Obstructive Sleep Apnea Treated by Independently Adjusted Inspiratory and Expiratory Positive Airway Pressures via Nasal Mask*

Physiologic and Clinical Implications

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Treatment of obstructive sleep apnea with nasal continuous positive airway pressure mandates simultaneous increases of both inspiratory and expiratory positive airway pressures to eliminate apneas as well as nonapneic oxyhemoglobin desaturation events. We hypothesized that the forces acting to collapse the upper airway during inspiration and expiration are of different magnitudes and that obstructive sleep-disordered breathing events (including apneas, hypopneas and nonapneic desaturation events) could be eliminated at lower levels of EPAP than IPAP. To test these hypotheses, a device was built that allows the independent adjustment of EPAP and IPAP (nasal BiPAP). Our data support the hypotheses that expiratory phase events are important in the pathogenesis of OSA and that there are differences in the magnitudes of the forces destabilizing the upper airway during inspiration and expiration. Finally, applying these concepts, we have shown that by using a device that permits independent adjustment of EPAP and IPAP, obstructive sleep-disordered breathing can be eliminated at lower levels of expiratory airway pressure compared with conventional nasal CPAP therapy. This may reduce the adverse effects associated with nasal CPAP therapy and improve long-term therapeutic compliance.

(Chest 1990; 98:317-24)

OSA = obstructive sleep apnea; CPAP = continuous positive airway pressure; IPAP = inspiratory positive airway pressure; EPAP = expiratory positive airway pressure; PSG = polysomnography; AI = apnea index; DEF = desaturation event frequency; OA = occlusive apnea; CA = central apnea; MA = mixed apnea; OH = obstructive hypopneas; CH = central hypopneas; HI = hypopnea index

Since its initial description in 1981, nasal CPAP has been the most effective nonsurgical method available for reversing upper airway occlusion during sleep in patients with the OSA.[1-6] It has been postulated that nasal CPAP acts to alleviate occlusive apnea either by splinting the upper airway open[1,7] or by increasing functional residual capacity, which in turn reflexly dilates the pharynx.[8-10] Uncertainty regarding the mechanism of action of nasal CPAP is also reflected by questions regarding the pathophysiologic changes which lead to upper airway occlusion during sleep in OSA patients. If airway closure occurs in response to subatmospheric intrapharyngeal pressure during inspiration,[11-15] then the IPAP component of CPAP is the critical element and the EPAP is of secondary importance. On the other hand, if the physiologic benefit of nasal CPAP on upper airway stability is mediated via augmentation of FRC, then the EPAP component of CPAP may be the critical factor. Another mechanism by which EPAP may act is suggested by recent work from our laboratory indicating that the airway narrows, or totally occludes, during the expiratory phase of the breaths preceding occlusive apnea.[16,17] Such narrowing of the upper airway at end-expiration may set the stage for total occlusion with the generation of subatmospheric intrapharyngeal pressure during the ensuing inspiratory effort. Conceivably, EPAP applied in the course of nasal CPAP administration prevents airway narrowing during expiration, thereby reducing the predisposition toward total occlusion with inspiration. In related work, Mahadevia et al[18] observed that the application of EPAP alone, without IPAP, reduced the frequency of apneas in patients with OSA. Thus, while physiologic studies suggest that differences exist between inspiration and expiration with respect to the magnitude of the forces contributing to airway collapse during sleep in OSA patients, it is likely that both inspiratory and expiratory positive pressures are important in preventing apnea.

Based on these considerations, we hypothesized that specific, not necessarily identical, levels of positive airway pressure must be present during the expiratory and inspiratory phases of the breathing cycle for successful relief of obstructive sleep-disor-

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This study was supported in part by a grant from Respironics, Inc, Merit Review Funding, the United Parkinson's Foundation, the Competitive Medical Research Fund of Presbyterian-University Hospital, and NHLBI training grant 2T32HL07563-06A1.
Manuscript received December 18; revision accepted February 12.
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dered breathing (including occlusive apneas, partial obstructions or obstructive hypopneas and related episodes of oxyhemoglobin desaturation). We further speculated that less pressure would be required during expiration to maintain adequate upper airway patency than during inspiration when, in addition to the inherent instability of the upper airway, the collapsing influence of any subatmospheric intraluminal pressure must be overcome. If these hypotheses are true, it would have important clinical, as well as physiologic, implications. As currently used in the treatment of obstructive sleep-disordered breathing, nasal CPAP is progressively increased as needed to eliminate apneas, obstructive hypopneas, and episodes of oxyhemoglobin desaturation. If the EPAP and IPAP components of therapy could be independently varied to prevent complete upper airway obstruction and the oxyhemoglobin desaturation events associated with persistent partial obstructions, successful treatment might be accomplished at lower pressure than if conventional nasal CPAP were employed. Such a decrease in pressure may reduce the objectionable sequelae related to mask pressure during nasal CPAP therapy.[19,20] To test our hypotheses, a device was constructed to allow the separate adjustment of EPAP and IPAP with the delivery of air, with or without oxygen enrichment, through a nasal mask.

Methods

Fifteen OSA patients and one patient with the sleep hypopnea syndrome[21] were studied during a full night diagnostic PSG, a full night PSG with the application of nasal CPAP, and a full night PSG during which a ventilatory assist device was utilized (BiPAP). Three OSA patients are not included in the data analyses either because the optimal settings of nasal CPAP and/or nasal BiPAP were attained too late during the night to allow a minimum of approximately one hour of sleep on these settings or because of technical difficulties.

BiPAP permits the operator to independently vary the magnitude of expiratory and inspiratory positive pressure, delivered through a nasal mask, with the exception that the level of EPAP cannot exceed the level of IPAP. The onset of IPAP is triggered by the generation of less than 30 ml/s of inspiratory flow by the patient who subsequently determines inspiratory time and flow. The EPAP mode is established when the inspiratory flow falls below a threshold level. By employing this design, BiPAP can be helpful in determining the timing of upper airway occlusion. An apnea which begins with upper airway occlusion during the expiratory phase will result in the absence of patient-generated inspiratory airflow during the ensuing inspiratory effort. This is recognized by failure to trigger the IPAP mode. In contrast, upper airway patency at end-expiration allows the patient to generate sufficient airflow with the onset of inspiration to trigger IPAP. In addition, a small negatively directed deflection in mask pressure is observed at the onset of inspiration. The onset of an apnea with the premature cessation of inspiratory airflow to the patient during the delivery of IPAP indicates inspiratory phase upper airway occlusion. Theoretically this may be seen if the level of IPAP is inadequate.

During all PSGs the EEG, EOG, and submental EMG were recorded using surface electrodes in the standard fashion.[22] Oxyhemoglobin saturation was recorded by pulse oximetry, and the ECG was recorded using a modified chest lead during all PSGs. During diagnostic PSGs, airflow was quantified by a face mask-pneumotachograph system in seven patients and was qualitatively recorded by thermocouples and capnography at the nose and mouth in six patients. Ventilatory effort was quantified by an esophageal balloon to reflect pleural pressure swings in six patients and was qualitatively recorded by respiratory inductance plethysmography in seven patients.[8] During PSGs where either nasal CPAP or nasal BiPAP was applied, mask pressure was monitored by a differential pressure transducer, and ventilatory effort was recorded qualitatively by respiratory inductance plethysmography. During the application of nasal CPAP, airflow was qualitatively inferred by monitoring fluctuations in mask pressure as well as expired carbon dioxide tension in the mask. During the application of nasal BiPAP, airflow was recorded semiquantitatively from an analog signal output from the BiPAP device, as well as by fluctuations in mask pressure which reflected patient generated respiratory cycling. Airflow at the mouth was detected by a thermocouple during the application of both nasal CPAP and BiPAP.

Efforts to alternate the order of the nasal CPAP and BiPAP trials were complicated by patient scheduling difficulties, as well as by attempts to have different technicians performing the nasal CPAP and nasal BiPAP studies in order that the technician conducting the second trial would be blinded from the results of the first trial. Accordingly, different technicians conducted the nasal CPAP and BiPAP PSGs in seven of the 13 patients. Five patients had PSG with nasal BiPAP prior to PSG with nasal CPAP, and eight were tested in the reverse order.

The algorithm for adjusting the levels of nasal CPAP and nasal BiPAP was designed to eliminate apneas and nonapneic desaturation events (Fig 1). The latter were employed as a criterion for adjusting pressure levels instead of hypopneas because the absence of a patient airflow signal output from the nasal CPAP device and the variable accuracy of end-tidal CO_2 during nasal CPAP therapy made identification of these events, as such, unreliable. It is likely, however, that in this patient population, nonapneic desaturations represent obstructive hypopneas. At the initiation of the nasal CPAP trial, mask pressure was set at 5 cm H_2O and raised in 2.5 cm H_2O increments until apneas and episodes of oxyhemoglobin desaturation were abolished. During the nasal BiPAP trials, in order to determine if relief of occlusive apnea is primarily dependent on the level of inspiratory or expiratory pressure, IPAP was always increased above the level of EPAP in response to those apneas occurring when both pressures were equal. In response to apneas recurring after IPAP had been raised above EPAP, the latter was raised. In this way, a given level of EPAP was administered to prevent apnea only after an equivalent level of IPAP had failed to do so. Since we hypothe-

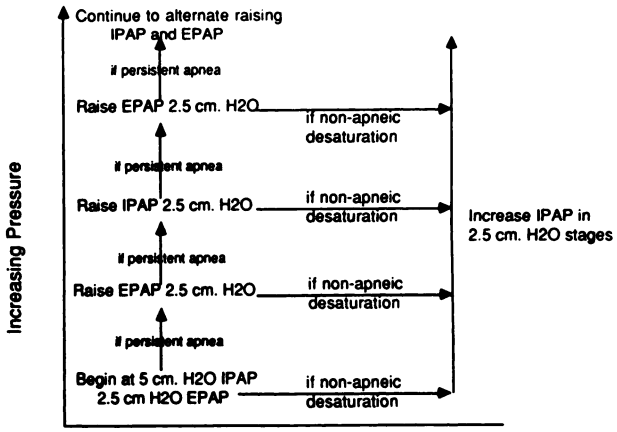

Figure 1. Algorithm for adjustment of inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) during the trial of nasal BiPAP.

sized that inspiratory instability of the upper airway is responsible for episodes of nonapneic desaturation (presumably related to obstructive hypopnea), the algorithm called for increasing IPAP only, and progressively in response to these events. Thus, IPAP was initially set at 5 cm H_2O and EPAP at 2.5 cm H_2O. With the initial apnea, EPAP was raised to 5 cm H_2O, matching the IPAP level. Persistent apneas then led to alternating increments of IPAP then EPAP in 2.5 cm H_2O increments. We observed that apneas and nonapneic desaturation occurred in mixed order throughout all PSGs. Consequently, apneas were frequently noted after the IPAP had been increased by 5 cm H_2O or more above EPAP in response to nonapneic desaturation. Under such conditions, EPAP was progressively increased in 2.5 cm H_2O increments until the apneas were abolished or until EPAP equaled IPAP. Once EPAP again equaled IPAP, the two pressures were alternately increased (IPAP first) in response to persistent apnea, as outlined previously. For desaturation in the absence of apnea, IPAP was progressively raised by 2.5 cm H_2O increments.

Data Analysis

Apnea was defined as the cessation of airflow for at least ten seconds. The various apnea patterns were defined as previously described.[8] Occlusive apnea was defined as the absence of airflow despite persistent ventilatory efforts and a central apnea was identified when there was absent airflow associated with the absence of ventilatory effort. A mixed apnea was one in which there was absent inspiratory effort for a period at least 1.5 times the interval between the two preceding inspiratory efforts, and with the resumption of effort, airflow was still not present. In our patients, virtually all apneas were occlusive in nature and there were few MAs and CAs. Thus, no distinction was made in the analyses with regard to the specific pattern of each apnea. Obstructive and central hypopneas were defined as a decrease in airflow by at least one-third in conjunction with an unchanged or increased ventilatory effort or reduced ventilatory effort. A desaturation event was defined as a reduction in SaO_2 by at least 5 percent. Apnea and hypopnea indices were defined as the average number of events per hour of sleep, and the DEF represents the average number of desaturation events per hour of sleep. The apnea + hypopnea index (A + H/I) reflects the average number of apneas plus hypopneas per hour of sleep. Because obstructive hypopneas, as defined, could not be reliably identified during the application of nasal CPAP, comparison of the HI and A + H/I during nasal CPAP and nasal BiPAP was not possible. In light of this, comparison of the DEFs on the two modalities was employed as a reflection of the frequency of all sleep-disordered breathing events. Although the accuracy of oximetry is questionable below saturations of 60 percent, such values nonetheless probably reflect severe hypoxemia. Consequently, for the sake of comparisons between nasal CPAP and BiPAP therapy, all oximeter readings were included in the analyses. Because of possible differences with respect to the influence of sleep stage on sleep-disordered breathing events, and to account for differences in sleep architecture among the study participants, the AI, DEF, and the HI (during the diagnostic PSG) were calculated separately for non-REM and REM sleep. During the trials of nasal CPAP and BiPAP, only data collected during sleep on the final (optimal) settings are reported.

Data are reported as mean ± SD. All statistical comparisons between data collected during nasal CPAP and BiPAP, with the exception of the percentage of sleep period time, were made by Student's paired *t*-test. Since a paired *t*-test cannot be performed on proportional data, the percentage of sleep period times on nasal CPAP and BiPAP were compared utilizing a Wilcoxon signed rank test. Significance was assessed at $p<0.05$.

This study was approved by the Institutional Review Board for Biomedical Research of the University of Pittsburgh and informed consent was obtained from each patient.

Results

All 13 patients, nine men and four women, were obese (body mass index = 57.41 ± 17.2). For the group, the forced vital capacity (percent predicted) was 77.23 ± 16.4 percent, the FEV_1 (percent predicted) was 80.15 ± 18.1 percent and the FEV_1/FVC was 0.77 ± 0.09. Seven patients had a restrictive pattern on spirometry, defined as an FVC<80 percent of predicted, and three patients had an obstructive pattern ($FEV_1/FVC<0.7$). All patients were normocapnic during wakefulness ($PaCO_2 = 38 \pm 4.2$). These patients had severe obstructive sleep-disordered breathing on diagnostic PSG (Table 1).

There were 11.08 ± 12.6 days (range one to 48 days) between the trials of nasal CPAP and nasal BiPAP.

Table 1—*Sleep-Disordered Breathing Parameters On Diagnostic Polysomnography*

Patient No.	Total* AI	Non-REM AI	REM AI	Total HI	Non-REM HI	REM HI	Total DEF	Non-REM DEF	REM DEF	Nadir SaO_2(%) non-REM†	Nadir SaO_2(%) REM†
1	63.7	62.7	108	20	20.1	12	107.8	107.8	108	64	60
2	84.9	84.7	83.6	20.9	24.6	2.14	90.1	89.8	91.7	61	48
3	24.1	19.78	41.9	36.1	42.3	10.22	46.1	34.7	92.8	82	44
4	91.3	91.2	87	18.3	19.4	3	102.4	101.8	112.5	66	47
5	1	0.22	12.6	13.9	11.1	53.6	19.4	15.7	82.5	82	68
6	72.9	73.2	63.1	36	36.9	18.9	116.7	43.5	87.6	52	47
7	28.9	30.3	20.8	87.9	88.5	82	69.3	67.4	79.6	70	75
8	83	81.8	87.1	87.9	8.2	0.82	89.3	87.3	96.2	55	43
9	62.2	62.1	61.8	104	11.4	0	65.9	65.7	67.5	51	37
10	56.2	56.1	. . .	31	31	. . .	78.2	78.2	. . .	79	. . .
11	42.8	43.9	26	27.8	28.5	15.6	64.6	64.5	62	54	33
12	35.6	36	25	27.1	27.2	24	89.4	90	75	47	59
13	75.2	75	76.3	8.9	10.1	1.4	49.6	52	34.1	5	4
Mean	55.52	55.15	57.77‡	39.98	27.64	18.72‡	76.06	69.11	82.46‡	59.08	47.08‡
± SD	27.3	27.5	31.7	31.6	21.2	25	27.4	27.2	21.3	20.2	18.4

*Total is average number of events per hour of total sleep time (non-REM plus REM sleep).
†Oximeter may not be accurate at values below 60 percent.
‡n = 12.

Table 2—*Sleep-Disordered Breathing Parameters During Nasal CPAP and Nasal BiPAP Trials*

Patient No.	Nasal CPAP, cm H_2O	Nasal BiPAP EPAP, cm H_2O	Nasal BiPAP IPAP, cm H_2O	Total AI, C*	Total AI, B†	Non-REM AI, C	Non-REM AI, B	REM AI, C	REM AI, B
1	10	5	10	0	0	0	0	0	0
2‡	15	10	15	4	0	1.72	0	0	0
3	15	7.5	12.5	1.6	0.9	1.76	0.7	1.38	1.2
4	15	12.5	15	2.7	1.1	4.74	1.8	0	0
5‖	15	12.5	17.5	2.5	4.7	2.52	5	0	3.8
6	12.5	10	17.5	0	0	0	0	0	0
7	12.5	10	12.5	0	0	0	0	0	0
8	17.5	12.5	17.5	0	0	0	0	0	0
9	15	5	12.5	6.9	0	6.9	0	. . .	0
10	10	7.5	10	0.5	0.3	0.83	0	0	15.4¶
11	17.5	7.5	17.5	5.1	0	7.4	0	1.3	0
12	12.5	7.5	12.5	0	0	0	0	0	0
13§	15	7.5	17.5	0	0	0	0	0	0
Mean	14.04	8.85**	14.42	1.79	0.54	1.99	0.58	0.22	1.7
±SD	2.4	2.6	2.9	2.3	1.3	1.7	1.4	0.5	4.5

*Apnea index over total sleep time on final settings of nasal CPAP.
†Apnea index over total sleep time on final settings of nasal BiPAP.
‡2 L/min of supplemental oxygen administered during nasal CPAP.
‖1 L/min of supplemental oxygen administered during nasal CPAP.
§Patient unable to tolerate greater than 15 cm H_2O nasal CPAP, 4L/min of supplemental oxygen administered during both nasal CPAP and nasal BiPAP.
¶Represents one central apnea during very brief REM time.
**Significantly different from nasal CPAP value ($p<0.001$).

There was no therapeutic intervention initiated between the two trials, nor was there a change in medication or weight. Total sleep time during the nasal CPAP trial was 221.77 ± 95.3 minutes and during the nasal BiPAP trial it was 129.69 ± 58.8 minutes ($p=0.002$). While there was a greater total sleep time on the final, optimal settings of nasal CPAP compared with nasal BiPAP, there was no difference with respect to the time spent in non-REM and REM sleep, as percentage of the sleep period time.

The effects of optimal levels of nasal CPAP and nasal BiPAP on breathing and oxygenation during sleep are shown in Tables 2 and 3. The final level of EPAP during the nasal BiPAP trials was significantly lower than the final level of CPAP (8.85 ± 2.6 vs 14.04 ± 2.4 cm H_2O, respectively, $p<0.001$). The final level of IPAP during nasal BiPAP therapy (14.42 ± 2.9 cm H_2O), however, did not differ from the final level of nasal CPAP ($p=0.5$). At optimal settings on nasal BiPAP, ten of the 13 patients (77 percent) had a 5 cm H_2O or greater difference between the level of IPAP and EPAP and four patients (31 percent) exhibited a

Table 3—*Parameters of Oxygenation During Sleep On Nasal CPAP And Nasal BiPAP*

Patient	Total DEF, C	Total DEF, B	Non-REM DEF, C	Non-REM DEF, B	REM DEF, C	REM DEF, B	Non-REM Nadir % SaO_2, C	Non-REM Nadir % SaO_2, B	REM Nadir % SaO_2, C	REM Nadir % SaO_2, B
1	0	0	0	0	0	0	90	92	90	91
2*	3	4.8	5.1	6.3	0	0	93	90	96	92
3	0	3.4	0	2.7	0	4.6	88	89	85	85
4	0	4.4	0	3.1	0	7.1	88	82	84	85
5†	0.6	6.1	0.6	5	0	9.4	90	90	92	87
6	0	0.9	0	0.7	0	1.8	89	89	89	88
7	0.9	3.2	2.3	3	5.1	3.2	90	91	90	90
8	1.5	1.7	0.6	1.2	2.4	2.4	81	83	80	83
9	1.7	0	1.7	0	. . .	0	80	87	. . .	89
10	0.2	0.7	0	0.7	0.8	0.6	86	90	88	93
11	3.9	0	1.9	0	7.2	0	86	87	84	84
12	0.4	0.3	0.5	0	0	1.6	87	90	87	88
13‡	7.1	0.33	2.9	0	12	12.8	77	90	70	80
Mean ± SD	1.48 ± 2.1	2.22 ± 2.1	1.2 ± 1.5	1.75 ± 2.1	2.29 ± 3.9	3.62 ± 4.1	86.54 ± 4.6	88.46 ± 3	86.25 ± 6.6	87.17 ± 3.9

*2 L/min of supplemental oxygen administered during nasal CPAP.
†1 L/min of supplemental oxygen administered during nasal CPAP.
‡4 L/min of supplemental oxygen administered during both nasal CPAP and nasal BiPAP.

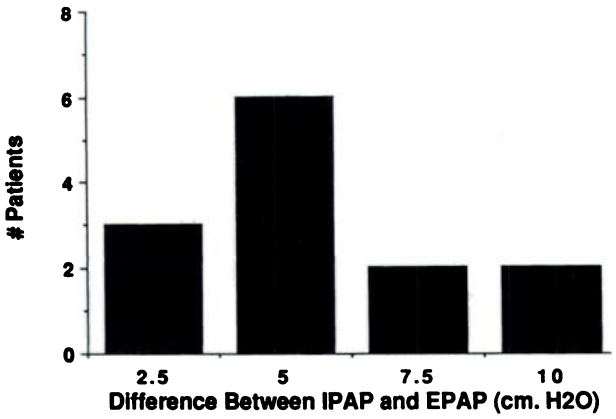

FIGURE 2. Distribution of the difference between IPAP and EPAP (cm H_2O) across the patient population on optimal settings of nasal BiPAP.

difference of at least 7.5 cm H_2O (Fig 2). Despite the lower EPAP, nasal BiPAP was as effective as nasal CPAP in reducing the total AI in our patients (0.54 ± 1.3 versus 1.79 ± 2.3 apneas per hour, nasal BiPAP and nasal CPAP, respectively) (Table 2). Even after adjusting for differences in non-REM and REM sleep time during the periods of data collection, there were no differences in AI during nasal BiPAP and CPAP administration (Table 2).

During nasal CPAP therapy, apneas were abolished when pressure was raised to a critical level, specific to each patient. During the nasal BiPAP trial, it was observed that virtually all apneas were associated with failure of the patient to trigger the IPAP, consistent with pre-existing occlusion of the upper airway at the initiation of the patient's inspiratory effort. Elimination of these apneas occurred only when EPAP reached a critical level (Fig 3). Episodes of oxyhemoglobin desaturation that persisted after eliminating apnea on nasal BiPAP were substantially reduced or eliminated when IPAP alone was increased (Fig 4).

On the night of nasal CPAP administration, the baseline awake SaO_2 was 92.08 ± 3 percent, and on the night of the nasal BiPAP trial, it was 91.85 ± 3.4 percent. Two patients received supplemental oxygen during the trials of nasal CPAP because of unacceptable degrees of oxyhemoglobin desaturation, arbitrarily defined as more than two episodes of oxyhemoglobin desaturation to levels between 80 and 85 percent, or a single reduction in saturation to below 80 percent on maximal achievable or tolerated pressures. In patient 5, apneas were abolished at 15 cm H_2O of nasal CPAP, although SaO_2 persistently fell below 85 percent. The inability to raise the CPAP further due to mask leaks made the addition of supplemental oxygen necessary. When nasal BiPAP was applied, however, sufficient flows were generated by the device to achieve 17.5 cm H_2O IPAP and 12.5 cm H_2O EPAP, with consequent relief from apnea and maintenance of oxyhemoglobin saturation without supplemental oxygen. Similarly, in patient 2, when nasal CPAP pressures could not be increased above 15 cm H_2O, the addition of 2 L/min of supplemental oxygen was required to maintain acceptable oxygenation despite the elimination of apneas. During the nasal BiPAP trial in this patient, however, satisfactory results were obtained on 15 cm H_2O IPAP and 10 cm H_2O EPAP, without the use of supplemental oxygen. Patient 13 required 4 L/min of oxygen supplementation during both nasal CPAP and nasal BiPAP therapy and even then, on nasal CPAP, an acceptable nadir of SaO_2 was not achieved (Table 3). It is noteworthy in this regard that this patient was significantly hypoxemic during wakefulness while breathing room air. In addition, while he was unable to tolerate greater than 15 cm H_2O nasal CPAP, he had no complaints on nasal BiPAP (IPAP = 17.5 cm H_2O, EPAP = 7.5 cm H_2O) which

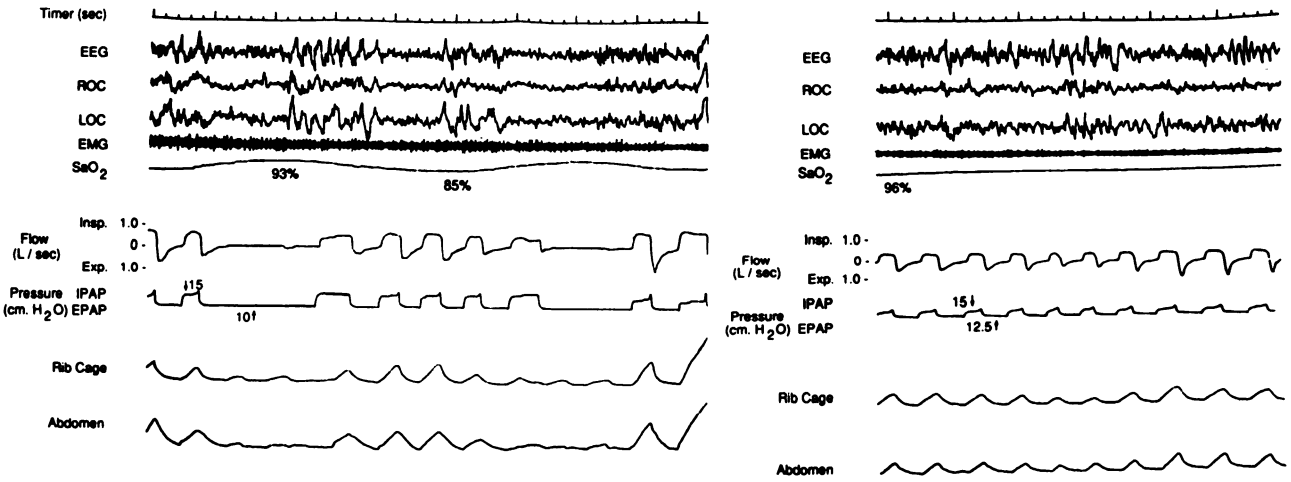

FIGURE 3. Representative tracing demonstrating elimination of apnea in the same patient by increasing EPAP during nasal BiPAP therapy. (a, *left*). Obstructive apnea during nasal BiPAP (IPAP = 15 cm H_2O, EPAP = 10 cm H_2O). (b, *right*). Elimination of obstructive apnea after an increasing EPAP to 12.5 cm H_2O.

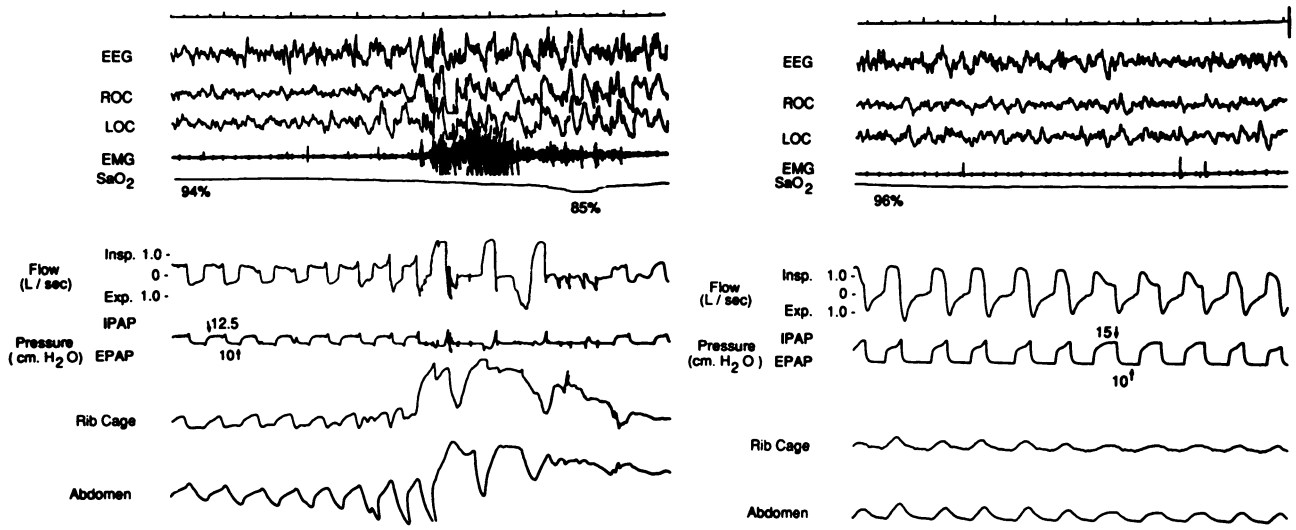

FIGURE 4. Representative tracing demonstrating relief of nonapneic oxyhemoglobin desaturation (obstructive hypopnea) (a, *left*) by increasing IPAP during nasal BiPAP therapy (b, *right*).

provided much better oxygenation relative to CPAP at 15 cm H_2O (Table 3). Thus, supplemental oxygen was required in three patients during the nasal CPAP trial, but only one of these individuals required it during nasal BiPAP.

There were no differences between nasal CPAP and BiPAP with regard to the DEF or nadir of SaO_2 over the entire period of data collection or specifically during non-REM and REM sleep (Table 3). These comparisons were probably influenced by the administration of supplemental oxygen to two patients during the nasal CPAP trial only and to one patient during both nasal CPAP and nasal BiPAP trials. The delivery of supplemental oxygen would be expected to minimize the frequency of desaturation events. Since two patients received oxygen during the nasal CPAP but not during the BiPAP trial, the comparison of DEFs and the nadirs of SaO_2 during the two trials may, if anything, be weighted to favor the former.

DISCUSSION

In this study, we have reinforced the concept that despite the absence of negative intrapharyngeal pressure, there is occlusion, or at least substantial narrowing of the upper airway during the expiratory phase preceeding apnea in OSA patients. Furthermore, we have shown that a critical level of EPAP is essential for uninterrupted upper airway patency during sleep in these patients. Finally, we have applied this concept, in conjunction with previous data, demonstrating the destabilizing influence of negative intrapharyngeal pressure during inspiration on the upper airway,[11-15] to show that effective treatment of obstructive sleep-disordered breathing may be achieved with lower levels of positive pressure during expiration than during inspiration.

Our findings have physiologic and clinical implications with respect to the pathogenesis of obstructive sleep-disordered breathing and the treatment of patients with this problem. It has been suggested that the pathophysiology of occlusive apnea is explained by collapse of upper airway structures secondary to the negative intrapharyngeal pressure generated during inspiratory effort.[11-15] If this were the sole mechanism, however, it would be expected that due to the design of the BiPAP device, IPAP would be triggered by the very low levels of inspiratory flow during that initial portion of inspiration immediately preceding upper airway collapse and that the ensuing positive pressure would preserve airway patency throughout the remainder of inspiration. What was observed, in fact, was that IPAP was not triggered by the first inspiratory effort of the apnea. This is consistent with the presence of complete or nearly complete upper airway occlusion before the onset of inspiratory effort. This extends previous work by us and others[15-17] supporting the importance of expiratory events in the pathogenesis of OSA. Furthermore, our data indicate that there is successful triggering of IPAP in conjunction with inspiratory effort with subsequent elimination of apneas only if a sufficient level of EPAP is provided. This observation is consistent with the hypothesis that EPAP maintains upper airway patency throughout expiration, until the onset of the next inspiratory effort, thereby allowing enough patient generated inspiratory flow to trigger delivery of IPAP. The IPAP then maintains airway patency throughout the remainder of inspiration.

It is possible, though unlikely, that patient-generated inspiratory airflow was initially present in conjunction with the first inspiratory effort of apnea, but was too low to be detected or to trigger IPAP. The

IPAP trigger of the BiPAP device is set to sense exceedingly low flows, and our airflow recording technique allowed detection of flows as low as 25 ml/s. Thus, even flows too low to trigger IPAP should still have been detectable. Even if such low levels of inspiratory flow were present, it would not reduce the importance of expiratory events in the pathogenesis of OSA or the significance of EPAP in its treatment. Under these conditions, it is probable that the airway was substantially narrowed during expiration,[14-17] constituting a predisposition for complete upper airway occlusion during the following inspiration.[11] The application of EPAP in this context would still contribute to alleviation of apnea by enhancing end-expiratory upper airway patency, thus allowing sufficient patient-generated inspiratory airflow to trigger IPAP.

The purpose of this study was not to investigate the specific pathophysiology underlying the loss of upper airway patency during sleep, or the mechanism by which EPAP acts to prevent occlusion remains speculative. However, our data indicating that reversal of apnea is dependent on a critical level of EPAP are consistent with the concept that positive intraluminal pressure functions as a pneumatic splint. Although our data do not exclude the possibility that EPAP mediated changes in FRC-influenced upper airway patency, several recent studies suggest that this is not the case.[7,23,24] Conceivably, EPAP influences the level of IPAP by its effect on upper airway hysteresis,[25] or by preventing the end-expiratory apposition of airway walls which may be coated with sticky secretions.[26,27] Thus, positive airway pressure during expiration and inspiration may be interactive in relieving occlusive apnea.

By virtue of the study design, we were unable to assess the minimal amount of IPAP required to prevent complete airway occlusion during inspiration. It is likely, however, that this pressure is not much, if at all, greater than the level of EPAP required to prevent complete loss of patency during expiration. The recent data of Smith et al[14] and Schwartz and co-workers[15] indicating that the airways of OSA patients may occlude with minimal, if any, negative intra-airway pressure support this hypothesis. On the other hand, we observed that nonapneic oxyhemoglobin desaturation could be prevented by raising IPAP alone, consistent with reversal of airway narrowing due to the relatively negative (or insufficiently positive) intraluminal pressures developed in conjunction with inspiratory effort. In this context, we observed that the degree to which IPAP exceeded EPAP during the nasal BiPAP trials generally reflected the additional pressure required to abolish nonapneic desaturation.

In taking advantage of the differences in forces acting to collapse the upper airway during inspiration and expiration, the application of the BiPAP device, with the capacity to independently adjust EPAP and IPAP, has relevance to the treatment of patients with obstructive sleep-disordered breathing. When employing conventional nasal CPAP to treat these individuals, it is obligatory to simultaneously raise both expiratory and inspiratory positive airway pressures in order to eliminate apnea as well as episodes of nonapneic oxyhemoglobin desaturation, attributable to obstructive hypopnea. With BiPAP, however, it may be possible to abolish the whole spectrum of obstructive sleep-disordered breathing events at lower pressures than can be used during the administration of conventional nasal CPAP. Conceivably, this could mitigate or eliminate some of the pressure-related problems associated with nasal CPAP therapy.[5,19,20,28]

Total sleep time on the final settings of nasal BiPAP was lower than on nasal CPAP. This difference can be explained by the need to separately vary inspiratory and expiratory pressures on nasal BiPAP in response to specific pertubations of breathing, with subsequent periods of observation to assess the results. Thus, it often took longer to arrive at the final, optimal settings of nasal BiPAP than the final settings of nasal CPAP, when only one pressure required manipulation. We do not believe that differences in total sleep time influenced our results, however, since the distribution of non-REM and REM sleep was the same during the application of nasal CPAP and BiPAP. In addition, among those five patients who slept for at least two hours on the optimal settings of both modalities, BiPAP achieved comparable relief of sleep-disordered breathing, at lower expiratory pressures relative to CPAP.

The observation that two patients who required supplemental oxygen during nasal CPAP administration did not require it during nasal BiPAP administration suggests that oxygenation does not suffer at the lower expiratory pressures associated with use of the latter device. While night-to-night variability cannot be excluded as an explanation for this observation, it is possible that the higher mean airway pressure during the nasal CPAP trial depressed cardiac output and contributed to the desaturation. BiPAP, with its lower airway pressure, may have had less effect on cardiac output thereby obviating the need for supplemental oxygen. Alternatively, the higher expiratory pressure during the nasal CPAP trial may have been associated with mechanical ventilatory depression and hypoventilation which was not present with the lower expiratory pressure during the nasal BiPAP trial.[19,20] Studies which include monitoring of transcutaneous carbon dioxide tension are in progress to evaluate this possibility.

In conclusion, our findings indicate that upper airway instability during expiration is an important factor in the pathogenesis of OSA. Furthermore, by using a device that permits the independent adjust-

ment of EPAP and IPAP, obstructive sleep-disordered breathing can be relieved at lower expiratory pressures than during conventional nasal CPAP therapy. This should reduce the potential for barotrauma, mechanical ventilatory depression, and reduction of cardiac output associated with high mean airway pressures, as well as other pressure-related side effects which have been associated with conventional nasal CPAP therapy. Further studies are in progress to evaluate the impact of nasal BiPAP on long-term patient compliance.

ACKNOWLEDGMENTS: The authors appreciate the assistance of Joyce Black, C.R.T.T., R.PSG.T., Lucy Seger, C.R.T.T., R.PSG.T., Karen Studnicki, C.R.T.T., and John Coates for their excellent assistance in data collection and scoring. The authors are grateful to Drs. Ronald A. Stiller, Michael Donahoe, and Frank Sciurba for their constructive critiques of the manuscript as well as Joseph Costantino Ph.D. for his assistance with the statistical analyses. The support of Glassrock Home Health Care is also appreciated.

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