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The role of the expiratory phase in obstructive sleep apnoea

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The role of the expiratory phase in obstructive sleep apnoea (OSA) is not well known. The aim of our study was to verify the contribution of expiratory narrowing to apnoea in a group of OSA patients by evaluating the effects of short-term treatment with continuous positive airway pressure (CPAP), intermittent positive pressure ventilation (IPPV) and bi-level positive airway pressure (BIPAP).

We studied a selected group of 10 OSA patients whose therapeutic pressure level of CPAP was at least 10 cm H_2O.

During CPAP therapy the mean apnoea/hypopnoea index (AHI) and oxyhaemoglobin desaturation index (ODI) decreased from 64·8 to 6·3 ($P<0·001$) and from 58·5 to 6·1 ($P<0·001$), respectively and mean nadir SAO_2 increased from 62·0 to 91·6 ($P<0·001$).

None of the patients reached optimal setting (elimination of snoring, reduction of apnoeas and non-apnoeic desaturation events at least to 15 or less per hour of sleep and maintenance of oxygen saturation approximately 90%) during IPPV and two patients did not tolerate final IPAP pressure levels. When a critical level of EPAP (BIPAP) was applied in the same night to these patients, optimal setting was reached in all subjects. During BIPAP, mean AHI decreased from 64·8 to 7·4 ($P<0·001$); ODI decreased from 58·5 to 7·6 ($P<0·001$) and nadir SAO_2 increased from 62·0 to 91·2 ($P<0·001$).

Our study confirms the essential role of a critical level of EPAP in successful ventilatory treatment in OSA, thereby indicating, in agreement with few previous studies, the critical role of end of expiratory occlusion in OSA pathogenesis.

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Introduction

Continuous positive airway pressure (CPAP) is the most effective non-surgical method available for reversing upper airway occlusion during sleep in patients with obstructive sleep apnoea (OSA) (1,2). CPAP is believed to act by splinting the upper airways open, but a role in increasing the functional residual capacity (FRC) with subsequent pharynx opening has also been postulated (3,4). In 1983, Mahadevia *et al.* (5) studied the effects of an expiratory positive pressure valve in sleep apnoea and suggested that airway closure could take place during the expiratory phase independently of the favouring collapsing effect of negative inspiratory pressure.

Studies by Sanders *et al.* (6,7) support the hypothesis that expiratory phase events are important in the pathogenesis of OSA, with airway narrowing at the end of expiration, perhaps setting the stage for total occlusion with generation of sub-atmospheric intrapharyngeal pressure during the ensuing inspiratory effort. Consequently, the effectiveness of CPAP in OSA could be due both to an expiratory effect (i.e. preventing total or near total closure at end expiration) and to an inspiratory effect (i.e. preventing the exaggeration of pharyngeal narrowing and/or closure by the inspiratory negative intraluminal pressure).

In relation to the differing roles of and contribution of expiration and inspiration to airway collapse during sleep in OSA patients, a bi-level positive airway pressure device (BIPAP Respironics Inc, Monroeville, PA, U.S.A.) has been developed that allows independent adjustment of inspiratory and expiratory pressures with the possibility of treating OSA patients with two different pressure levels.

Sanders *et al.* (8) have shown that with optimal setting of inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) by BIPAP, obstructive sleep breathing disorders can be eliminated at lower levels of expiratory air pressure. Under these conditions, the application of EPAP at a critical pressure level, preventing airway occlusion during end expiration, could allow for sufficient subsequent inspiratory efforts to trigger IPAP, with resulting disappearance of apnoeas in the BIPAP mode.

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The aim of our study was to verify the contribution of expiratory narrowing to apnoea in a group of OSA patients, with nightly evaluation of the effects of short-term treatment with CPAP, with IPAP alone (intermittent positive pressure ventilation; IPPV), or with IPAP and EPAP (BIPAP).

Materials and Methods

We studied a group of 10 OSA patients selected on the basis of a therapeutic CPAP pressure level of at least 10 cm H_2O. Patients were recruited for the study from a group of 80 OSA patients who had been referred to our Centre during a period of 1 year. The selection criteria were: presence of severe OSA (AHI >40 h^{-1}) with at least 85% of obstructive events; consensus to the ventilation treatment; therapeutic CPAP pressure level of at least 10 cm H_2O; no history or clinical evidence of primary central nervous system dysfunction, primitive cardiac disease or neuromuscular disease; no presence of right heart failure or respiratory failure; no pulmonary disease; no previous ventilatory treatment; no drug therapy; and no alcohol abuse. Prior to initiating the study patients were informed about the research protocol, and written consent was obtained. Patients were selected after a full night basal polysomnography (PSG_b) without ventilatory support. Following PSG_b the patients were given the opportunity to become familiar with ventilatory support and various nasal interfaces including masks and prongs. Subsequently patients were submitted to overnight CPAP titration (PSG_t). In the subsequent night, following CPAP administration at the previously determined therapeutic level for about 30 min of sleep to stabilize the ventilatory pattern of the subject, we reduced EPAP level to the minimum (about 2 cm H_2O) in order to administer IPAP-only treatment (IPPV). Thereafter, EPAP was increased until breathing was normal, or the previously determined CPAP level was attained.

During PSG the electroencephalogram (EEG) (two leads), electro-oculogram (EOG) (two leads), submental electromyogram (EMG), and electrocardiogram (ECG) readings were recorded continuously with surface electrodes in the standard fashion (9). Airflow was qualitatively recorded by thermocouples at the nose and mouth, and quantified by a pneumotacograph system connected to the nasal mask. Ribcage and abdominal ventilatory movements were also recorded continuously using respiratory inductance plethysmography, with oxyhaemoglobin saturation recorded by pulsoximetry (Nellcor, Puritan Bennet) and end tidal CO_2 recorded by capnography (Nellcor). Snoring was recorded by a microphone attached to the neck. Mask pressure was continuously recorded during PSG_t with CPAP, IPPV and BIPAP. All sleep data were recorded continuously on a multichannel polygraph recorder (Respisomnographe, Sefam, Nancy, France; Knightscan software Version 1.80). Sleep stage was determined by the criteria of Rechtschaffen and Kales (9).

In all patients the three ventilatory modes, CPAP, IPPV, and BIPAP, were administered using a BIPAP S/T Respironics device in the spontaneous mode (S-mode). Nasal CPAP was titrated by increasing pressure from an initial level of 2·5 cm H_2O, in increments of 2·5 cm H_2O to reach a therapeutic effect at a level sufficient to achieve the optimal setting of eliminating snoring, reducing apnoeas and non-apnoeic desaturation events to at least 15 or less per hour of sleep, and maintaining oxygen saturation at approximately 90%. IPPV was administered by progressively increasing IPAP until the therapeutic CPAP value, or the maximum level tolerated, was reached. Finally, while the same IPAP pressure level was maintained, we applied EPAP in increasing amounts until the optimal setting was obtained.

DATA ANALYSIS

In our study we considered apnoeas (cessation of airflow for at least 10 s); hypopnoeas (defined as non-apnoeic events, associated with a reduction in SaO_2 by at least 4%, which is more readily evaluated during CPAP than simple airflow decrease, and represents obstructive hypopnoeas); the apnoea/hypopnoea index, AHI (number of events per hour of sleep); the oxyhaemoglobin desaturation index, ODI (number of desaturation reduced events by at least 4% per hour of sleep); and the lowest nocturnal oxyhaemoglobin saturation, nadir. Because almost all events in our patients were obstructive (apnoic or non-apnoeic events with the presence of ventilatory effort), no distinction was made in the analysis between the specific patterns of each apnoea.

Data are given as mean (SD). Statistical comparisons were performed using the Student's paired t-test with $P<0·05$ judged to be statistically significant.

Results

The study was performed in nine men and one woman in whom OSA had been diagnosed. Anthropomorphic characteristics, pulmonary function and parameters of gas exchange are shown in Table 1. The mean age (SD) of the group was 45·4 (14·4) years, with a mean body mass index (BMI) of 36·7 (9·5) kg m^{-2}. All the patients were normoxic and normocapnic. No patients had an obstructive ventilatory defect (FEV_1/FVC <70%). All patients had predominantly obstructive sleep apnoea on PSG_b (more than 90% of events were mixed or obstructive), with a mean AHI of 64·8 (15·1) (range 43–83), a mean ODI of 58·5 (13·8) (range 40–75) and a mean nadir of 62·0% (14·0) (range 31–76). Sleep period time (SPT) was 93·4% of total sleep time (TST), stages I–II NREM sleep were 79% of SPT, stages III–IV were 2% and REM sleep was 11%.

According to protocol, therapeutic CPAP pressure was at least 10 cm H_2O [mean 11·6 (2·6) cm H_2O; range 10–18]. The effects of the three ventilatory modes on breathing and oxygenation during sleep are shown in Table 2 and Fig. 1.

During CPAP therapy, mean AHI and ODI decreased, respectively, from 64·8 to 6·3 ($P<0·001$) and from 58·5 to 6·1 ($P<0·001$), and mean nadir increased from 62·0 to 91·6 ($P<0·001$). Stages I–II NREM sleep decreased to 50% of

TABLE 1. Mean (SD) anthropomorphic characteristics, pulmonary functions and parameters of gas exchange of 10 patients

Sex (M/F)	Age (years)	BMI ($kg\ m^{-2}$)	FEV_1 (% pred.)	FVC (% pred.)	FEV_1/FVC (%)	PaO_2 (mmHg)	$PaCO_2$ (mmHg)
9/1	45·4 (14·4)	36·7 (9·5)	77·4 (13·7)	75·3 (13·0)	86·5 (6·7)	82·0 (13·2)	38·8 (2·9)

SPT and stages III–IV increased to 26%, while REM sleep increased to 16%.

During IPPV, sleep-related disordered breathing persisted in all patients, either because patients did not tolerate the highest pressure level (two patients), or because IPAP alone was unable to suppress completely apnoeic and hypopnoeic events. The mean IPAP level pressure was 12·7 (2·6) cm H_2O. In three patients we were able to increase IPAP pressure above the therapeutic CPAP level. During this ventilatory treatment, AHI decreased from 64·8 to 45·0 ($P<0·05$), ODI decreased from 58·5 to 41·3 ($P<0·05$) and nadir increased from 62·0 to 80·6 ($P<0·01$). In all patients we observed that virtually all apnoeas were associated with failure of patients to trigger IPAP, even if IPAP had increased above therapeutic pressure levels (Figs 2 and 3). When EPAP (BIPAP) was administered in these patients with unchanged IPAP pressure, apnoeas were eliminated at a critical EPAP level specific to each patient (Fig. 3). SPT decreased to 70%, stages I–II, NREM sleep decreased to 70%, stages III–IV were 2% and REM sleep was 8% of SPT.

During BIPAP optimal setting was reached in all patients, with mean IPAP value at 12·7 (2·6) cm H_2O, and mean EPAP level at 8·2 (2·4) cm H_2O. During BIPAP, AHI decreased from 64·8 to 7·4 ($P<0·001$), ODI decreased from 58·5 to 7·6 ($P<0·001$) and nadir increased from 62·0 to 91·2 ($P<0·001$).

In spite of the lower EPAP, compared to CPAP, pressure (8·2 *vs.* 11·6; $P<0·001$) BIPAP was as effective as CPAP in reducing total AHI (7·4 *vs.* 6·3; P=n.s.), ODI (7·6 *vs.* 6·1; P=n.s.) and nadir (90·9 *vs.* 91·6; P=n.s.).

During BIPAP application stages I–II NREM sleep were present during 50% of the SPT, stages III–IV during 25% and stage REM sleep during 15%.

While there was a greater SPT on the final optimal setting during CPAP application compared with BIPAP, there was no difference with respect to the time spent in the NREM and REM stages as percentages of the SPT. The sleep efficiency during IPPV was lower than during CPAP or BIPAP application and was associated with many arousals and with a less-rested patient.

Discussion

It is currently believed that obstructive apnoeas are due to collapse of the upper airway (UA), secondary to negative intraluminal pressure generated by the inspiratory muscles, during inspiration in patients with inherent instability of this upper airway (10–13).

Sanders and Moore (6) however, have found that, in patients with OSA, not only inspiratory but also expiratory airway resistance increase during sleep, thus suggesting that UA obstruction is not limited to inspiration.

More recently, some reports (8,14–17) using different methods have suggested the occurrence of end-expiratory upper airway narrowing in patients with OSA, suggesting that a critical level of expiratory positive airway pressure is essential for uninterrupted upper airway patency during sleep. This is in keeping with previous findings by Mahadevia *et al.* (5), who reported that 10 cm H_2O of expiratory positive airway pressure significantly reduced the frequency and duration of apnoeas along with the degree of nocturnal oxygen desaturation.

Our study, which is based on the different response during sleep of OSA patients to short-term application of CPAP, IPPV and BIPAP, supports these previous findings and shows the importance of expiratory events in the pathogenesis of obstructive sleep apnoea. OSA is not an 'inspiratory' problem, therefore, but an expiratory–inspiratory phenomenon. Indeed, we have shown that if a sufficiently high pressure is not applied during expiration, the patient is unable to trigger inspiratory airflow during the following inspiration even in the presence of high inspiratory pressure, as seen in the IPPV mode and in the BIPAP mode when EPAP was below the optimal level.

Considering that the trigger for IPAP in this type of device is possible with a low inspiratory flow, it is unlikely that failed triggers were due to a too-low trigger sensibility. On the contrary, it seems likely that inspiratory flow generation and the IPAP trigger are impossible to achieve due to UA end exipiratory occlusion, strongly suggesting that the airway narrows and/or occludes during expiration, prior to the appearance of the negative inspiratory intraluminal pressure.

When EPAP (BIPAP) was applied at the critical pressure level under these conditions, sufficient to maintain UA patency during expiration, the patient was able to generate an inspiratory flow to trigger IPAP. This, if adequate, overcame the collapsing influence of sub-atmospheric intraluminal pressure, thereby avoiding inspiratory occlusion and apnoea and maintaining airway patency throughout the remainder of inspiration. The situation is probably more complex due to the role of other forces, such as mucosal adhesion surface forces which have not yet been well studied. That a more complex mechanism is involved is suggested by the fact that once a critical EPAP level is achieved, as shown in Fig. 3, three to four breaths were necessary before thoraco-abdominal paradoxic breathing

TABLE 2. Nocturnal polysomnographic indexes during basal PSG and CPAP, IPPV and BIPAP ventilatory treatments

Patients	CPAP ($cm H_2O$)	IPPV ($cm H_2O$)	BIPAP IPAP ($cm H_2O$)	BIPAP EPAP ($cm H_2O$)	Basal AHI ($n h^{-1}$)	CPAP AHI ($n h^{-1}$)	IPPV AHI ($n h^{-1}$)	BIPAP AHI ($n h^{-1}$)	Basal ODI ($n h^{-1}$)	CPAP ODI ($n h^{-1}$)	IPPV ODI ($n h^{-1}$)	BIPAP ODI ($n h^{-1}$)	Basal nadir (%)	CPAP nadir (%)	IPPV nadir (%)	BIPAP nadir (%)
1	10	14	14	8	43	4	40	6	40	2	30	4	68	94	78	93
2	10	10	10	8	83	2	60	4	75	2	56	4	70	93	76	92
3	10	15	15	6	47	6	40	6	42	5	37	6	76	91	75	91
4	12	12	12	8	80	8	58	9	70	9	58	9	70	90	86	90
5	10	12	12	6	81	4	20	4	75	2	38	3	58	91	79	90
6	18	18	18	12	60	10	*	12	55	10	*	18	31	90	*	90
7	12	12	12	8	51	2	34	8	42	3	30	8	54	94	81	91
8	10	10	10	6	79	4	49	5	70	3	33	4	67	92	85	92
9	14	14	14	12	62	15	59	12	58	15	48	10	76	90	85	92
10	10	10	10	8	62	8	*	8	58	10	*	10	50	91	*	91
Mean	11·6	12·7	12·7	8·2	64·8	6·3	45·0	7·4	58·5	6·1	41·3	7·6	62·0	91·6	80·6	91·2
SD	2·6	2·6	2·6	2·4	15·1	4·1	14·1	2·9	13·8	4·6	11·3	4·5	14·0	1·6	4·3	1·5

*Patients did not tolerate the final IPAP pressure level.

AHI: apnoea/hypopnoea index; ODI: oxyhaemoglobin desaturation index; nadir: minimal nocturnal saturation.

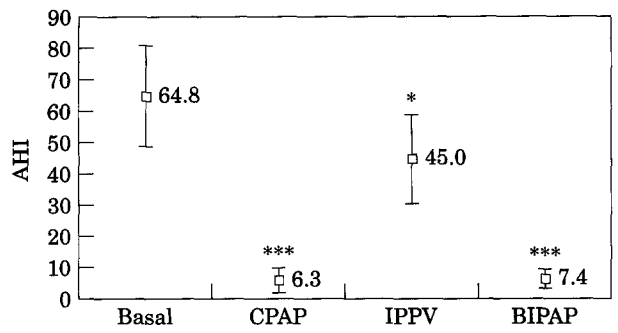

FIG. 1. Apnoea/hypopnoea index (AHI) during basal PSG (PSG_b), without ventilatory support and in the subsequent nights during treatment with CPAP, IPPV, BIPAP. The obtained values for each treatment were compared with values recorded in PSG_b: $*P<0.05$; $**P<0.01$; $***P<0.001$. Data area means; error bars show SD.

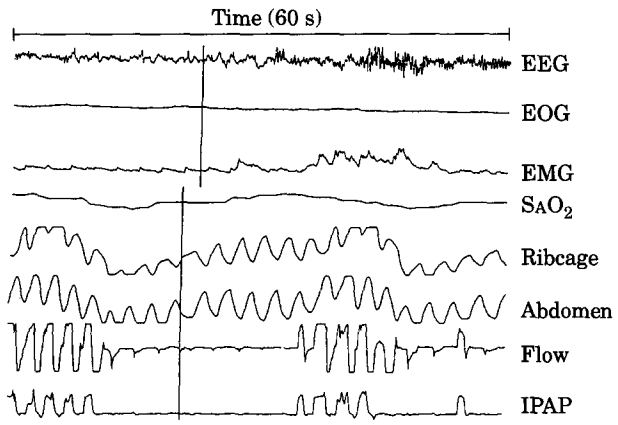

FIG. 2. Representative trace demonstrating failure of patient to trigger IPAP, with persisting apnoea during application of IPPV. IPAP = 10 cm H_2O.

disappeared totally and breathing became regular and normal.

Moreover, we have reinforced the concept that successful IPAP triggering and apnoea elimination occurred only when EPAP reached a critical level, specific to each patient. Even though the IPAP pressure level during BIPAP was pre-established according to protocol, we have confirmed the experience of others (8) that effective treatment of obstructive breathing disorders may be achieved with lower levels of positive pressure during expiration than inspiration and at a lower pressure than used in conventional CPAP.

Finally, during IPPV with IPAP alone we observed a decrease of AHI and ODI and, in particular, an increase of nadir, due to IPAP-induced reduction of non-apnoeic desaturation events (8). Consequently, it is possible to deduce from our study that, during these non-apnoeic desaturation events (attributable to obstructive hypopnoeas in patients affected by simple OSA), IPAP is triggered because of airway patency persisting at sufficient levels at the end of expiration. Montserrat (18), utilizing the forced oscillation technique, has recently reported that in most

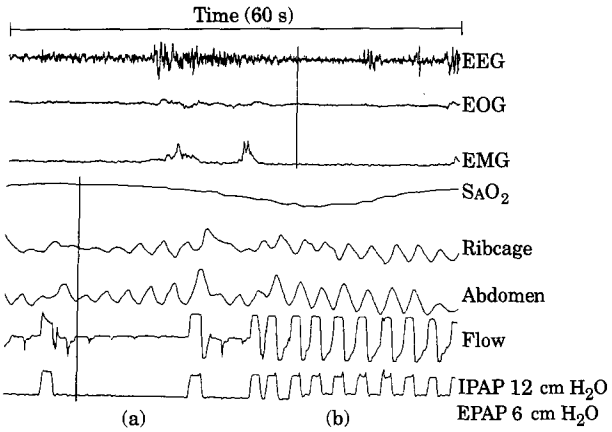

FIG. 3. In the same patient as in Fig. 2: (a) trace demonstrating failure of the patient to trigger IPAP with persistence of obstructive apnoea, by increasing IPAP (12 cm H_2O), during IPPV; (b) trace demonstrating elimination of apnoea, unchanged IPAP (12 cm H_2O) by administering a critical level of EPAP (6 cm H_2O) during application of BIPAP. Note that after the EPAP of 6 cm H_2O is reached, partial paradoxic thoracoabdominal breathing persists for four high-amplitude breaths until tidal volume decreases towards normal values and the paradox disappears.

patients the beginning of an apnoea is preceded by brief obstruction, mainly during expiration, while during hypopnoeas, obstructive periods are mainly inspiratory. The significance of these observations, however, requires further investigation.

In conclusion, these findings indicate that loss of airway patency in patients with OSA during sleep is not exclusively an inspiratory phenomenon and that end-expiratory occlusion is critical in OSA pathogenesis. Furthermore, our study confirms the essential role of a critical level of expiratory positive airway pressure in successful ventilatory treatment in patients with OSA.

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