NEW RESEARCH

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Predictors of Response to a Nasal Expiratory Resistor Device and Its Potential Mechanisms of Action for Treatment of Obstructive Sleep Apnea

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SCIENTIFIC INVESTIGATIONS

Study Objective: A one-way nasal resistor has recently been shown to reduce sleep disordered breathing (SDB) in a subset of patients with Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS). The purpose of this study was to examine characteristics predictive of therapeutic response to the device and provide pilot data as to its potential mechanisms of action.

Patients, Interventions, and Measurements: 20 subjects (15M/5F, age 54 ± 12 years, BMI 33.5 ± 5.6 kg/m^2) with OSAHS underwent 3 nocturnal polysomnograms (NPSG) including diagnostic, therapeutic (with a Provent® nasal valve device), and CPAP. Additional measurements included intranasal pressures and PCO_2, closing pressures (Pcrit), and awake lung volumes in different body positions.

Results: In 19/20 patients who slept with the device, RDI was significantly reduced with the nasal valve device compared to the diagnostic NPSG (27 ± 29/h vs 49 ± 28/h), with 50% of patients having an acceptable therapeutic response. Among demographic, lung volume, or diagnostic NPSG measures or markers of collapsibility, no significant predictors of therapeutic response were found. There was a suggestion that patients with position-dependent SDB (supine RDI > lateral RDI) were more likely to have an acceptable therapeutic response to the device. Successful elimination of SDB was associated with generation and maintenance of an elevated end expiratory pressure. No single definitive mechanism of action was elucidated.

Conclusions: The present study shows that the nasal valve device can alter SDB across the full spectrum of SDB severity. There was a suggestion that subjects with positional or milder SDB in the lateral position were those most likely to respond.

Keywords: Expiratory positive airway pressure, nasal valve, obstructive sleep apnea, sleep apnea therapy

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Provent® Sleep Apnea Therapy (Ventus Medical, Belmont, CA) is a novel and easy to use device based on a nasal valve that produces expiratory resistance. This device has recently become available for treatment of obstructive sleep apnea/hypopnea syndrome (OSAHS). In 2 recent studies evaluating the effectiveness of the nasal valve device, half of the subjects with known OSAHS of varying severity demonstrated an 80% reduction in the Apnea Hypopnea Index (AHI) while using the device.[1,2] As the effect of the device on AHI was independent of the severity of the sleep disordered breathing (SDB), obesity, and other demographic factors, it has been difficult to define which patient population will respond favorably to the nasal valve device. In addition, the mechanism of action of the device still remains undefined.[1,2]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Current data suggest that up to 50% of patients with OSAHS may respond to nEPAP applied with a one-way nasal resistor device. The purpose of the present study was to confirm these data, identify the patient population for whom nEPAP therapy may be beneficial and the relative role of possible mechanisms of action.

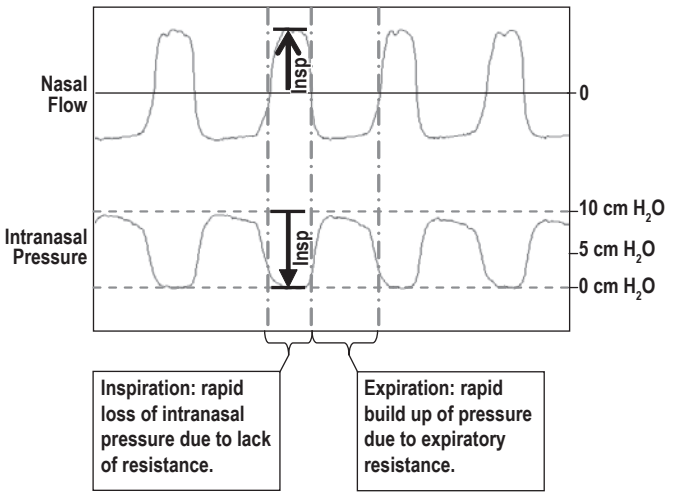
Study Impact: Our data confirmed that 50% of patients with OSAHS had a therapeutically acceptable response with no clear factors identified that predicted response. Establishment and maintenance of an expiratory positive pressure was closely associated with acceptable therapeutic response, suggesting a role for mechanical factors including increased tracheal traction, but upper airway effects and stimulation by retained CO_2 as contributing mechanisms could not be ruled out.

A commentary on this article appears in this issue on page 23.

The nasal valve device consists of a small valve attached externally to each nostril with adhesive tape. The valve acts as a one-way resistor, producing expiratory resistance while leaving inspiration unaffected. It differs fundamentally from the current standard pressure treatment for obstructive sleep disordered breathing, nasal continuous positive airway pressure (CPAP), in that it provides no positive pressure to the airway during inspiration. Mahadevia, et al.[3] showed in 1983 that the application of expiratory positive airway pressure (EPAP) via a threshold valve reduced frequency and duration of apneas in patients with OSAHS, but other studies, as well as clinical experience, did not confirm Mahadevia's findings. In 2008, Heinzer et al.[4] showed no significant change in SDB by application of EPAP of 10 cm H_2O. Despite this, the recently published studies[1,2]with successful outcomes using the nasal valve device suggest that this type of therapy needs to be reevaluated.

As pointed out in a recent editorial by White,[5] there are several possible mechanisms of action for EPAP: (1) dilatation of

Figure 1—15-second window showing airflow and pressure tracings recorded during the NPSG with the nasal valve device in place, demonstrating increased pressure during expiration with no pressure during inspiration



the upper airway by the pressure generated during expiration, with carryover of this dilatation into inspiration, (2) mild hypercapnia resulting from hypoventilation induced by the expiratory resistance of nasal expiratory positive pressure (nEPAP), resulting in increased respiratory drive to the upper airway, (3) induction of lung hyperinflation by the elevated end-expiratory pressure, resulting in reduced upper airway collapsibility due to the increased tracheal traction.[6,7]

A therapeutic effect of the nasal valve device on SDB has been demonstrated in only a subset of patients.[1,2] It is therefore desirable to define patient characteristics predictive of therapeutic response. Predictive characteristics may relate to patient demographics, severity of SDB, anatomic factors determining the degree of airway collapsibility, and/or the potential mechanisms of action of the device. As the degree of airway collapsibility has been shown to be influenced by lung volume acting through tracheal traction,[6,7] we were interested in both static lung volumes and positional changes in lung volume as potential predictive characteristics of the nasal valve device responsiveness.

The purpose of the present study was to (1) confirm efficacy of nEPAP therapy using the nasal valve device, (2) attempt to identify the patient population for whom nEPAP therapy may be appropriate, and (3) examine the relative role of the several possible mechanisms of action of the nasal valve device.

METHODS AND MATERIALS

Subject Selection

Twenty subjects (15M/5F, age 54.3 ± 12.0 years, BMI 33.5 ± 5.6 kg/m^2) with clinical OSAHS defined by Apnea plus Hypopnea with 4% desaturation Index (AHI4%) > 5/hr on full overnight polysomnography were recruited for the present study from subjects seen at the New York University Sleep Disorders Center. Subjects were excluded if they were unable to breathe through the nose because of significant nasal congestion/obstruction, or if they had congestive heart failure, central sleep apnea, or neuromuscular diseases associated with weakness. Patients with known alveolar hypoventilation or with elevated arterial PCO_2, elevated serum bicarbonate, or unexplained periods of sustained desaturation on polysomnogram were excluded.

All subjects underwent or had recently undergone full-night diagnostic PSG for diagnosis. On 2 separate nights, therapy was applied. On one of the therapeutic nights (full-night study), patients wore the nasal valve device (Provent®, Ventus Medical, Belmont, CA). On a separate full night, patients wore CPAP which was titrated; during this night the CPAP circuit was used to also measure the critical closing pressure (Pcrit) (see below). The order of these therapeutic nights (but not the diagnostic night) was randomized. Patients also underwent daytime assessment of sitting, supine, and lateral awake lung volumes. All testing except for the diagnostic PSG was completed within 3 months, and the diagnostic PSG was always performed within one year prior to enrollment.

Diagnostic Polysomnography Procedure

The in-laboratory PSG was performed according to standard clinical guidelines and included frontal, central, and occipital electroencephalogram, electrooculogram, submental electromyogram to monitor sleep; an anterior tibialis electromyogram to monitor leg movements; a unipolar electrocardiogram for cardiac monitoring; pulse oximeter for oxygen saturation; piezoelectric strain gauges for chest and abdominal movements; and a multiposition switch for determining sleep position. A nasal cannula pressure transducer system (Protech PTAF2, Woodinville WA) was used to measure airflow, and an oral thermistor was used to detect mouth breathing.

Therapeutic (Nasal Valve Device) Polysomnography Procedure

This in-laboratory PSG was performed on a separate night and was identical to the diagnostic NPSG except for respiratory monitoring. Nasal flow was recorded with a pneumotachograph (Hans Rudolph Inc, Kansas City MO) attached to an unpressurized nasal mask placed over the nasal valve device. The static volume of the nasal mask and pneumotachograph system was < 110 cc, which was within the range reported in other studies of sleep ventilation.[8] Preliminary testing in patients not wearing the nasal valve device showed that monitoring of nasal flow with this unpressurized mask produced a signal essentially identical to the signal from a nasal cannula.

During this night of testing, the patients wore the nasal valve device (80 cm H_2O*sec/L), which consists of 2 separate adhesive valves designed to produce nEPAP, on each nostril. These had been modified by Ventus Medical, Inc. to allow for attachment of a small catheter that gave access to the intranasal cavity behind the valve for intranasal pressure monitoring (one naris) and end-tidal CO_2 (recorded from the other naris). This intranasal pressure tracing was *not* used to record airflow. **Figure 1** shows the airflow and pressure tracings recorded during the NPSG with the nasal valve device in place, demonstrating increased pressure during expiration with no pressure during inspiration.

Analysis of Expiratory Pressure

For each patient, pressure data from the intra-nasal cavity were analyzed across the night and tabulated during at least 3 periods of NREM sleep in the supine and lateral positions when there was no evidence of SDB (wherever this was possible). The intranasal pressure at end expiration was identified for each breath and averaged over 3 consecutive breaths to define each measurement. We tabulated the range of intranasal pressures throughout the whole night that was associated with absence of SDB ≥ 5 min during sleep. To address the relationship of therapy to pressure, a further analysis was performed restricting the dataset to time spent in supine stage N2 sleep. Within this restricted set, we analyzed the time spent above and below the lowest effective nEPAP pressure (LEP_N2) after LEP_N2 was defined as the lowest pressure during supine N2 sleep that was effective at eliminating SDB for at least 5 min.

Analysis of End-Tidal CO_2 Signal

PCO_2 values were obtained across the night during the awake periods of nasal breathing, as well as during ≥ 3 periods of NREM sleep in the supine and lateral positions during both effective and ineffective intranasal pressures. The values of intranasal end tidal CO_2 as reported are the average of values obtained from 3 consecutive breaths.

Diagnostic and Therapeutic (nEPAP) PSG scoring:

For the PSG data, sleep, arousals and periodic legs movements were scored by American Academy of Sleep Medicine (AASM) standards.[9] Respiratory events were scored manually as follows: *Apneas* were identified when the airflow amplitude on the nasal cannula was < 10% of baseline and no flow occurred on the oral thermistor. *Hypopneas 4%* were identified when airflow amplitude was reduced by 30% from baseline and the event was followed by 4% O_2 desaturation. AHI4% was defined as the sum of apneas and hypopneas4% divided by total sleep time. In order to identify subtle obstructive events, we also performed a calculation of the respiratory disturbance index (RDI) which included both the AHI and additional events when airflow amplitude was < 50% but without 4% oxygen desaturation or, alternatively, whenever a discernable change occurred in the airflow amplitude (50%-80% of baseline) and the event was followed by 4% O_2 desaturation within 30 sec or an EEG arousal within 5 sec, as suggested by recent criteria of the AASM.[9]

Passive Pcrit Procedure

The in-laboratory PSG on nasal CPAP was performed as per standard clinical guidelines. Flow was recorded via a pneumotachograph (Hans Rudolph Inc, Kansas City, MO) attached between the nasal mask and CPAP tubing. Measurements were performed during stage N2 sleep in the supine position and with the head elevated on one pillow. Two modified CPAP machines (Fisher and Paykel SleepStyle 2000, Auckland, New Zealand) were used to deliver pressures from +20 cm H_2O to −20 cm H_2O. Pressure at the mask (Pn) was measured continuously. CPAP was titrated manually during the first hour of the study to a level which eliminated all sleep disordered breathing events, including obstructive apneas, hypopneas, and runs of flow limitation. The optimal pressure was defined as the pressure at which flow limitation disappeared and was used as the "holding pressure" for subsequent passive Pcrit maneuvers. For each measurement, Pn was abruptly decreased from the holding pressure to a predetermined pressure for 6 breaths before being returned back to holding pressure. Measurements were separated by ≥ 1 min before repeating a pressure drop. The maximum flow (VImax) for the last 3 breaths (#4-6) during the pressure drop was assessed and used in determining the passive Pcrit. During successive maneuvers Pn was progressively lowered until an apnea was produced (VImax = zero). The Pn where the VImax went to zero from a positive flow was termed the passive critical pressure (Pcrit). The Pcrit was reassessed for reproducibility on ≥ 2 occasions in supine N2 sleep in each patient. In the 4 cases where zero flow (apnea) could not be reached without producing an arousal, the Pcrit was extrapolated as per the criteria described by Patil et al.[10] If an EEG arousal or awakening occurred during a pressure drop, then that measurement was not included in the analysis. At least 2 minutes of stable stage N2 sleep was required prior to proceeding with further measuremen

Lung Volumes

Standard spirometry and body plethysmography (Sensormedics, Yorba Linda, CA) were performed during the daytime in the sitting position to determine Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), Functional Residual Capacity (FRC), Expiratory Reserve Volume (ERV), and Total Lung capacity (TLC) in each subject. Lung volumes were measured within 8 weeks of the PSG study with nEPAP. At the same setting, and while awake, FRC was determined by Nitrogen (N_2) washout in the sitting position. Lung volume data was excluded if either the patient's FEV1/FVC ratio on spirometry was < 70%, or if the difference between N_2 washout and plethysmography lung volumes was > 750 cc. N_2 washout FRC measurements were repeated in the supine and right-lateral positions in random order.

Statistical Analysis

Measures of sleep disordered breathing between baseline and on the nasal valve were compared using paired *t*-tests.

For purposes of evaluating potential predictors of therapeutic response to the nasal valve device in a given patient, we compared anthropomorphic and sleep variables between subjects with both > 50% reduction in RDI and RDI < 20/h on therapy with those that met neither condition. The value of RDI = 20/h was chosen based on previous data showing that this is the upper limit of normal in asymptomatic individuals.[11]

The protocol was approved by the IRB of the NYU School of Medicine; all patients provided informed consent.

RESULTS

During the diagnostic NPSG (n = 20), mean AHI4% was 34 ± 30/h overall, and mean RDI (AHI4% plus RERAs) was 49 ± 28/h. RDI supine was 58 ± 31/h, and RDI lateral was 39 ± 30/h. **Table 1** shows the individual patient data from the diagnostic night and the response to the nasal valve device on the night that it was used. One patient was unable to sleep with the device in place and is excluded from **Table 1**. In the 19 subjects who tolerated the use of the nasal valve device during sleep, the

Table 1—Measures of SDB overall, in supine position, and REM sleep at baseline and on the nasal valve device

	Diagnostic NPSG				NPSG with nasal valve device therapy		
	Subject #	Overall RDI in events/h	Supine RDI in events/h	REM RDI in events/h	Overall RDI (%Change from diagnostic)	Supine RDI (%Change from diagnostic)	REM RDI (%Change from diagnostic)
Therapeutically Acceptable Responders	1	55.3	77.3	74.8	7.3 (-87%)	7.3 (-90%)	22.8 (-70%)
	2	97.4	97.4	no REM	18.6 (-81%)	18.6 (-81%)	42.6 (NA)
	3	41.4	40.9	75.8	12.6 (-70%)	12.6 (-70%)	60 (-21%)
	4	39.8	39.3	31.3	6.9 (-83%)	9.2 (-80%)	8.9 (-72%)
	5	24.0	51.3	6.0	2.8 (-88%)	0.8 (-99%)	no REM (NA)
	6	33.6	44.0	75.5	3.6 (-89%)	3.7 (-90%)	13.2 (-83%)
	7	19.3	21.3	37.1	9.1 (-53%)	9.1 (-60%)	52.2 (41%)
	8	46.0	51.0	68.7	19.1 (-58%)	19.1 (-60%)	15.9 (-77%)
	9	21.8	35.0	55.7	9.3 (-57%)	9.5 (-70%)	23.3 (-58%)
	10	32.8	31.8	4.0	9.1 (-72%)	25.5 (-20%)	2.6 (-35%)
	Mean ± SD	**41.1 ± 23**	**43.5 ± 16**	**47.7 ± 29**	**9.8 ± 5.5 (-73.8% ± 14)**	**11.5 ± 7.6 (-71% ± 24%)**	**26.8 ± 20 (-39.8% ± 45%)**
Partial Responders	11	33.5	97.4	40.8	19 (-44%)	36.5 (-60%)	28.3 (-31%)
	12	40.7	no supine	32	20.7 (-49%)	11.2 (NA)	no REM (NA)
	13	44.7	47.6	84.8	24.9 (-44%)	27.8 (-40%)	69.9 (-18%)
	14	77.6	82.3	40.8	34.4 (-56%)	53.3 (-40%)	25.7 (-37%)
	Mean ± SD	**49.1 ± 5**	**75.8 ± 26**	**49.6 ± 24**	**24.7 ± 7 (-48% ± 5.7%)**	**32.2 ± 18 (-47% ± 15%)**	**41.3 ± 25 (-28.7% ± 9.7%)**
Non-Responders	15	35.7	36.2	14.6	57.6 (+61%)	No supine (NA)	24 (64%)
	16	88.3	119.9	71.4	66.1 (-25%)	105.4 (-10%)	46.3 (-35%)
	17	123.7	125.7	105.3	121.9 (-1%)	123.5 (+2%)	109.3 (+4%)
	18	49.1	58.8	43.7	32.3 (-34%)	62.5 (+10%)	8.7 (-80%)
	19	23.4	22.5	57.5	41.6 (+74%)	40.6 (+80%)	51.4 (-11%)
	Mean ± SD	**64 ± 41**	**76.6 ± 47**	**58.5 ± 34**	**63.7 ± 35 (15% ± 50%)**	**83 ± 38 (-18% ± 42%)**	**47.9 ± 38 -11.6% ± 53%**

overall mean AHI4% was lowered to 19.9 ± 26/h ($p < 0.05$), and RDI was lowered to 27 ± 29/h ($p < 0.0001$). However, there was wide variability between patients in the therapeutic efficacy: in 10 patients we considered the reduction in RDI therapeutically acceptable because it met usual clinical criteria with both > 50% reduction in RDI from the diagnostic studies and an absolute RDI < 20/h, which is the upper limit of normal we use for respiratory scoring in our laboratory. In these 10 patients, the mean AHI4% was reduced from 26.5 ± 26 events/h on the diagnostic study to 6 ± 6 events/h while using the nasal EPAP device. From the group of patients who did not meet both criteria for therapeutically acceptable response (RDI < 20/h and > 50% reduction), we identified 4 additional patients as "partial responders"—those having a substantial drop (> 40%) in RDI. The remaining 5 patients were labeled "non-responders." In the therapeutically acceptable responders, the reduction in RDI was not caused by a decrease in the time spent in the supine position (percent time spent supine 71% ± 22% on the diagnostic study and 76% ± 25% on the study using the nasal valve device); furthermore, in all 3 therapeutic response groups, the RDI supine showed the same therapeutic pattern of improvement as the overall RDI (**Table 1**). In the therapeutically acceptable response group, 3 of the 10 subjects had persistent severe SDB during REM sleep. One patient did not have REM sleep while on the nasal valve device, but had a baseline REM RDI of only 6/h on the diagnostic night. The remaining 6 subjects all had significant improvement in REM as well as overall sleep. There was no significant change in weight between the time of the diagnostic NPSG and NPSG with the nasal valve device in the responders (−0.2 ± 1.4 kg), the non-responders (1 ± 2.4 kg), or overall (−0.75 ± 0.3 kg).

Despite their improvement in SDB events, the 10 patients with therapeutically acceptable results did not show statistically significant improvement in their sleep variables with the nasal valve device compared to the diagnostic sleep study. However, in these patients a trend towards improvement was seen for all sleep variables: sleep efficiency (diagnostic: 72% ± 14% vs therapeutic: 78% ± 14%), percent time N1 (diagnostic: 26 ± 13 vs therapeutic: 23 ± 8), percent time REM (diagnostic:11 ± 5 vs therapeutic: 13 ± 5), percent delta sleep (diagnostic: 8 ± 11 vs therapeutic: 11 ± 8) or arousal index (diagnostic: 32 ± 15.1/h vs therapeutic: 25 ± 12/h). Of note, all patients were either on their first night of using the nasal valve device or had only used it for < 3 nights prior to their NPSG with the device.

Table 2—Potential predictors of therapeutic response

				Nasal valve device study data			Diagnostic RDI data (events/hour)	
	Subject #	CPAP[&] ($cm H_2O$)	Passive Pcrit ($cm H_2O$)	Effective Expiratory Pressures[#] ($cm H_2O$)	CO_2 during effective nEPAP (mm Hg)	CO_2 awake (mm Hg)	RDI_{Supine} / $RDI_{Lateral}$	RDI_{REM} / RDI_{NREM}
Therapeutically Acceptable Responders	1	10	2.1	17 - 21	47	40	5.2	1.5
	2	12	3	12 - 16	39	--		
	3	13	-3	6 - 7	42	--	0.8	2.2
	4	9	--	4 - 12	38	38	0.8	0.7
	5	5	-2	7 - 10	50	46	5.5	0.2
	6	4	--	2 - 9	43	38	2.0	2.7
	7	8	--	11 - 13	45	41	1.3	2.1
	8	8	-2	15 - 22	32	38	1.8	1.6
	9	5	-2	0 - 5	46	46	6.7	1.3
	10	7	1	1 - 5	46	46	0.9	0.1
	Mean (SD)	**8.1 (± 3)**	**-0.4 (± 2.4)**		**43.7 (± 3.5)**	**41.6 (± 3.8)**	**2.8 (± 2.3)**	**1.6 (± 1.1)**
Partial Responders	11	11		9 - 16	38	35	5.1	1.3
	12	7	-2	5 - 12	44	--		0.8
	13	11	1.1	5 - 23	48	46	1.2	2.2
	14	12	2.5	11 - 14	52	48	1.1	0.5
	Mean (SD)	**10.3 (± 2.2)**	**0.5 (± 2.3)**		**45.2 (± 6.6)**	**43.0 (± 7)**	**2.5 (± 2.3)**	**1.2 (± 0.7)**
Non Responders	15	7	--	*	--	--	1.2	0.4
	16	9	--	*	44	42	1.4	0.8
	17	13	5	*	--	--	1.0	0.8
	18	11	-3.7	4 - 11	51	--	1.4	0.9
	19	5	0	*	42	44	0.9	3.2
	Mean (SD)	**9.0 (± 3.2)**	**0.4 (± 4.4)**		**45.8 (± 3.9)**	**43 (± 1.4)**	**1.2 (± 0.2)**	**1.2 (± 1.1)**

*No effective pressure generated. [&]Therapeutic CPAP value obtain on prior full night CPAP titration. [#]Range of effective end expiratory pressures measured intranasally

Predictors of Therapeutic Response to the Nasal Valve Device

Examination of potential predictors of therapeutic response showed that the group with a therapeutically acceptable response and the group with no response did not differ with respect to age, BMI, baseline SDB severity based on RDI, passive Pcrit, or prescribed CPAP level. **Table 2** summarizes data grouped by class of therapeutic response to the nasal valve device and shows that therapeutic response could also not be predicted by intranasal pressure required to eliminate SDB, CO_2 levels (awake or asleep with the valves in place), or ratio of REM to NREM RDI at baseline. However, there was a trend for the ratio of supine to lateral RDI at baseline to be higher in the group with therapeutically acceptable response compared to non-responders (2.8 ± 2.3 vs 1.2 ± 0.2), though this did not reach statistical significance. The lateral RDI at baseline (25.6 ± 19.4/h vs 59.8 ± 43.9/h, P = NS) and the ratio of apneas to hypopneas in the lateral position at baseline (0.25 vs 1.3, P = NS) also tended to be lower in the responders, again suggesting that positional variability of RDI may be predictive of the response to nEPAP (**Figure 2**).

As expected, with the device in place there was a change in the pattern of flow during expiration: (1) there was elimination of the pause at end-expiration that is usually seen during normal spontaneous breathing; (2) there was a prolongation of the expiratory phase when compared to breathing during sleep without the device in place.

Relationship of awake lung volumes to therapeutic response of the nasal valve device

Figure 3 shows awake lung volumes (FRC) obtained without the device; data shown are the FRC in the sitting, supine, and lateral positions. In **Figure 3**, subjects are grouped by response to the nasal valve device (therapeutic, partial, and no response). Sitting FRC values ranged from 46% to 107% predicted but did not differ between groups. FRC dropped by 18%-23% from sitting to supine and increased by 12%-16% from supine to lateral position, but there were no differences between the groups.

End-Expiratory Pressure and Therapeutic Response

Fifteen of the 19 subjects who tolerated the nasal valve device had periods ≥ 5 min during which SDB was abolished and

Figure 2—When comparing the group with therapeutically acceptable response to the non-responders, the lateral RDI at baseline tended to be lower (6 ± 19.4/h vs 59.8 ± 43.9/h, p = NS), while the ratio of supine to lateral RDI at baseline tended to be higher (2.8 ± 2.3 vs 1.2 ± 0.2), suggesting that positional variability of RDI may be predictive of the response to NEPAP

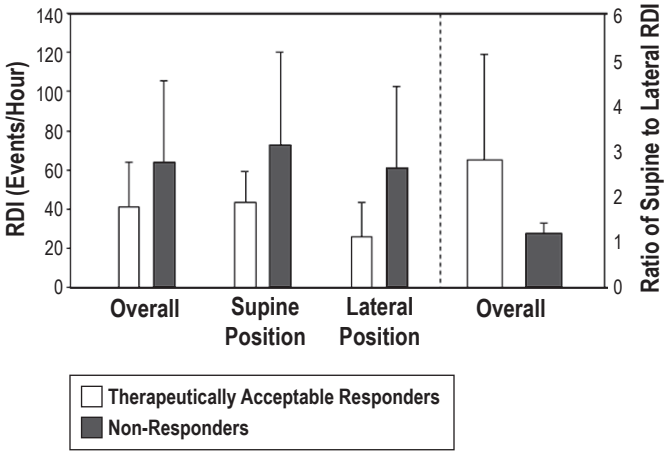
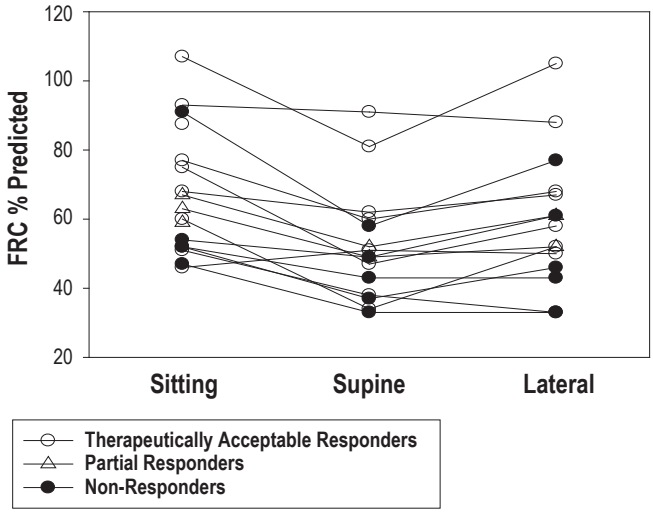


Figure 3—Awake lung volumes (FRC) obtained without nEPAP; data shown are the FRC in sitting supine and lateral positions



In this figure subjects are grouped by response to the nasal valve device (therapeutic, partial, and no response).

Table 3—RDI during periods above and below the LEP during supine N2 sleep in therapeutically acceptable and partial responders

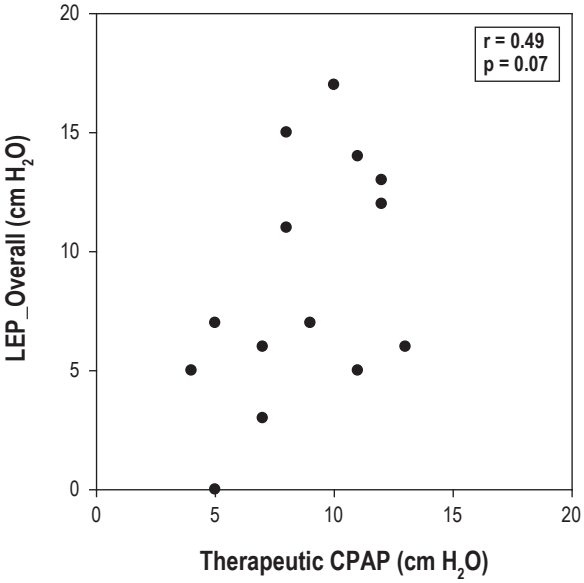
	Subject #	TST (min)	LEP_N2* (cm H_2O)	%TST above LEP	RDI above LEP (events/h)	RDI below LEP (events/h)
Therapeutically Acceptable Responders	1	117.0	17	70	0	12
	2	133.5	12	78	1.1	16.5
	3	153.0	6	78	0.5	6.8
	4	166.5	7	86	1.2	20
	5	40.0	7	76	0	0
	6	96.0	5	76	1.6	13
	7	49.5	11	86	8.6	0
	8	115.0	15	52	3.2	46.6
	9	194.5	0	100	5.6	–
	10	58.0	3	25	8.3	37.3
	Mean ± SD	**112.3 ± 52**	**8.3 ± 5.4**	**72.7 ± 21**	**3.0 ± 3.3**	**16.9 ± 16**
Partial Responders	11	51.5	14	57	0	76
	12	44.5	6	54	0	12
	13	185.5	5	42	5.4	29
	14	85.5	13	22	14	63
	Mean ± SD	**91.8 ± 65**	**9.5 ± 4.7**	**43.8 ± 16**	**4.9 ± 6.6**	**45.0 ± 30**

*LEP_N2 = the lowest pressure during supine N2 sleep that was effective at eliminating SDB for at least 5 min

during which there was consolidated sleep, allowing us to evaluate the relationship of end-expiratory pressure and therapeutic response. Within each patient, end-expiratory pressure varied widely (as much as from 5-23 cm H_2O) across the night, particularly in different positions and sleep stages. However, as the pressure at each moment was set by the patient/valve interaction and not titratable, it was not possible to test whether there was a single consistent minimal pressure needed for therapy.

Table 3 shows the data during N2 supine sleep only. During those times when the pressure achieved was above LEP_N2 (the lowest pressure shown to be *at least transiently* effective), RDI fell to near zero; during those times when pressure achieved was below LEP_N2, the RDI remained elevated. This suggests, but does not prove, that this pressure would have been effective throughout all supine N2 sleep had it been constrained. Furthermore, the patients with therapeutically acceptable response spent a greater proportion of sleep above LEP_N2 compared to the partial responders (72.7% ± 21% vs 43.8% ± 16%, respectively). One subject demonstrated an LEP_N2 of zero during some periods of the night despite obvi-

Figure 4—Lowest effective expiratory pressure (LEP) which was sufficient in ameliorating SDB throughout the entire night against therapeutic CPAP



Each point represents data from one subject.

ous SDB during other portions of the night when no intranasal pressure was generated during N2 sleep in the supine position. We suspect that this is similar to what is seen during diagnostic studies in patients with OSAHS where there are periods seen without SDB.

Based on the above analysis suggesting that within each patient a lowest effective pressure existed for each condition (e.g., position and sleep state), we obtained the one value (LEP_overall) that would have been effective over all positions and sleep states in that patient. Since this represents an algorithm similar to that used in titration of CPAP, we examined the relationship for each patient of the LEP_overall and the separately titrated clinically prescribed CPAP. **Figure 4** demonstrates that there was a trend towards higher CPAP in patients with higher LEP_overall, but this did not reach statistical significance. ($r = 0.49$, $p = 0.07$).

Failure to Generate/Maintain Therapeutic Pressure

Periods during which there was therapeutic failure of the nasal valve device (recurrence of SDB) were closely related to (i) the inability to build up end-expiratory pressure as breathing shifted from mouth to nose (at sleep onset), or (ii) loss of previously established therapeutic pressure, which generally related to onset of a mouth leak and occurred predominantly after transient arousals. Examples of these patterns are shown in **Figures 5** and **6**.

Of the 19 patients who tolerated the nasal valve device, 4 had no periods where SDB was abolished (therapeutic non-responders). In 1 of these 4 patients, the intranasal pressure remained near 0 cm H_2O during the entire study, presumably due to persistent mouth breathing. In the other 3 patients, the maximal nasal pressures achieved were 4, 7, and 13 cm H_2O, but did not result in reduction of SDB.

Figure 5—Two-min periods during sleep with the nasal valve device in one patient

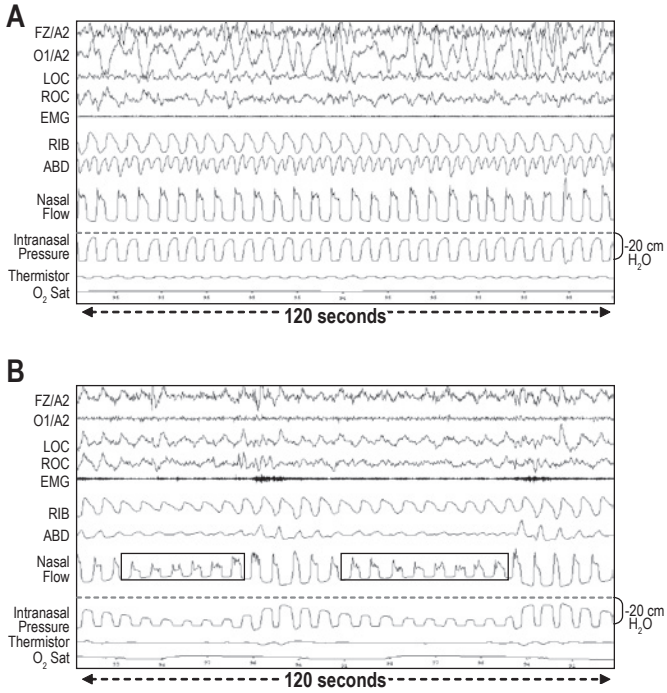
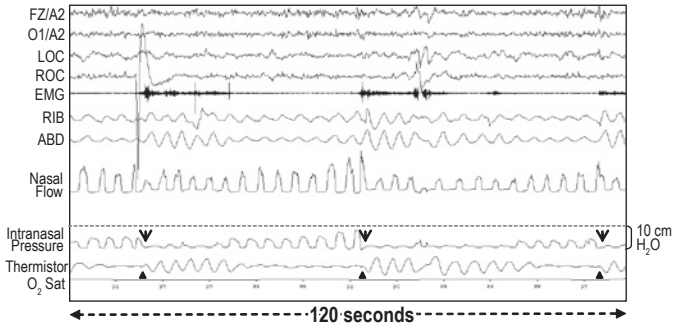


Figure 5A shows maintenance of 17 cm H_2O of end-expiratory pressure without evidence of sleep disordered breathing. **Figure 5B** shows evidence of sleep disordered breathing events during a period of lower end expiratory pressures.

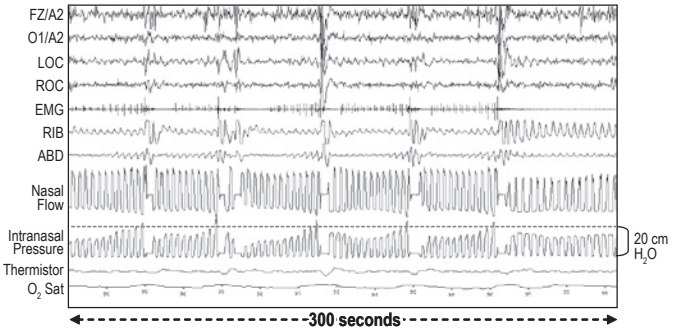
Figure 6—Repeat episodes of mouth breathing (arrowhead▲) resulting in immediate loss of intranasal pressure (arrow↓)



Mouth closure results in reestablishment of therapeutic intranasal pressures.

In a fifth patient with overall non-therapeutic response to the nasal valve device, we noted only transient benefit, despite what appeared to be an "effective" pressure of 8 cm H_2O. In this patient, pressure rose intermittently to a much higher value than the apparently effective pressure of 8 cm H_2O (up to 20 cm H_2O), and many arousals occurred that were not typical of obstructive respiratory events (see **Figure 7**). It is possible that these events may have been due to high intranasal pressures causing arousal; and this is supported by

Figure 7—Period of regular arousals which appear to be related to rapid increases in intranasal pressure (up to 22 cm H_2O) without evidence of sleep disordered breathing



Patient with therapeutic nEPAP pressure of 8 cm H_2O elsewhere during the study.

the observation that the expiratory pressure was highest just prior to the arousal.

DISCUSSION

This study shows that use of the nasal valve device produced improvement in SDB in 75% of patients with OSAHS across wide range of SDB severity, with 50% of patients reaching a clinically significant reduction in RDI. While this confirms previous small studies showing that in some patients the device is effective, we could not demonstrate associations between therapeutic success/failure of the nasal valve device and demographics, baseline severity of SDB, pattern of SDB related to sleep stage (e.g., REM dependence), therapeutic CPAP level, passive Pcrit, or awake lung volumes. Thus these appear NOT to be the predictors that will help select patients for therapy with this device. Our data do, however, suggest that patients with position-dependent SDB (supine RDI > lateral RDI) were more likely to have an acceptable therapeutic response to the nasal valve device, although due to the small sample size these results did not reach statistical significance. The patients who had good response to the nasal valve device also tended to have the lowest lateral RDIs and the lowest ratios of apnea to hypopnea in the lateral position. From our data, we cannot distinguish whether the key finding was "milder" upper airway collapsibility (lower apnea/hypopnea ratio, but not lower RDI or a directly measured passive Pcrit) or a more modifiable physiology (positional RDI). Confirmation of these associations in a larger group of subjects would be necessary before they can be used in selecting patients for this nasal valve device therapy.

Successful elimination of SDB was closely associated with sustained generation of an elevated end-expiratory pressure, but the magnitude of the lowest effective therapeutic pressure varied widely across subjects and appeared to depend on position and sleep state within subjects. When pressure achieved fell below "effective" levels, SDB recurred. Some of these periods of inadequate pressure were transient, as after an arousal; other drops in pressure and loss of therapeutic efficacy were more prolonged, including during REM sleep. This establishes that pressure is the root cause of effectiveness of the device, although *inspiratory* pressure is not affected. The reduced effectiveness during REM in some patients supports this observation. While responders and partial responders had improvements in RDI even during REM (**Table 1**), REM RDI on therapy was still substantially higher than overall RDI. This is likely because within each subject intranasal pressures generated during REM sleep were lower and more variable than pressures generated during other stages of sleep.

The close association between elevated end-expiratory pressure and improvement of SDB is consistent with at least two different mechanisms of action of the device: (1) dilatation of the upper airway by the pressure generated during expiration with carryover of this dilatation into inspiration; and (2) induction of lung hyperinflation by the elevated end-expiratory pressure resulting in reduced upper airway collapsibility due to the increased tracheal traction.

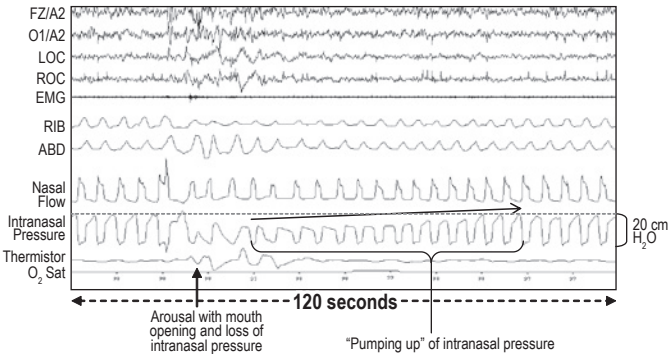
Our data do not allow us to conclusively rule out the role of an increase in neural drive either directly related to a load compensation reflex or to inducing significant hypoventilation by the expiratory resistance. Published evidence does exist demonstrating that respiratory muscle activity in normal awake subjects increases during expiratory loading and may carry over to inspiration and have parallel effects on upper airway muscle tone,[12] though it is unclear if this occurs during sleep. However, in the present study we did not measure muscle activity and cannot rule out this as a potential mechanism of action.

It is generally accepted that ventilatory response to CO_2 due to resistive loads (inspiratory and expiratory) are reduced.[12] The PCO_2 levels seen in our data during use of nasal valve device were mildly elevated in both the therapeutically acceptable responders and non-responders (43.7 ± 3.5 cm H_2O and 45.8 ± 3.9 cm H_2O, respectively), and there was no statistical difference between the two groups. These values, however, are consistent with those reported in normal sleep. Since we do not have baseline levels of CO_2 in the diagnostic studies, we cannot rule out development of mild hypercapnia as a mechanism for stimulating an increase in neural drive. We also could not examine whether PCO_2 changed between effective and ineffective periods of nasal valve device therapy within a single subject, as a stable end-tidal PCO_2 cannot reliably be determined during the unstable ventilatory pattern that defines SDB.

Thus, although we cannot completely rule out increased PCO_2 as contributing to increased upper airway tone, we suspect that the most important mechanism of the effectiveness of nEPAP was related to pressure causing either a local effect in dilating the upper airway or causing an increase in lung volume. A role for increased lung volume (reducing upper airway collapsibility via tracheal traction) is most strongly suggested by the "pumping" up of end-expiratory pressure over multiple breaths (**Figure 8**). Supporting this, some subjects reported that use of the device was associated with a feeling of increased volume of the chest during nasal breathing.

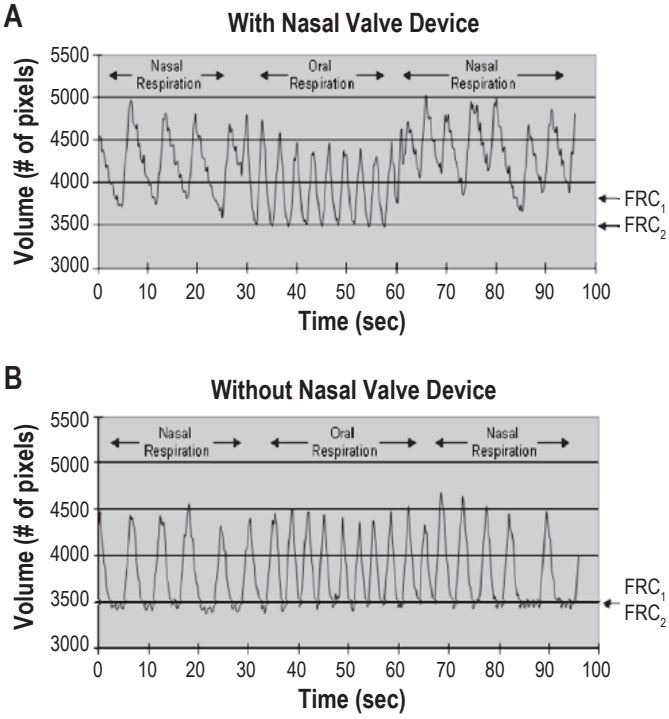
In order to directly confirm an effect of nEPAP on lung volume, we performed additional experiments in 3 normal volunteers while awake: MRI scans were acquired with and without the nasal valve device, using a gradient echo sequence that was developed for real-time imaging of the lung at a frequency of 10 images per second. **Figure 9** shows a time series of lung

Figure 8—Arousal resulting in mouth opening and loss of therapeutically acceptable intranasal pressure (20 cm H_2O)



Therapeutic pressure is reestablished after gradual "pumping up" of intranasal pressure.

Figure 9—Time series of lung volumes obtained in one subject from MRIs using a gradient echo sequence that was developed for real-time imaging of the lung at a frequency of 10 images per second



Subjects breathed quietly with normal tidal breaths through the nose and through mouth with (A) and without (B) the nasal valve device in place. **Figure 9A** shows breathing with the device in place (nasal respiration with device vs oral respiration bypassing device). **Figure 9B** shows period of breathing without the device (nasal vs. oral respiration).

volumes obtained from the MRI in one subject while breathing quietly with normal tidal breaths through the nose and then through the mouth with and without the valves in place. Custom software was used to calculate lung volume shown in one subject in **Figure 9**, with **Figure 9A** showing breathing with the valves in place (nasal breathing with nEPAP), and **Figure 9B** showing a control period of breathing without the nasal valve device (mouth breathing bypassing nEPAP). The change from mouth to nose breathing (engaging the device) resulted in an estimated 500 cc increase in lung volume, whereas in the control period without the device, changing from mouth to nose had no effect on end expiratory lung volume. Similar data was obtained in the other 2 normal volunteers. A change of 500 cc in the FRC is consistent with previous data showing a similar increase as a result of either 5 cm H_2O of CPAP or 5 cm H_2O external negative pressure applied to the chest.[7] In the same study, Owens et al.[7] also showed that an increase of 500 cc in the FRC was associated with directly measured improvement of upper airway collapsibility during sleep manifested by a decrease in Pcrit of 3.4 cm H_2O.

An important limitation of this additional data collection was that we did not directly assess lung volumes *during sleep* (the MRI study was in a convenience sample of awake subjects different from the subjects described in our primary study). Our results suggest that these measurements need to be made in future studies to directly confirm the relationship between effects of the nasal valve device, lung volume, and therapeutic effectiveness. Similarly, it may be desirable to evaluate the effect of the nasal valve device on the upper airway caliber while constraining lung volume to prevent hyperinflation. However, this experiment poses many technical problems and it is not clear that patients will tolerate the necessary chest wall restriction while wearing an expiratory resistor.

A prominent finding in the present study was the close relationship between the presence of an elevated end-expiratory pressure in any given patient and the inspiratory therapeutic effect. However, due to the present primarily resistive design of the nasal valve device, the pressure achieved could not be titrated within a patient study. Throughout our data, the pressure achieved varied widely and may have been influenced by changes in tidal volume, flow rate, respiratory rate, and expiratory time, and possibly also by changes in expiratory muscle activation or in chest wall compliance (as between NREM vs REM). Because of this variation in the pressure achieved within a study, it was difficult to assess which of two mechanisms predominated when there was intermittent failure of the nEPAP. Thus we cannot establish whether transient inability to generate pressure or changes in the patient's upper airway physiology (as due to position, sleep state, etc.) may have been the cause of a variable therapeutic response to the nasal valve device. The use of a threshold valve in future studies may overcome this methodological limitation.

This pilot study was not able to establish predictors of success or a single definitive mechanism of action; but does help define a restricted list of candidates for further investigation. We did not design this to be a conclusive clinical trial of efficacy, as this is ongoing elsewhere. Our study shows that the nasal valve device can alter SDB across the full spectrum of SDB severity, making nEPAP treatment, as with this device, a potentially important therapeutic option in a subset of patients. While we did not find any consistent demographic or PSG-related predictor to identify therapeutic responders to nasal valve device therapy, our data strongly suggest that demographics,

baseline severity of SDB, pattern of SDB related to sleep stage, therapeutic CPAP level, passive Pcrit, and awake lung volumes are not predictive. We did show that subjects with positional or milder SDB in the lateral position may be more likely to respond, but this observation needs to be confirmed with a larger study. Therapeutic efficacy of the device was associated with the ability to *generate* and *maintain* elevated end-expiratory pressures. Mouth leak and arousal were the primary reasons for inability to sustain a therapeutic pressure in the 50% of subjects with incomplete therapeutic efficacy. Although we believe tracheal traction (via increased lung volume) was the primary mechanism of action, we could not rule out the possibility of a carryover effect of residual end expiratory pressure into inspiration or increased CO_2 as contributing mechanisms.

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DISCLOSURE STATEMENT

This study was sponsored by Ventus Medical, the manufacturer of Provent. Dr. Ayappa has received research support from Fisher & Paykel Healthcare, and Ventus Medical and holds multiple US and foreign patents covering techniques and analysis algorithms for the diagnosis of OSAHS and techniques for administering CPAP. Several of these have been licensed to Fisher & Paykel Healthcare and Advanced Brain monitoring. Dr. Rapoport has received research support from Fisher & Paykel Healthcare, and Ventus Medical and holds multiple US and foreign patents covering techniques and analysis algorithms for the diagnosis of OSAHS and techniques for administering CPAP. Several of these have been licensed to Biologics, Fisher & Paykel Healthcare, Advanced Brain monitoring, and Tyco. The other authors have indicated no other financial conflicts of interest.