Nocturnal ventilatory support in patients with cystic fibrosis: comparison with supplemental oxygen

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Nocturnal ventilatory support in patients with cystic fibrosis: comparison with supplemental oxygen. D. Gozal. ©ERS Journals Ltd 1997.

ABSTRACT: Progressive deterioration of lung function in cystic fibrosis (CF) patients may lead to significant hypoxaemia and hypercapnia, especially during sleep.

The effects of bilevel noninvasive positive pressure nasal mask ventilation (NIPPV) on respiration and sleep were compared to those of low-flow oxygen therapy in six CF patients (mean±SD age 22.3±4.7 yrs, with severe lung disease (forced expiratory volume in one second (FEV1) 29.4±3.4% predicted).

Compared to the control night, NIPPV and oxygen therapy significantly improved overall night-time oxygen saturation during both rapid eye movement (REM) and non-rapid eye movement (NREM) sleep stages. However, significant increases in transcutaneous CO_2 tension occurred during oxygen therapy, while NIPPV markedly improved alveolar ventilation during all sleep states. Sleep architecture and arousals remained unchanged during NIPPV and oxygen therapy treatment nights.

We conclude that noninvasive positive pressure ventilation improves sleep-related hypoxaemia and hypercapnia in severe cystic fibrosis patients without affecting sleep. The long-term compliance and benefits of noninvasive positive pressure ventilation remain unclear.

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With advancing lung disease, patients with cystic fibrosis (CF) may develop clinically significant hypoxaemia and hypercapnia during sleep, particularly during rapid-eye movement (REM) sleep [1, 2]. Domiciliary administration of supplemental oxygen improves nocturnal oxygenation in these patients, but it either does not modify or significantly aggravates concomitant alveolar hypoventilation [3, 4]. Respiratory stimulants such as theophylline may ameliorate certain aspects of gas exchange during sleep in CF but also markedly disrupt sleep architecture [5]. Thus, noninvasive positive pressure ventilation (NIPPV) has been advocated in patients with chronic obstructive pulmonary disease (COPD) in an effort to improve diurnal quality of life, provide respiratory muscle rest, and prevent or reverse the cardiovascular sequelae of intermittent or chronic hypoxaemia and hypercapnia [6].

In a recent study of seven CF patients, REGNIS *et al.* [4] demonstrated significant improvements in nocturnal oxygenation during both REM and non-REM (NREM) sleep when nasal continuous positive airway pressure (CPAP) was administered [4]. Sleep architecture was unaffected and transcutaneous CO_2 tension (Ptc,CO_2) measurements were not different during nasal CPAP and control nights. However, these investigators did not compare CPAP with supplemental oxygen.

The purpose of the present study was to compare the respiratory and sleep benefits derived from the use of NIPPV or night-time low-flow oxygen in CF patients with moderate to severe lung disease and significant gas exchange abnormalities during sleep.

Materials and methods

Subjects

Six subjects with CF, aged 13–28 yrs (mean±SD, 22.3±4.7 yrs) completed the study. Two additional patients did not tolerate NIPPV and had to be excluded from the study. Patients with CF were recruited from the Section of Paediatric Pulmonology at Tulane Hospital for Children. All patients had pulmonary symptoms, signs, and radiological changes consistent with CF, and were diagnosed by pilocarpine iontophoretic sweat chloride tests. All subjects with CF were receiving pancreatic enzymes, vitamin supplements, nebulized bronchodilators and deoxyribonuclease (DNAase) (Pulmozyme, Genentech, CA, USA) at the time of the study, and some were also receiving inhaled or intravenous antibiotics. Subjects with CF were studied when clinically stable, either as out-patients or at the end of a 2–3 week hospital stay. Informed consent was obtained from each subject and from his or her legal guardian when appropriate, and the study was approved by the Institutional Review Board.

Pulmonary function testing

All patients underwent pulmonary function testing in the pulmonary function laboratory at the Tulane University Medical Center, located at sea level (mean atmospheric pressure 101.3 kPa (762 mmHg)). All measurements for each subject were performed on the same day. The vital capacity (VC) and its subdivisions were

measured from a slow exhalation with a wedge spirometer (Collins DSIIa, Braintree, MA, USA). The best forced VC, forced expiratory volume in one second (FEV1), mean forced expiratory flow during the middle half of forced vital capacity (FEF25%–75%), and maximal expiratory flow-volume curves obtained from forced expiration into the wedge spirometer, were selected and corrected for body temperature and ambient pressure, saturated with water vapour (BTPS). Functional residual capacity was measured with a body pressure plethysmograph (SensorMedics 2800 Autobox, Yorba Linda, CA, USA) by the method of DuBois *et al.* [7]. Residual volume (RV) and total lung capacity (TLC) were calculated, and the RV/ TLC ratios determined from the actual values. Individual test results were analysed and considered abnormal if they were greater than ±2 SD from available reference values appropriate for age, height and gender [8].

Overnight polysomnography

Subjects were studied for 8 h in a quiet, darkened room with an ambient temperature of 24°C. Patients received their regular medications, and no drugs were used to induce sleep. The following parameters were measured: chest and abdominal wall movement by respiratory inductance plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, NY, USA); cardiac frequency by electrocardiograph (ECG); airflow with a thermistor (Physitemp; Clifton, NJ, USA); Ptc,CO_2 using heated (43°C), calibrated transcutaneous electrodes (Sensor-Medics Transcend Cutaneous Gas System; Sensor-Medics, Yorba Linda, CA, USA); and arterial oxygen saturation (Sa,O_2) by pulse oximetry (Nellcor N 200; Nellcor Inc., Hayward, CA, USA), with simultaneous recording of the pulse waveform. Capillary blood gas samples were drawn during wakefulness prior to and following completion of each sleep study. Ptc,CO_2 values were considered reliable only if Ptc,CO_2 and CO_2 tension ($P$$CO_2$) values were within 10% of each other. The electro-oculogram (EOG), two-channels of electroencephalogram (EEG: C3/A2 and C4/A1), and chin electromyogram (EMG) were also monitored.

Scoring of respiratory variables during sleep was performed in 60 s epochs as described previously [9–11]. Apnoea was defined as cessation of air flow for 10 s or longer even if unaccompanied by concomitant oxygen desaturation. Apnoeas of less than 10 s duration were also included if they lasted for more than one respiratory cycle and were associated with oxygen desaturation of >4%. Obstructive events were defined as above in the presence of respiratory effort as evidenced from continued thoracoabdominal motion, while in central apnoea no evidence of thoracic or abdominal motion was present. The mean Sa,O_2 (after validation by an adequate pulse waveform signal) and Ptc,CO_2 values recorded for each 60 s were retained for analysis. Nonrespiratory variables were also scored using standard criteria [12]. Total sleep time (TST) was defined as total recording time minus the sleep latency. Arousals were calculated by dividing the total number of arousals by TST.

Protocol

Each patient participated in the three designated sleep studies within a 15 day period. All patients were initially studied in room air. If clinically significant hypoxaemia and/or hypercapnia were present in this initial study, they were randomly assigned to receive NIPPV or supplemental oxygen in the second night. For the third night, the remaining treatment modality was administered.

After a mask-fitting session, patients were encouraged to wear the NIPPV nasal mask (Respironics Inc., Murraysville, PA, USA) during daytime hours for habituation purposes. To determine the oxygen flow or NIPPV to be employed during the sleep study nights, several trials were conducted during 1–2 h afternoon naps while measuring Sa,O_2 and Ptc,CO_2. During these sessions, one patient did not tolerate application of the nasal mask while the other patient refused to continue pressure titration procedures on the basis of marked breathing discomfort. For the six patients who completed the study, the mean flow of supplemental oxygen blended into the NIPPV circuit was 2.2±0.5 L·min-1, and mean airway pressures were titrated to 16.3±1.9 and 5.3±1.1 cmH2O for inspiratory (IPAP) and expiratory (EPAP) pressures, respectively. In addition, the NIPPV ventilator (BiPAP STD; Respironics Inc., Murraysville, PA, USA) was set in the assist/control mode in all patients, with a respiratory back-up frequency of 12 breaths·min-1, a IPAP:EPAP duration ratio of 1, and a FI,O_2 of 21%.

Data analysis

Results are presented as mean±SD. Data from control, oxygen therapy and NIPPV nights were compared using paired t-tests or the nonparametric multi-independent group Kruskal-Wallis H-test as appropriate. A p-value of less than 0.05 was considered significant.

Results

Demographic, anthropometric, and pulmonary function data for the six CF patients studied are shown in table 1. In general, all patients had moderate to severe lung disease with FEV1 ranging 25–35% of predicted values. All patients had Pa,O_2 below 9.0 kPa (68 mmHg) and two were slightly hypercapnic during wakefulness (Pa,CO_2 >6 kPa (45 mmHg)).

During sleep in room air (control), patients demonstrated significant oxyhaemoglobin desaturation (fig. 1) and alveolar hypoventilation (fig. 2). Oxygen desaturation and Ptc,CO_2 elevation were more likely to occur during REM epochs (table 2), and nadir Sa,O_2 (range 62–67%) and highest Ptc,CO_2 (range 8.9–9.9 kPa) were recorded during REM sleep. There were no significant obstructive apnoeic events during control or treatment nights.

Administration of supplemental oxygen was associated with significant improvements in mean oxygen saturation throughout the night (fig. 1), and this effect was present during both REM and NREM sleep (table 2). A significant increase in REM density occurred during oxygen therapy (p<0.02, Kruskal-Wallis H-test). NREM duration, sleep latency and arousal index were similar to those recorded during control night (table 2). Improved oxygenation in these patients was accompanied by

significant increases in Ptc,CO_2, which encompassed both REM and NREM sleep (table 2; fig. 2).

As mentioned in the Materials and methods section, two patients were excluded because they did not tolerate NIPPV. In the remaining six patients, no particular problems were reported regarding mask fitting or pressure titration procedures. Four of the six patients preferred the use of supplemental oxygen to NIPPV, despite morning headache being present in two patients upon awakening following oxygen therapy. As with oxygen therapy, NIPPV did not significantly modify sleep latency, total sleep time, NREM density, or arousal index

Table 1. – Individual anthropometric and pulmonary function measurements in six cystic fibrosis (CF) patients

Patient No.	Age yrs	Gender M/F	Weight kg	Height cm	BMI kg·m⁻²	FVC % pred	FEV1 % pred	FEF25%–75% % pred	TLC % pred	RV/TLC %	Pa,O_2 mmHg	Pa,CO_2 mmHg
1	13	F	34.0	134	18.9	45.6	32.2	16	112	58	63	40
2	16	M	45.0	149	20.3	42.8	34.4	14	104	61	67	47
3	17	M	48.8	156	18.4	38.9	27.6	9	98	60	54	48
4	21	F	51.0	144	24.6	42.2	29.8	7	89	57	49	43
5	23	F	36.6	148	16.7	36.5	25.3	9	123	64	53	42
6	19	M	49.2	163	18.5	37.6	26.9	7	119	67	55	44
Mean	18.2	-	49.4	149	19.6	40.6	29.4	10.3	107.5	61.2	56.8	44
SD	3.6	-	6.8	10	2.7	3.5	3.4	3.7	12.9	3.8	6.8	3

M: male; F: female; BMI: body mass index; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; FEF25%–75%: mean forced expiratory flow during the middle half of FVC; TLC: total lung capacity; RV: residual volume; % pred: percentage of normal predicted value. 1 mmHg = 0.133 kPa.
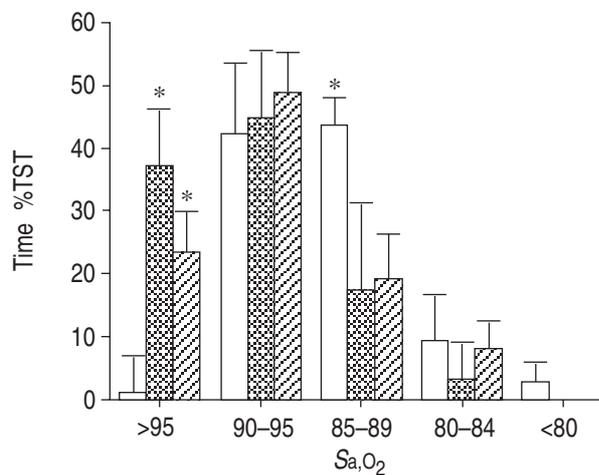

Fig. 1. – Mean (±SD) percentage of total sleep time (TST) spent at each level of arterial oxygen saturation (Sa,O_2) during control (☐), low-flow oxygen (▨), and nasal bilevel positive pressure ventilation (NIPPV; ▨). Both oxygen therapy and NIPPV resulted in significantly more sleep time being spent at oxyhaemoglobin saturations >95% while significantly less time was spent at low haemoglobin saturations, in particular <90%. *: p<0.05, *versus* control.
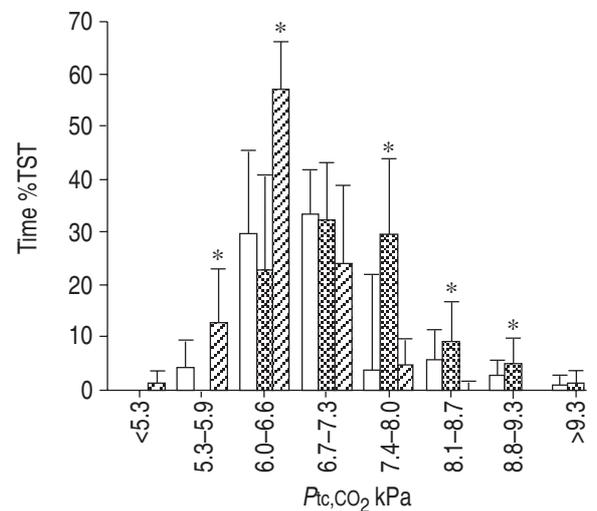

Fig. 2. – Mean (±SD) percentage of total sleep time (TST) spent at each level of transcutaneous CO_2 tension (Ptc,CO_2) during control (☐), low-flow oxygen (▨), and nasal bilevel positive pressure ventilation (NIPPV; ▨). NIPPV resulted in significantly more sleep time being spent at Ptc,CO_2 <6.7 kPa, while in oxygen therapy significantly more time was spent at high Ptc,CO_2, in particular >7.3. *: p<0.05, *versus* control.

Table 2. – Sleep architecture in six cystic fibrosis (CF) patients breathing room air, supplemental oxygen, or receiving bilevel noninvasive positive pressure ventilation (NIPPV)

Sleep measures	Room air	Oxygen therapy	NIPPV	p-value
TST min	378±49	386±30	390±29	NS
Sleep latency min	24±6	18±2	23±4	NS
NREM min	228±36	242±23	241±29	NS
NREM %TST	60±3	63±3	62±4	NS
REM min	47±18*#	70±30*	57±23#	*<0.02; #<0.03
REM %TST	12±3*#	18±7*	15±5#	*<0.02; #<0.03
Undetermined %TST	28±4	19±9	24±6	NS
Total arousals h	49.7±10.6	38.2±3.7	47.7±3.6	NS
Arousal index	8.1±2.6	6.0±0.8	7.4±0.7	NS
Sa,O_2 in NREM %	88±5*§ (80–92)	94±1* (92–96)	93±2§ (90–95)	*§<0.001
Sa,O_2 in REM %	79±7*§ (67–86)	90±2* (89–93)	88±3§ (85–92)	*<0.001; §<0.008
Ptc,CO_2 in NREM kPa	6.4±0.4*# (6.1–7.2)	7.1±0.9*§ (6.4–8.5)	5.7±0.4§# (5.4–6.4)	*<0.02; §<0.001; #<0.01
Ptc,CO_2 in REM kPa	6.9±0.8*# (6.4–8.3)	7.9±0.7*§ (7.3–9.1)	6.0±0.4§# (5.7–6.7)	*§<0.003; #<0.01

Values are mean±SD, and range in parenthesis. TST: total sleep time; NREM: non-rapid eye movement sleep; arousal index: total arousals/TST; Ptc,CO_2: transcutaneous CO_2 tension; NS: nonsignificant; *: oxygen therapy *versus* room air; #: NIPPV *versus* room air; §: oxygen therapy *versus* NIPPV.

(table 2). As with oxygen therapy, a significant increase in total REM duration occurred with NIPPV (p<0.03, Kruskal-Wallis H-test). Mean S_{a,O_2} was significantly improved compared to control during REM (p<0.008, Kruskal-Wallis H-test) and NREM (p<0.001, Kruskal-Wallis H-test), such that overall oxygen saturations were similar in oxygen therapy and NIPPV (p=NS). In contrast with oxygen therapy, however, significant decreases rather than increases in P_{tc,CO_2} occurred with NIPPV during REM and NREM epochs (table 2; fig. 2).

Discussion

The present study shows that NIPPV is as effective as supplemental oxygen in improving moderate to severe CF patients during REM and NREM sleep. Moreover, in contrast with oxygen therapy, which induced significant increases in P_{tc,CO_2}, NIPPV improved ventilation during sleep. The beneficial effects on sleep-disordered breathing were achieved without adversely impacting on sleep architecture or arousal index.

Before discussing our results, some methodological points deserve comment. First, patients were obviously aware of the nature of the intervention being administered during the second and third nights of the study. However, although all participants were familiar with the experimental protocol, they were naive to the actual purpose of the study, and both patients and sleep laboratory technicians were unaware of sleep study results until completion of the third night polysomnographic study. Second, randomization of the treatments during the second and third experimental nights (three patients received oxygen therapy and three received NIPPV during the second sleep study recording) should have prevented a potential preferential bias. Finally, P_{tc,CO_2} measurements have been reported to drift downwards over time, and changes in electrode position after 4 h of sleep may modify recorded P_{tc,CO_2} values [13]. However, such electrode-related artefacts would have affected all our recordings similarly, independent of the treatment being administered. In addition, our precautions to compare actual P_{tc,CO_2} readings with P_{CO_2} values obtained from a capillary blood sample drawn at two different time points of the sleep study further ensure that despite the potential inaccuracy of P_{tc,CO_2} measurements, the trends obtained throughout the study remain valid.

Daytime oxygen saturation is either not predictive of sleep-related desaturation [14, 15] or may actually assist in the prediction of nocturnal hypoxaemia [16]. Irrespective of the value of waking S_{a,O_2} in identifying CF patients at risk for oxyhaemoglobin desaturation during sleep, vulnerable periods during which hypoxaemia is more likely to occur include REM sleep [1, 2, 4, 17] and acute infectious pulmonary exacerbations [18]. Indeed, during REM sleep epochs, significantly lower S_{a,O_2} and increased P_{tc,CO_2} occurred in our patients (table 2), and were possibly mediated by a reduction of functional residual capacity occurring during transition to this sleep stage and reflecting the typical decrease in motor tone which accompanies REM [2, 4].

Our results are in close agreement with SPIER et al. [3], who reported improved oxygenation with supple-

mental oxygen and no changes in sleep quality. However, in contrast with SPIER et al. [3], low-flow oxygen was associated with significant increases in P_{tc,CO_2} in our patients, and two patients reported morning headaches suggestive of clinically significant carbon dioxide retention. Despite the potential for development of severe hypercapnia and the uncertain value of long-term domiciliary oxygen therapy in CF [19], it has been our impression that low-flow oxygen remains the preferred modality of respiratory support by hypoxaemic CF patients. The long-term clinical implications of hypercapnia in these patients are, however, unclear. Indeed, hypercapnia and acidosis may increase pulmonary vascular tone independent of hypoxia [20], and have also been associated with diminished psychosocial function [21]. In addition, repeated hypercapnic episodes alter ventilatory drive [22], and prolonged hypercapnia may blunt CO_2 chemosensitivity [23].

The major difference between oxygen therapy and NIPPV treatments was the prevention and amelioration of sleep-related hypercapnia with NIPPV. These findings, and those of REGNIS et al. [4] who found no changes in P_{tc,CO_2} during nasal CPAP, suggest that NIPPV provides not only mechanical support for the maintenance of upper airway patency and end-expiratory lung volume (EELV), but may also assist in overcoming any EELV-associated increases in elastic load, thereby reducing the work of breathing and possibly allowing for some degree of respiratory muscle rest [4, 6]. Such inherent advantages of NIPPV could lead, if used regularly, to significant improvements in ventilatory drive [24], daytime functional capacity, and quality of life in CF.

Information regarding potential benefits and experience with NIPPV in patients with COPD in general [25–27], and more particularly in CF patients [4], is rather limited. In a recent study of 14 patients with severe COPD, NIPPV with oxygen resulted in significant improvements of daytime blood gases, sleep efficiency, and quality of life when compared to oxygen alone [27]. In this particular study, only one patient withdrew from the study because of intolerance to NIPPV. However, other studies have reported higher intolerance rates to mask ventilation, and different methods have been suggested to achieve optimally comfortable settings [28, 29]. Despite our precautions to ensure habituation to the nasal mask and ventilatory settings, two of our eight patients withdrew from the study. When the remaining six patients were asked about their preferences regarding home therapy, four chose low-flow oxygen. Of the two patients who selected NIPPV for home therapy, one has been relatively noncompliant, while the other reports great satisfaction with his therapy, to which he attributes an increased level of daytime activity and wellbeing. Therefore, although NIPPV demonstrates significant potential for the management of severely compromised CF patients, further studies appear necessary for identification of those patients most likely to accept and comply with such therapeutic modality, and for determination of the short and long-term benefits of such intervention.

In conclusion, noninvasive positive pressure ventilation appears to be as effective as low-flow oxygen in preventing sleep-induced hypoxaemia in severe cystic

fibrosis patients. Improved oxygenation was achieved without modification of sleep quality and efficiency. An additional and potentially clinically important benefit of noninvasive positive pressure ventilation may lie in the normalized or at least significantly improved alveolar ventilation obtained with noninvasive positive pressure ventilation throughout the night. Despite concerns about reduced patient tolerance and compliance, noninvasive positive pressure ventilation should be entertained as a viable and feasible therapeutic modality in cystic fibrosis patients with advanced lung disease.

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