

SCIENTIFIC INVESTIGATIONS

## A Pilot Evaluation of a Nasal Expiratory Resistance Device for the Treatment of Obstructive Sleep Apnea

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**Background:** Obstructive sleep apnea (OSA) is a major problem in need of new treatment approaches. The present pilot study tests the hypothesis that the application of expiratory resistance via a nasal valve device would improve breathing during sleep in subjects with OSA and in primary snorers.

**Methods:** Thirty men and women were recruited from the community and from the Stanford University Sleep Disorders Clinic. Twenty-four had at least mild OSA (AHI >5), and 6 were primary snorers. Subjects underwent 2 nights of polysomnographic evaluation, one with and one without a new nasal resistance device with the order of nights counterbalanced across participants. The device consisted of a small valve inserted into each nostril calibrated to provide negligible inspiratory resistance, but increased expiratory resistance with a back pressure between 60 and 90 cm H<sub>2</sub>O\*sec/Liter (at 100 mL/sec flow). Standard polysomnography was conducted to compare participants' sleep both

with and without the device, with the scoring conducted blind to treatment condition.

**Results:** The apnea-hypopnea (AHI) ( $p < 0.001$ ) and oxygen desaturation (O<sub>2</sub>DI) ( $p < 0.01$ ) indices both significantly decreased, and the percentage of the night spent above 90% saturation ( $p < 0.05$ ) significantly increased with device use. The observed amount of snoring ( $p < 0.001$ ) was significantly decreased with device use, and there were no significant changes in measures of sleep architecture.

**Conclusions:** The results of this pilot study are suggestive of a therapeutic effect of expiratory nasal resistance for some OSA patients and indicate that this technique is worthy of further clinical study.

**Keywords:** AHI, SpO<sub>2</sub>, OSA

**Citation:** Colrain IM; Brooks S; Black J. A pilot evaluation of a nasal expiratory resistance device for the treatment of obstructive sleep apnea. *J Clin Sleep Med* 2008;4(5):426-433.

The pathophysiology of obstructive sleep apnea (OSA) is complex and has often been viewed as relating exclusively to upper airway collapse during inspiration. As indicated by Schwab and Gefter,<sup>1</sup> however, dynamic imaging of the upper airway during respiration reveals 5 distinct phases of the respiratory cycle in terms of the relationship between tidal volume and upper airway cross-sectional area: onset of inspiration; mid inspiration; end of inspiration; maximum expiration; and the end-expiratory pause. The recruitment of airway dilator muscles leads to a small increase in airway caliber at the onset of inspiration, at least during wakefulness, and even in obstructive sleep apnea syndrome (OSAS) patients. This, airway dilator muscle activity is designed to balance the negative pressure and keep airway caliber relatively constant. Maximal expiration is associated with the largest airway caliber, yet during the final phase, at the end of expiration, airway caliber is smallest. Schwab and Gefter<sup>1</sup> hypothesized that it is in this phase when there is neither positive pressure present nor inspiratory phasic activation of upper airway dilator muscles, that the risk of air-

way occlusion is the greatest. Indeed, Morrell et al.<sup>2</sup> reported significant narrowing of the upper airway during expiration in breaths preceding apnea, and a recent computerized tomography (CT) study in awake patients demonstrated the lowest cross-sectional area of the upper airway at the uvula during expiration, with the area during expiration showing the largest difference between control and severe OSA patients.<sup>3</sup>

All of the above highlight the possible utility of treating OSA via the use of increased expiratory resistance or expiratory positive airway pressure (EPAP), to increase airway caliber during the critical end-expiratory period. Many years ago, Mahadevia et al.<sup>4</sup> presented data indicating that EPAP might be an effective treatment for obstructive sleep apnea.

The present paper reports a pilot study designed to evaluate the efficacy of a nasal device that creates increased expiratory nasal resistance, in the treatment of OSA. Unlike previous EPAP applications, the device does not require the use of a positive airway pressure pump, but rather uses small bidirectional valves designed to be worn just inside each nostril. The valves allow for minimally impeded inspiratory airflow but produce increased resistance to expiration with a back pressure between 60 and 90 cm H<sub>2</sub>O\*sec/Liter at 100 mL/sec of flow. The study tested the hypothesis that the device would produce a significant decrease in obstructive breathing events during sleep as indexed by the AHI and measures of oxygen saturation during sleep.

Submitted for publication January, 2008

Accepted for publication May, 2008

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## METHODS

### Participants

Subjects over the age of 18 years were recruited from the community via advertising and from the Stanford Sleep Disorders Clinic following their participation in a diagnostic polysomnogram. All prospective subjects underwent an initial telephone screen. Inclusion criteria required an affirmative response to one of the following questions: (1) “Do you snore most nights?” or (2) “Do you or your sleeping partner notice snorts, gasps or pauses in your breathing while you sleep?”

Subjects were excluded if they met any of the following criteria: BMI > 35 kg/m<sup>2</sup>; actively using CPAP or bilevel PAP; exhibiting any flu-like or upper respiratory illness symptoms at time of assessment; history of severe nasal allergies or sinusitis or difficulty breathing through the nose; persistent blockage of one or both nostrils; any previous operation or trauma to the nose; or any nasal or facial abnormalities that would not allow adequate placement of the device. In addition subjects were excluded if they had a previous diagnosis of insomnia, narcolepsy, periodic limb movement disorder, respiratory failure, or history of any other unstable or serious medical conditions (angina/myocardial infarction, cancer, stroke, dementia, congestive heart failure). Female subjects of childbearing age were excluded if they were pregnant or intending to become pregnant.

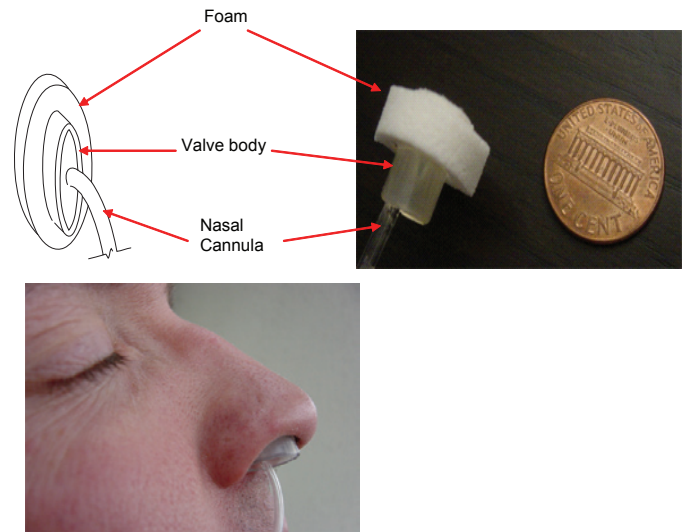
### Polysomnography Procedures

Data collection occurred at either the Human Sleep Laboratory at SRI international (26 subjects) or at the San Francisco site of Pacific Sleep Medicine. Data were collected at the SRI site using Compumedics E-Series amplifiers and Profusion 2 software. The Pacific Sleep Medicine site used Grass Technologies Aurora PSG and Grass TWin software.

Standard clinical polysomnography was conducted with the following signals collected on each night: EEG: (C<sub>3</sub>-A<sub>2</sub>, C<sub>4</sub>-A<sub>1</sub>, O<sub>1</sub>-A<sub>2</sub>, O<sub>2</sub>-A<sub>1</sub>); EOG (both eyes); EMG: (bilateral submentalis); ECG (right clavicle to left 4th intercostal space); abdominal and thoracic effort via piezoelectric sensor belts; left and right anterior tibialis activity via piezo sensors; nasal airflow (via cannulae); oral airflow (via thermistor); oxygen saturation (SpO<sub>2</sub>) via finger sensor; body position (via a mercury switch on the thoracic belt); and snoring movement via a Pro-Tech model 1696 piezo sensor placed 3 cm lateral and superior to the laryngeal prominence of the thyroid cartilage, in a line from this peak to the right ear lobe.

### Event Definition

Each breath during sleep was classified as either normal, snoring, apneic, or hypopneic. Apneas and hypopneas were scored according to the “Chicago” research criteria.<sup>5</sup> The apnea-hypopnea index (AHI) was calculated as the total number of apneas and hypopneas per hour of sleep. The oxygen desaturation index (O<sub>2</sub>DI) was calculated as the total number of 3% decreases in oxygen saturation per hour of sleep. Snoring events were not scored if they occurred in association with an apnea or hypopnea, avoiding double counting of events. Snor-



**Figure 1**—Schematic (upper left panel) and photograph (upper right panel) of the expiratory resistance device showing the various parts and relative size. Photograph of a single device positioned as per the study (lower left panel).

ing events required  $\geq 4$  consecutive breaths demonstrating snoring on the piezo sensor.

### Expiratory Resistance Device

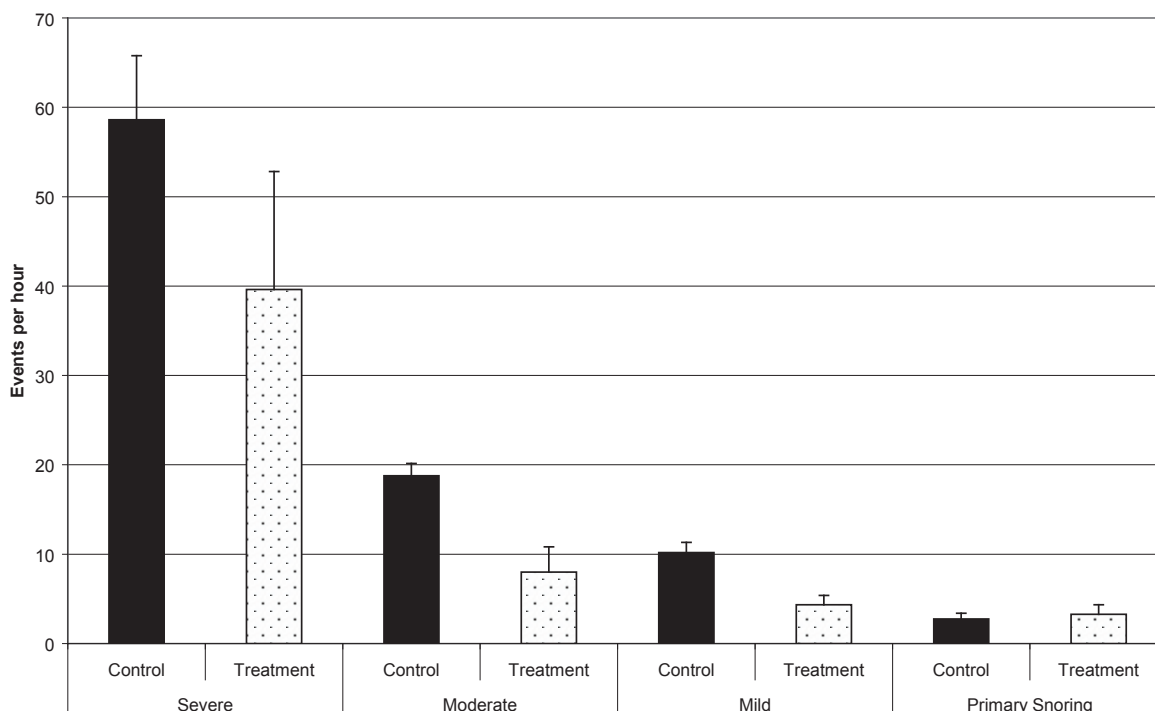
The expiratory resistance device consists of 2 nasal inserts composed of soft foam surrounding a valve body constructed of a urethane copolymer (Pebax). The valve body houses a silicone valve mechanism that serves to increase the expiratory pressure by creating expiratory resistance resulting in airway positive back-pressure during expiration while not affecting inspiratory airway pressure. For the purpose of this study, the device was attached to nasal cannulae, which provided airflow data during the sleep study. (See Figure 1 for a description of the device and its placement). The valves were precalibrated to provide back pressure resistance values of between 60 and 90 cm H<sub>2</sub>O\*sec/liter at a flow rate of 100 mL/sec. The calibration routine involved the passing of air from a REMStar CPAP (Respironics, Murrysville, PA) device through an Omega FL-3840 (Omega Engineering, Stamford, CT) G Flow meter. Differential pressure was measured on either side of the device using an Omega PX26 (Omega Engineering, Stamford, CT) pressure transducer.

The order of the treated and untreated nights was counterbalanced, with 14 subjects randomly assigned to having the control night first and 16 the treatment night first.

### Analysis of the Polysomnogram Data

Data from both sites were converted to European Data Format (EDF)<sup>6</sup> and uploaded to a data server. The data were then sent to a highly experienced registered polysomnographic technologist for scoring using standard criteria.<sup>7</sup> The scorer was kept blind to the type of night and the nature of the device being studied. Reports were then uploaded to the server, unblinded, and made available for analysis.

## Apnea-Hypopnea Index



**Figure 2**—Histogram of the apnea-hypopnea index shown on treatment and control nights for the 6 severe subjects (untreated AHI between 32.5 and 83.8), the 7 moderate subjects (untreated AHI between 16.2 and 26.5), the 11 mild subjects (untreated AHI between 5.1 and 14.7) and the 6 primary snoring subjects (untreated AHI values <5). Data are presented as group means with error bars representing the standard error scores. There was a significant difference between treatment and control nights in the mild, moderate, and severe OSA groups,  $p < 0.001$ .

### Subjective Experience of the Device

Subjects were given a questionnaire on the morning following the device night to determine their subjective experience of the night. Questions asked related to comfort, whether the device required adjustment during the night, ease of nasal breathing while awake, and the comfort relative CPAP if they previously used CPAP.

### Statistical Analysis

All analyses were conducted using SPSS 15.0. Sleep architecture and breathing variables were analyzed using nonparametric 2-tailed Wilcoxon signed rank tests to assess differences between the control and treatment nights. Assignment to one of 4 disease severity groups was based on the control night AHI, with the 4 groups being “primary snorers” (AHI < 5); “mild” (AHI  $\geq 5$  to 15); “moderate” (AHI  $\geq 15$  to 30) and “severe” (AHI  $\geq 30$ ).

Sleep architecture data were analyzed for the entire group, and then separately for the primary snorers, to test specifically for a “device” effect. Analyses of snoring data were conducted for the whole group. Analyses of the AHI and oxygenation variables were conducted for those meeting at least minimum diagnostic criteria for OSA (i.e., those in the mild, moderate, and severe OSA groups). The impact of body position (supine vs. nonsupine) was assessed in subjects showing at least mild apnea when supine or nonsupine and for whom at least half an hour of data was available for each body position on each night.

### RESULTS

Twenty-two men and 10 women were enrolled in the protocol. Two subjects failed to sleep for at least 3 hours on each of the 2 nights, and thus data from 30 subjects (20 men) were available for analysis. OSA severity was determined using the control night AHI. Six subjects were considered “severe” (AHI  $\geq 30$ ), 7 were “moderate” (AHI  $\geq 15$  to 30), 11 were “mild” (AHI  $\geq 5$  to 15), and 6 were considered to be primary snorers (AHI < 5).

The men ranged in age from 29.6 to 64.7 years, with an average age of  $50.1 \pm 9.8$  years; BMI ranged from 20.4 to 35.4 kg/m<sup>2</sup> (average  $28.2 \pm 4.0$  kg/m<sup>2</sup>). Women ranged in age from 19.7 to 62.3 years (average  $49.0 \pm 12.9$  years); BMI values ranged from 20.8 to 34.6 kg/m<sup>2</sup> (average of  $27.0 \pm 5.34$  kg/m<sup>2</sup>). Twenty-one subjects were Caucasian, 6 Asian or Pacific Islander, and 3 African American.

### AHI, Oxygenation, and Snoring

Analysis of mild, moderate, and severe OSA subjects revealed significant effects indicative of treatment benefit for AHI and O<sub>2</sub>DI. Thus AHI ( $Z = -3.714$ ,  $p < 0.001$ ; Figure 2) and the oxygen desaturation index (O<sub>2</sub>DI) ( $Z = -2.857$ ,  $p < 0.01$ ; Figure 3) both decreased with treatment. The percentage of the night spent above 90% saturation ( $Z = -2.068$ ,  $p < 0.05$ ) increased with treatment, and the nightly minimum oxygen saturation value (O<sub>2</sub>min) ( $Z = -1.676$ ,  $p = 0.09$ ) displayed a trend of increasing with treatment. In the whole group (including primary

**Table 1a**—Breathing Variables for Subjects Rank Ordered by Control Night AHI

| Sex    | Severity | Age  | BMI  | AHI     |        | O <sub>2</sub> DI |        | MinSpO <sub>2</sub> |        | % TST SpO <sub>2</sub> >90 |        | % TST Snoring |        |
|--------|----------|------|------|---------|--------|-------------------|--------|---------------------|--------|----------------------------|--------|---------------|--------|
|        |          |      |      | Control | Treat. | Control           | Treat. | Control             | Treat. | Control                    | Treat. | Control       | Treat. |
| Male   | snorer   | 34.8 | 25.8 | 4.4     | 2.5    | 1.39              | 0      | 94                  | 95     | 100.0                      | 100.0  | 27%           | 8%     |
| Female | snorer   | 46.6 | 32.5 | 4       | 3      | 3.57              | 2.33   | 86                  | 93     | 99.6                       | 100.0  | 14%           | 0%     |
| Male   | snorer   | 37.8 | 25.1 | 3.4     | 8.3    | 1.59              | 8.07   | 88                  | 91     | 100.0                      | 100.0  | 0%            | 15%    |
| Female | snorer   | 38.3 | 34.6 | 3       | 0.6    | 1.75              | 0.37   | 91                  | 91     | 100.0                      | 100.0  | 23%           | 0%     |
| Female | snorer   | 51.3 | 20.8 | 1.2     | 2.2    | 1.78              | 1.82   | 90                  | 92     | 100.0                      | 100.0  | 34%           | 2%     |
| Female | snorer   | 19.7 | 23.1 | 0.5     | 3      | 0.43              | 1.62   | 93                  | 92     | 100.0                      | 100.0  | 5%            | 6%     |
| Mean   | snorer   | 38.1 | 27.0 | 2.8     | 3.3    | 1.8               | 2.4    | 90.3                | 92.3   | 99.9                       | 100.0  | 17.2          | 5.2    |
| SD     |          | 10.9 | 5.4  | 1.6     | 2.6    | 1.0               | 2.9    | 3.0                 | 1.5    | 16.0                       | 0.0    | 13.2          | 5.8    |
| Male   | mild     | 48.1 | 31.5 | 14.7    | 3      | 1.42              | 1.06   | 90                  | 90     | 99.9                       | 100.0  | 21%           | 5%     |
| Female | mild     | 62.3 | 33.7 | 14.2    | 6      | 9.1               | 6.09   | 78                  | 80     | 97.4                       | 99.0   | 47%           | 0%     |
| Male   | mild     | 52.6 | 21.7 | 13.6    | 9.9    | 0.4               | 3.71   | 93                  | 91     | 100.0                      | 100.0  | 20%           | 3%     |
| Male   | mild     | 53.6 | 25.1 | 13.2    | 1      | 6.7               | 0.61   | 89                  | 94     | 100.0                      | 100.0  | 39%           | 8%     |
| Male   | mild     | 60.2 | 34.4 | 12.1    | 8      | 5.02              | 3.58   | 84                  | 88     | 99.4                       | 100.0  | 70%           | 31%    |
| Male   | mild     | 64.7 | 30.9 | 12      | 2.5    | 3.37              | 2.29   | 88                  | 90     | 99.9                       | 100.0  | 22%           | 12%    |
| Male   | mild     | 63.7 | 31.9 | 8.2     | 5      | 4.72              | 1.95   | 87                  | 88     | 99.1                       | 100.0  | 24%           | 2%     |
| Male   | mild     | 29.6 | 25.4 | 7.6     | 8.8    | 3                 | 7.52   | 90                  | 88     | 100.0                      | 100.0  | 40%           | 5%     |
| Female | mild     | 54.8 | 20.8 | 5.7     | 0.7    | 1.04              | 0.26   | 89                  | 92     | 99.9                       | 100.0  | 13%           | 0%     |
| Female | mild     | 44.2 | 29.3 | 5.5     | 2.8    | 1.95              | 2.45   | 89                  | 90     | 100.0                      | 100.0  | 16%           | 5%     |
| Male   | mild     | 54.3 | 20.4 | 5.1     | 0.2    | 0.62              | 0      | 92                  | 87     | 100.0                      | 100.0  | 10%           | 0%     |
| Mean   | mild     | 53.5 | 27.7 | 10.2    | 4.4    | 3.4               | 2.7    | 88.1                | 88.9   | 99.6                       | 99.9   | 29.3          | 6.5    |
| SD     |          | 10.2 | 5.2  | 3.8     | 3.4    | 2.8               | 2.4    | 4.1                 | 3.6    | 77.8                       | 30.2   | 18.0          | 8.9    |

Data are presented for primary snorers and mild OSA subjects together with mean and standard deviation data for each group. Age: years; BMI: kg/m<sup>2</sup>; AHI: apnea-hypopnea index defined as the number of events per hour of TST; O<sub>2</sub>DI: oxygen desaturation index defined as the number of 3% desaturations per hour of TST; MinSpO<sub>2</sub>: the minimum oxygen saturation value seen while asleep; % TST SpO<sub>2</sub> >90; percentage of sleep time spent with an oxygen saturation of greater than 90%; % TST Snoring: percentage of total sleep time spent snoring, where snoring events were only counted if they were independent of apneas or hypopneas

**Table 1b**—Breathing Variables for Subjects Rank Ordered by Control Night AHI

| Sex    | Severity | Age  | BMI  | AHI     |        | O <sub>2</sub> DI |        | MinSpO <sub>2</sub> |        | % TST SpO <sub>2</sub> >90 |        | % TST Snoring |        |
|--------|----------|------|------|---------|--------|-------------------|--------|---------------------|--------|----------------------------|--------|---------------|--------|
|        |          |      |      | Control | Treat. | Control           | Treat. | Control             | Treat. | Control                    | Treat. | Control       | Treat. |
| Female | moderate | 50.7 | 28.5 | 26.5    | 6      | 20.43             | 3.83   | 72                  | 90     | 96.9                       | 100.0  | 11%           | 25%    |
| Male   | moderate | 54.2 | 29.8 | 19.6    | 3.6    | 9.04              | 1.21   | 70                  | 90     | 93.6                       | 100.0  | 62%           | 7%     |
| Male   | moderate | 53.5 | 27.3 | 18.7    | 10.4   | 8.84              | 8.25   | 75                  | 74     | 96.7                       | 98.0   | 25%           | 7%     |
| Male   | moderate | 45   | 27.3 | 17.2    | 23.8   | 8.75              | 20.07  | 83                  | 82     | 97.2                       | 95.0   | 41%           | 7%     |
| Male   | moderate | 45.4 | 28.1 | 17      | 6.6    | 13.37             | 4.47   | 76                  | 89     | 98.6                       | 100.0  | 47%           | 16%    |
| Female | moderate | 60.8 | 23.8 | 16.3    | 1.9    | 9.82              | 1.12   | 85                  | 92     | 99.9                       | 100.0  | 0%            | 4%     |
| Female | moderate | 60.8 | 23.2 | 16.2    | 3.7    | 11.29             | 1.5    | 84                  | 90     | 99.8                       | 100.0  | 29%           | 13%    |
| Mean   | moderate | 52.9 | 26.9 | 18.8    | 8.0    | 11.6              | 5.8    | 77.9                | 86.7   | 97.5                       | 99.0   | 30.7          | 11.3   |
| SD     |          | 6.5  | 2.5  | 3.6     | 7.5    | 4.2               | 6.8    | 6.1                 | 6.5    | 2.2                        | 1.9    | 21.3          | 7.3    |
| Male   | severe   | 51.6 | 25.8 | 83.8    | 90.2   | 67.7              | 6.2    | 56                  | 59     | 16.7                       | 36.0   | 0             | 0      |
| Male   | severe   | 60.2 | 29.9 | 70.8    | 67.8   | 42.3              | 34.9   | 77                  | 71     | 92.1                       | 93.0   | 0             | 0      |
| Male   | severe   | 38.4 | 28.9 | 58      | 31.8   | 31.53             | 25     | 77                  | 73     | 93.3                       | 92.0   | 19%           | 15%    |
| Male   | severe   | 61.8 | 33.8 | 56.2    | 13.5   | 37.93             | 12.92  | 87                  | 90     | 99.2                       | 100.0  | 11%           | 0%     |
| Male   | severe   | 46.9 | 35.4 | 50.3    | 24.9   | 35.33             | 13.57  | 88                  | 88     | 99.1                       | 100.0  | 33%           | 20%    |
| Male   | severe   | 45.1 | 25.7 | 32.5    | 9.5    | 16.49             | 12.96  | 83                  | 80     | 98.0                       | 96.0   | 46%           | 41%    |
| Mean   | severe   | 50.7 | 29.9 | 58.6    | 39.6   | 38.7              | 27.9   | 78                  | 78.8   | 83.1                       | 86.2   | 18.2          | 12.7   |
| SD     |          | 9.1  | 4.0  | 17.6    | 32.3   | 16.8              | 21.6   | 11.8                | 11.6   | 32.7                       | 24.8   | 18.5          | 16.4   |
| Mean   | All OSA  | 52.6 | 28.0 | 24.8    | 14.2   | 14.6              | 9.9    | 82.6                | 85.3   | 94.9                       | 96.2   | 26.9          | 9.4    |
| SD     |          | 8.7  | 4.3  | 22.1    | 21.8   | 16.9              | 15.2   | 8.6                 | 8.4    | 16.8                       | 13.0   | 19.0          | 10.7   |

Data are presented for moderate and severe OSA subjects together with mean and standard deviation data for each group and the mean and standard deviation data for all OSA subjects.

snorers), the percentage of the night spent snoring decreased significantly ( $Z = -3.962$ ,  $p < 0.001$ ).

The impact of body position was tested in 25 subjects. As expected, AHI on control nights was higher when supine ( $27.4 \pm 23.3$ ) than when nonsupine ( $16.6 \pm 24.1$ ). There was a significant difference between control and device nights when supine ( $Z = -3.404$ ,  $p = 0.001$ ) and when nonsupine ( $Z = -2.472$ ,  $p$

$= 0.013$ ). Twenty-one subjects decreased AHI from control to device nights (mean difference of  $10.4 \pm 13.9$ ) when supine; 18 subjects also had lower AHI with the device when not supine (mean difference of  $6.0 \pm 11.8$ ), with no significant effect of body position on the control device night differences ( $Z = -1.830$ ,  $p = 0.067$ ) (see Table 1).



**Table 2**—Sleep Architecture Variables as a Function of Treatment Condition for Each of the 4 Groups Broken Down by Severity of Untreated OSA, Mean (SD)

|                | Primary snorers<br>n = 6 |               | Mild OSA<br>n = 11 |              | Moderate OSA<br>n = 7 |              | Severe OSA<br>n = 6 |               |
|----------------|--------------------------|---------------|--------------------|--------------|-----------------------|--------------|---------------------|---------------|
|                | Control                  | Treatment     | Control            | Treatment    | Control               | Treatment    | Control             | Treatment     |
| TST            | 395.5 (97.9)             | 347.5 (126.1) | 331.8 (26.1)       | 349.0 (45.1) | 376.5 (34.9)          | 365.1 (66.0) | 303.4 (40.0)        | 322.5 (59.1)  |
| SE%            | 76.8 (21.5)              | 81.6 (9.9)    | 80.3 (9.9)         | 81.4 (12.2)  | 85.4 (7.1)            | 80.9 (8.3)   | 74.3 (9.3)          | 74.9 (13.8)   |
| SOL            | 43.9 (83.7)              | 15.2 (13.3)   | 14.7 (4.9)         | 15.7 (14.0)  | 10.7 (9.0)            | 8.2 (6.2)    | 6.1 (6.5)           | 8.0 (10.3)    |
| ROL            | 78.1 (66.5)              | 146.7 (71.8)  | 106.1 (42.8)       | 60.9 (32.9)  | 82.3 (48.6)           | 117.2 (72.6) | 135.8 (34.8)        | 107.2 (39.6)  |
| WASO           | 88.2 (72.3)              | 58.3 (23.5)   | 69.2 (41.9)        | 67.5 (48.5)  | 59.2 (27.2)           | 75.9 (31.3)  | 104.9 (51.2)        | 108.6 (67.1)  |
| Wake Index     | 3.4 (1.5)                | 5.0 (2.7)     | 7.3 (3.1)          | 5.7 (3.5)    | 6.3 (1.9)             | 8.0 (2.9)    | 17.9 (17.7)         | 18.9 (17.8)   |
| Stage shifts   | 133.5 (52.2)             | 119.3 (40.4)  | 131.6 (73.5)       | 154.0 (49.0) | 166.1 (37.2)          | 185.0 (34.4) | 283.8 (187.9)       | 306.0 (198.5) |
| Stage 1 shifts | 26.5 (16.7)              | 30.7 (12.4)   | 50.4 (17.3)        | 40.8 (19.1)  | 52.5 (16.0)           | 61.3 (17.8)  | 108.8 (85.9)        | 106.3 (83.4)  |
| % Stage 1      | 12.9 (11.6)              | 15.4 (13.3)   | 21.8 (14.4)        | 15.1 (10.3)  | 22.8 (11.5)           | 25.0 (11.7)  | 42.8 (22.9)         | 39.4 (27.0)   |
| % Stage 2      | 53.8 (14.1)              | 58.2 (17.7)   | 47.1 (3.0)         | 50.1 (6.8)   | 48.0 (13.0)           | 47.0 (11.6)  | 35.9 (19.2)         | 37.2 (21.0)   |
| % SWS          | 10.2 (7.6)               | 8.7 (6.5)     | 11.2 (7.8)         | 9.5 (7.8)    | 6.3 (6.6)             | 7.1 (5.6)    | 5.2 (7.2)           | 4.1 (6.0)     |
| % REM          | 23.1 (8.0)               | 17.7 (10.5)   | 20.0 (6.0)         | 25.3 (5.2)   | 22.9 (7.3)            | 21.0 (5.8)   | 16.2 (5.0)          | 19.4 (5.1)    |

TST: total sleep time in minutes; SE%: sleep efficiency calculated as TST/time in bed; SOL: sleep onset latency (to stage 1 sleep) in minutes; ROL: REM onset latency in minutes; WASO: minutes of wakefulness after initial sleep onset; Wake Index: number of wake periods (>15 sec) per hour; Stage shifts: total number of sleep stage/state changes per night; Stage 1 shifts: number of shifts from stage 2, SWS, or REM to stage 1 sleep; % Stage 1, % Stage 2, % SWS & % REM: percentage of TST spent in each sleep stage.

### Sleep Architecture Variables

Analysis of all subjects revealed no significant differences in any of the sleep variables between control and treatment nights. When the primary snorers were assessed separately, the only significant difference was found for the % time spent in REM sleep ( $Z = -1.992$ ,  $p = 0.046$ ), with  $21.13\% \pm 6.9\%$  on the control night and  $20.70\% \pm 6.2\%$  on the treatment night. When the mild, moderate, and severe subjects were assessed, no sleep architecture variables were significantly different between treatment and control nights (see Table 2).

### Subjective Experience of the Device

In answer to the question “How comfortable was the fit of the Ventus device within your nose immediately after insertion?” 6 subjects found it to be “very comfortable,” 14 found it to be “somewhat comfortable,” 9 found it to be “somewhat uncomfortable,” and 1 found it to be “very uncomfortable.” When the same question was asked relating to comfort in the morning just prior to removal, 12 subjects found it to be “very comfortable,” 10 found it to be “somewhat comfortable,” 6 found it to be “somewhat uncomfortable,” and 2 people found it to be “very uncomfortable.”

When asked “Did you have to adjust the Ventus device at any point during the night?” 2 subjects did not remember, 22 reported that they did not need any adjustments, 6 needed 1 adjustment, and no one reported needing more than one adjustment. None of the subjects removed the device or had it come out of the nostrils

Subjects were also asked “How comfortable was the breathing through your nose (with the Ventus device in place) while you were awake?” Five subjects reported it to be “very comfortable,” 11 “somewhat comfortable,” 10 “somewhat uncomfortable,” and 1, “very uncomfortable.” In a related question, they were asked “Did the Ventus device cause you to breathe through your mouth, or make you feel like you wanted to breathe through your mouth?” Twenty-seven subjects reported

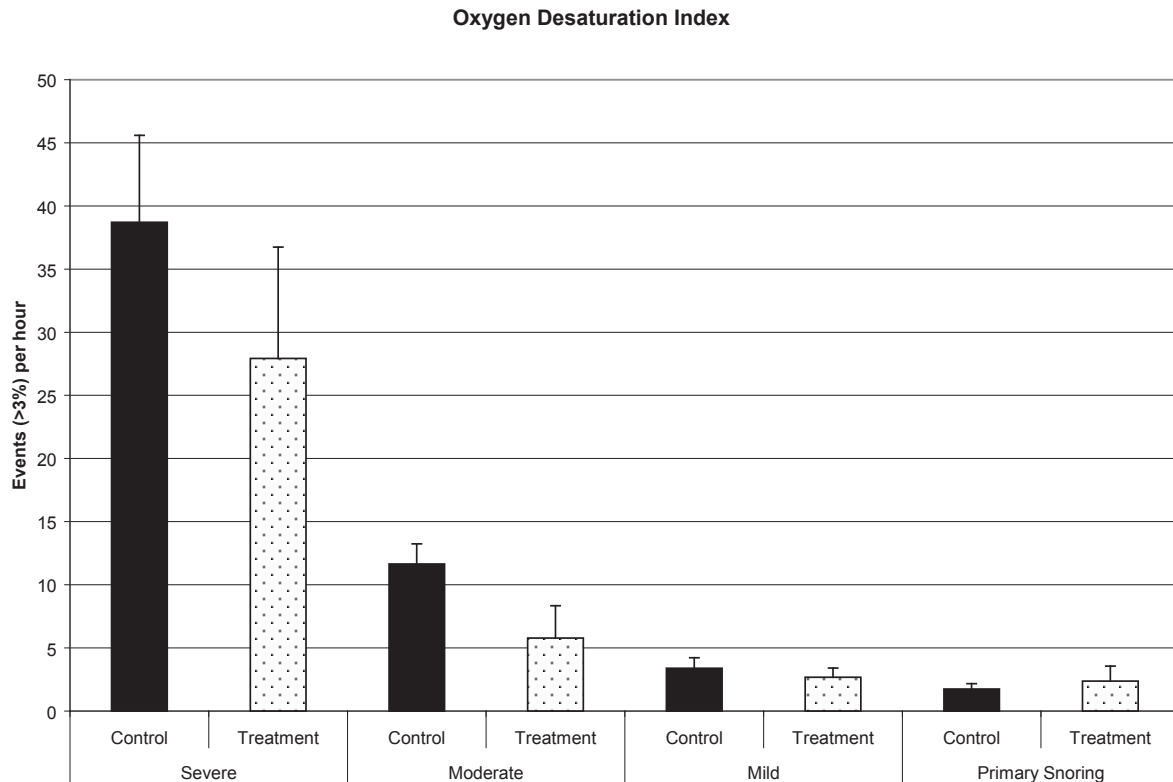
the need or desire to mouth breathe while awake, 2 did not, and 1 did not answer the question.

Of the 11 subjects who had previously used CPAP, 10 reported CPAP to be “much” less comfortable than the Ventus device and 1 “somewhat” less comfortable.

### DISCUSSION

The nasal expiratory resistance device reduced measures of sleep disordered breathing in a small sample of individuals with pathology ranging from mild to severe OSA, with no negative impact on observed objective sleep architecture parameters. Specifically, AHI and  $O_2DI$  and other measures of nocturnal oxygenation significantly improved. In addition, the percentage of time spent snoring was decreased in the OSA patients as well as in a group of primary snorers. The 2 most extreme subjects (control AHI values of 83.8 and 70.8 events/h) did not display any treatment benefit.

Few previous studies have evaluated the efficacy of increased expiratory resistance in isolation in the treatment of OSA, although obviously nasal CPAP provides positive pressure during expiration as well as inspiration. Mahadevia et al.<sup>4</sup> studied 9 patients with OSA. EPAP was applied to the expiratory limb of a nonbreathing valve via a water column in 6 subjects and a resistive valve in a tight fitting mask in the remaining 3 subjects. There was a significant decrease in apnea index from  $30.72 \pm 20.92$  to  $3.39 \pm 4.05/h$ , and a significant decrease in the duration of the events from  $47.1 \pm 24.5$  sec to  $13.1 \pm 8.3$  sec. There were also significant improvements in all measures of oxygen saturation. Importantly, all 9 subjects showed benefits of EPAP treatment including the 2 subjects with untreated AI values >50/h. EPAP had a positive impact on sleep structure, with significant increases in SWS, mirroring significant decreases in time spent in stages 1 and 2. However, the evaluations were based on relatively small amounts of data, with a range of 2.3 to 4.5 h of total sleep time on the treatment nights and 2.9 to 4.5 h of total sleep time on control nights. In addition, the pulmonary function of many of the subjects was compromised (3 had  $PCO_2$  values approaching 50 mm



**Figure 3**—Histogram of the oxygen desaturation index shown on treatment and control nights for the 6 severe subjects, the 7 moderate subjects, the 11 mild subjects, and the 6 primary snoring subjects (untreated AHI values <5). Data are presented as group means with error bars representing the standard error scores. There was a significant difference between treatment and control nights in the mild, moderate, and severe OSA groups,  $p < 0.01$ .

Hg, 4 had FEV/FVC values <80% of expected, and 5 subjects had partial pressures of oxygen  $\leq 70$  mm Hg (resting  $SpO_2 < 94\%$ ). Not surprisingly, 6 of the 9 subjects were obese, including 3 with BMI  $> 39$  kg/m<sup>2</sup>. Mahadevia commented on an EPAP-mediated improvement in wake supine  $SpO_2$ , and speculated that this was due to an increase in functional residual capacity (FRC).

McGinley et al.<sup>8</sup> used nasal insufflation of heated humidified air at 20 L/min flow via a nasal cannula. They reported significant improvement in breathing during sleep (with measurements lasting  $> 6$  h on average) in 11 OSA patients, with pathology ranging from mild to severe (AHI of 5 to 60), with no impact on measures of sleep architecture. They measured supraglottic pressure in a subset of 7 patients; they observed an increase in end-expiratory supraglottic pressure of  $1.8 \pm 0.1$  cm H<sub>2</sub>O and a reduction in the magnitude of supraglottic inspiratory-expiratory pressure swings. The authors speculated that even this modest pressure increase might produce an increase in lung volume, although they did not rule out other possible causative factors, such as reduced dead space and reduced lability of respiratory control as a secondary consequence of increased sleep stability.

The evaluation of snoring as an additional dependent variable provides additional data as to the potential benefits of expiratory resistance, and unlike the subjects in the study of Mahadevia et al., the majority of the subjects in the present study (21 of 30) were not obese. These data together with those of McGinley et al. (in which only 2 subjects were obese) shows efficacy of increased expiratory resistance in subjects who do not have a preexisting obesity-related decrease in FRC. In addition, unlike the 2 earlier studies, none of the subjects in either the

present study or that of McGinley reported respiratory disease, although ventilatory function was not assessed in either study.

The failure to show effects in the 2 most extreme patients needs to be examined, although an explanation would require a greater understanding of the mechanisms by which the device effected improvements in AHI, O<sub>2</sub>DI and/or snoring in the majority of the less severe subjects. It may be that there is a threshold of disease above which increased expiratory resistance used in this study alone is not effective. Regardless of the cause, the lack of improvement requires caution in contemplating the use of a nasal expiratory resistance device such as that presently studied in patients with severe disease.

The subjective experience of the device was positive; the majority of subjects found it comfortable, and all subjects with prior experience rated it more comfortable than CPAP. Importantly, no subjects experienced the device falling out of the nose or felt the need to remove it, and the majority required no adjustment of the device throughout the study. As expected, most subjects felt more comfortable mouth breathing while awake when the device was in place. However, it should also be noted that the subjects were instructed to breathe through their mouths while awake, with the expectation that they would revert to nasal breathing upon sleep onset. This was based on prior experience with the device, indicating that wakeful nasal breathing was uncomfortable in some users of the device.

There was no significant improvement in sleep architecture variables detected with device use, despite improvements in breathing, a finding that needs explanation. Although long-term CPAP use reliably produces a decrease in stage 1 sleep and an

increase in SWS, there are a surprisingly small number of studies assessing the impact of the first night of CPAP treatment on sleep architecture. These do, however, show the typical stage 1 and SWS effects, although the disease severity tends to be higher and the baseline sleep values worse than we are reporting in the present study.<sup>9-12</sup> It is also the case that on both the first night<sup>12</sup> and in longer term studies, not all subjects show improvements in stage 1 and SWS.<sup>13</sup>

In the present study, sleep quality, although not improved, showed no evidence of negative effect of device use. At least one previous EPAP study during wakefulness was not able to be conducted during sleep due to a “pronounced tendency to arouse subjects from sleep.”<sup>14</sup> The lack of improved sleep could represent a transient sleep disruption which may improve with time. It is also possible that changes in sleep architecture might occur over time with continued use of the device. Examination of the sleep quality in the primary snoring group did not reveal any negative impact of device use on sleep in those with minimal sleep related breathing pathology. The question of device impact on sleep quality needs to be resolved in a more extensive study, involving subjects with more severe apnea and poorer baseline sleep quality.

However, even if future studies do not show an improvement in sleep quality, an argument can be made for the utility of a treatment that reduces respiratory pathology during sleep without associated sleep improvements. There is now converging evidence of an association between apnea and increased incidence of cardiovascular and cerebrovascular morbidity and mortality,<sup>15</sup> probably mediated by oxidative stress produced by intermittent hypoxia,<sup>16</sup> in addition to increased sympathetic activations associated with arousals.<sup>17</sup> A treatment that reduces O<sub>2</sub>DI is thus likely to have health benefits even in the absence of improvements in sleep quality.

There are several limitations in the study that argue for cautious interpretation of the data. First, the data presented are from a single night of treatment, and thus cannot address the issue of whether the effects on sleep disordered breathing will persist over multiple nights or habituate. Second, while each subject in the study served as his/her own control, no placebo nasal device was used during a control night of the study. Thus, it remains possible that benefits may have accrued due simply to the insertion of devices in the nose leading to reflex upper airway dilation. A third and related issue is that the device studies had a single level of resistance. Other levels of resistance and intranasal pressure may yield varying therapeutic effects. Evaluation of different ranges of resistance needs to be conducted to determine those optimal for varying degrees of pathology. Fourth, nothing can be inferred as to the potential therapeutic benefit to obese patients due to the exclusion of subjects with BMI >35. Finally, this study did not assess the degree to which the effectiveness of the device can be altered by subject-dependent factors that might change control of breathing and the relationship between respiratory timing and pressure. Determination of the extent to which subjects are able to maintain a positive expiratory pressure through to the onset of the next inspiration would be helpful in informing mechanism of action. Qualitatively, we have noticed an elimination of expiratory pause in many of the respiratory waveforms when the device is in place. While this would appear to support a hypothesis that there is an elevated

pressure at the critical end-expiratory period, it remains a speculation in the absence of intranasal pressure data.

Despite the lack of optimization or titration and the lack of improvement in sleep architecture, for at least the first night of use, the device clearly had a beneficial impact on breathing during sleep, with substantial reductions in AHI, and O<sub>2</sub>DI and improvements in oxygenation in subjects with OSA. These results are obtained from the use of a simple device to accomplish the increased expiratory resistance, making the findings readily testable in an expanded patient set, and clinically generalizable if confirmed.

## DISCLOSURE STATEMENT

This study was supported by a contract from Ventus Medical Inc. Dr. Black serves as a scientific advisor to and has financial interests in Ventus Medical. Dr. Brooks has consulted for, been a scientific advisor to, and has financial interests in Ventus Medical. Dr. Colrain has indicated no other financial conflicts of interest.

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