ we demonstrated that the symptoms and signs of patients with UARS differ from those of patients with moderate to severe OSAH. Patients with UARS differ by having a high prevalence of female sex, sleep-onset insomnia, headaches, irritable bowel syndrome, and alpha-delta sleep. Taken together with the high prevalence of depression, gastroesophageal reflux, and bruxism that the 2 groups of patients with sleep-disordered breathing share,⁹ it is evident that the symptoms and signs of UARS are those of the functional somatic syndromes.³¹⁻³³ In this preliminary study, we examined a sample of patients with a functional somatic syndrome, fibromyalgia; demonstrated a high prevalence of inspiratory flow limitation during sleep; and demonstrated an improvement in functional symptoms when inspiratory flow limitation was prevented with nasal CPAP. These findings add support to the hypothesis that inspiratory flow limitation during sleep plays a role in the development of the functional somatic syndromes.

REFERENCES

1. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995;38:19-28.
2. Goldenberg DL. Fibromyalgia syndrome a decade later: what have we learned? *Arch Intern Med* 1999;159:777-85.
3. Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S. Alpha sleep characteristics in fibromyalgia. *Arthritis Rheum* 2001; 44:222-30.
4. Sergi M, Rizzi M, Braghiroli A, et al. Periodic breathing during sleep in patients affected by fibromyalgia syndrome. *Eur Respir J* 1999;14:203-8.
5. Alvarez Lario B, Alonso Valdivielso JL, Alegre Lopez J, Martel Soteres C, Viejo Banuelos JL, Maranon Cabello A. Fibromyalgia syndrome: overnight falls in arterial oxygen saturation. *Am J Med* 1996;101:54-60.
6. May KP, West SG, Baker MR, Everett DW. Sleep apnea in male patients with the fibromyalgia syndrome. *Am J Med* 1993;94:505-8.
7. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. *Chest* 1993;104:781-7.
8. Gold AR, Marcus CL, Dipalo F, Gold MS. Upper airway collapsibility during sleep in upper airway resistance syndrome. *Chest* 2002;121:1531-40.
9. Gold AR, Dipalo F, Gold MS, O'Hearn D. The symptoms and signs of upper airway resistance syndrome: a link to the functional somatic syndromes. *Chest* 2003;123:87-95.
10. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990;33:160-72.
11. Flagg W, Coburn S. Polygraphic aspects of sleep apnea. In C. Guilleminault and W. Dement, editors. *Sleep Apnea Syndromes*. Alan R. Liss, New York; 1978:357-63.
12. Rechtschaffen A, Kales A. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Bethesda: US Dept of Health, Education and Welfare; 1968.
13. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 1992;15:173-84.
14. Wolfe F, Skevington SM. Measuring the epidemiology of distress: the rheumatology dis-

- tress index. *J Rheumatol* 2000;27:2000-9.
15. Wolfe F, Pincus T, Listening to the patient: a practical guide to self-report questionnaires in clinical care. *Arthritis Rheum* 1999;42:1797-808.
 16. Wolfe F, Kleinheksel SM, Cathey MA, Hawley DJ, Spitz PW, Fries JF, The clinical value of the Stanford Health Assessment Questionnaire Functional Disability Index in patients with rheumatoid arthritis. *J Rheumatol* 1988;15:1480-8.
 17. Meenan RF, Gertman PM, Mason JH, Measuring health status in arthritis. The arthritis impact measurement scales. *Arthritis Rheum* 1980; 23:146-52.
 18. Farney RJ, Walker JM, Cloward TV, Rhondeau S, Sleep-disordered breathing associated with long-term opioid therapy. *Chest* 2003;123:632-9.
 19. Kraiczki H, Hedner J, Dahlöf P, Ejnell H, Carlson J, Effect of serotonin uptake inhibition on breathing during sleep and daytime symptoms in obstructive sleep apnea. *Sleep* 1999;22:61-7.
 20. Berry RB, Yamaura EM, Gill K, Reist C, Acute effects of paroxetine on genioglossus activity in obstructive sleep apnea. *Sleep* 1999;22:1087-92.
 21. Bader GG, Kampe T, Tagdäe T, Karlsson S, Blomqvist M, Descriptive physiological data on a sleep bruxism population. *Sleep* 1997;20:982-90.
 22. Manu P, Lane TJ, Matthews DA, Castriotta RJ, Watson RK, Abeles M, Alpha-delta sleep in patients with a chief complaint of chronic fatigue. *South Med J* 1994;87:465-70.
 23. Rowley JA, Zhou X, Vergine I, Shkorkani MA, Badr MS, Influence of gender on upper airway mechanics: upper airway resistance and Pcrit. *J Appl Physiol* 2001;91:2248-54.
 24. Montserrat JM, Ferrer M, Hernandez L, et al. Effectiveness of CPAP treatment in daytime function in sleep apnea syndrome: a randomized controlled study with an optimized placebo. *Am J Respir Crit Care Med* 2001;164:608-13.
 25. McArdle N, Devereux G, Heidarnajad H, Engleman HM, Mackay TW, Douglas NJ, Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999;159:1108-14.
 26. Kribbs NB, Pack AI, Kline LR, et al., Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993;147:887-95.
 27. Baraniuk JN, Clauw DJ, Gaumond E, Rhinitis symptoms in chronic fatigue syndrome. *Ann Allergy Asthma Immunol* 1998;81:359-65.
 28. Cleveland CH, Jr., Fisher RH, Brestel EP, Esinhart JD, Metzger WJ, Chronic rhinitis: an underrecognized association with fibromyalgia. *Allergy Proc* 1992;13:263-7.
 29. Gracely RH, Petzke F, Wolf JM, Clauw DJ, Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum* 2002;46:1333-43.
 30. Ferguson KA, The role of oral appliance therapy in the treatment of obstructive sleep apnea. *Clin Chest Med* 2003;24:355-64.
 31. Barsky AJ, Borus JF, Functional somatic syndromes. *Ann Intern Med* 1999; 130:910-21.
 32. Wessely S, Nimnuan C, Sharpe M, Functional somatic syndromes: one or many? *Lancet* 1999;354:936-9.
 33. Aaron L, Buchwald D, A review of the evidence for overlap among unexplained clinical conditions. *Ann Intern Med* 2001;134:868-81.