Sleep and Respiratory Function After Withdrawal of Noninvasive Ventilation in Patients With Chronic Respiratory Failure

Thierry Petitjean MD, François Philit MD, Michele Germain-Pastenne MD, Bruno Langevin MD, and Claude Guérin MD PhD

BACKGROUND: In patients with restrictive thoracic disease, little is known about changes in sleep and breathing if the patient stops using nocturnal noninvasive ventilation (NIV). Better understanding of those changes may affect NIV management and improve our understanding of the relationship of night-to-night variability of respiratory and sleep variables and morning gas exchange. METHODS: With 6 stable patients with restrictive chronic respiratory failure who were being treated with home NIV we conducted a 5-step study: (1) The subject underwent an in-hospital baseline sleep study while on NIV, then next-morning pulmonary function tests. (2) At home, on consecutive nights, the subject underwent the same sleep-study measurements while not using NIV, until the patient had what we defined as respiratory decompensation (oxygen saturation measured via pulse oximetry [S_{pO_2}] < 88% or end-tidal CO_2 pressure [P_{ETCO_2}] > 50 mm Hg, with or without headaches, fatigue, or worsening dyspnea). Each morning after each home sleep-study night off NIV, we also measured S_{pO_2} and P_{ETCO_2}. (3) The patient returned to the hospital for a second overnight assessment, the same as the baseline assessment except without NIV. (4) The patient went home and restarted using NIV with his or her pre-study NIV settings. (5) After the number of nights back on home NIV matched the number of nights the patient had been off NIV, the patient returned to the hospital for a third in-hospital assessment. We measured static lung volumes, maximum inspiratory and expiratory static mouth pressure, breathing pattern, arterial blood gases, S_{pO_2}, P_{ETCO_2}, and full overnight polysomnography values. RESULTS: Respiratory decompensation occurred 4–15 days after NIV discontinuation (mean 6.8 d). On the first and second in-hospital assessment nights, respectively, the mean nadir nocturnal S_{pO_2} values were 84 ± 2% and 64 ± 4%, the total apnea-hypopnea index values were 0 ± 0 and 9 ± 2, and the obstructive hypopnea index values were 0 ± 0 and 7 ± 1 episodes per total sleep hour. Respiratory events started on the first night off NIV. Spirometry, muscle strength, and sleep architecture did not change significantly. With resumption of NIV, baseline conditions were recovered. CONCLUSIONS: NIV discontinuation in patients with restrictive chronic respiratory failure previously stabilized on NIV promptly leads to nocturnal respiratory failure and within days to diurnal respiratory failure. Stopping NIV for more than a day or two is not recommended. *Key words. chronic respiratory failure, respiratory decompensation, restrictive thoracic disease, noninvasive ventilation, NIV, sleep, apnea, hypopnea.* [Respir Care 2008;53(10):1316–1323. © 2008 Daedalus Enterprises]

Introduction

It is well known that patients with kyphoscoliosis have episodes of hypoxemia and hypoventilation during sleep, in particular during rapid-eye-movement sleep.[1] These nocturnal episodes are important because they impact daytime

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living and lead to chronic hypercapnia and chronic respiratory failure. Noninvasive ventilation (NIV) via nasal mask benefits patients with neuromuscular[2,3] and chest-wall disorders[1-3] by improving nocturnal and diurnal gas exchange and clinical symptoms and reducing morbidity.[4] However, NIV may be discontinued briefly for various reasons, such as a technical equipment problem,[5] travel,[6] nasal irritation, or upper-airway congestion.[7] In one study, brief NIV interruption in patients with chronic respiratory failure was associated with deterioration in daytime functioning.[7] Other investigations did not replicate that result but did find worsened nocturnal gas exchange and sleep disturbance.[8-11] There are no data on the temporal changes of sleep architecture and respiratory events after cessation of NIV, so the time until nocturnal changes is unknown. That information is important for NIV management and for determining how NIV improves daytime symptoms and respiratory function.[8,9] Therefore, we measured the changes in sleep and breathing variables and daytime respiratory function after stopping home nocturnal NIV, and analyzed the correlation between the nighttime data and daytime functioning. Our hypothesis was that impairment of sleep architecture and efficiency after stopping NIV would lead initially to nocturnal respiratory failure and eventually to diurnal respiratory failure.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria
Restrictive chest-wall disease (total lung capacity ≤ 65% of predicted)
Chronic respiratory failure with hypercapnia (P_{aCO_2} > 50 mm Hg)
Daytime and nocturnal clinical symptoms prior to commencing NIV
Home NIV cleared symptoms and normalized gas exchange
Good adherence to home NIV, as measured by the hour-counter on the home ventilator
Stable respiratory condition for the last 3 months
Obstructive sleep apnea syndrome ruled out by previous sleep study
Written informed consent
Exclusion Criteria
Daytime hypoventilation symptoms (eg, dyspnea, headaches and sleepiness) despite nocturnal NIV
Chronic obstructive pulmonary disease
Current or previous use of psychotropic drugs
Refusal to participate

NIV = noninvasive ventilation

Methods

The study was approved by our institutional ethics committee.

Patients

We recruited from our population of ambulatory patients with chronic respiratory failure treated with home NIV and regularly followed in our pulmonary department (Table 1).

Daytime Respiratory Function Testing

We measured oxygen saturation via pulse oximetry (S_{pO_2}) (Datex-Ohmeda, Louisville, Colorado), expiratory end-tidal carbon dioxide pressure (P_{ETCO_2}) (Capnogard, Novametrix, Wallingford, Connecticut), and arterial blood gases (Ciba-Corning, Halstead, England) while the patient was seated and at rest for at least half an hour. Oxygen consumption and CO_2 production were measured at rest with a Douglas bag and a mouthpiece. Mixed expired CO_2 was measured with an infrared analyzer (LB2, Beckman Instruments, Fullerton, California), and mixed expired O_2 was measured with a polarographic analyzer (OM11, Beckman Instruments, Fullerton, California).

Lung volumes were obtained with a body box plethysmograph (5500, MediSoft, Sorinnes, Belgium), according to American Thoracic Society guidelines.[10] Functional residual capacity was measured with the helium technique (spirometer 2450, SensorMedics/Cardinal Health, Dublin, Ohio).[11] We used the predicted values from the European Community for Coal and Steel.[12] Breathing pattern was measured via mouthpiece, with the subject sitting, and calculated from an average of 10 respiratory cycles during quiet breathing for at least 5 min.

Static maximum inspiratory and expiratory airway pressures were measured with the subject sitting, starting at residual volume and at total lung capacity, respectively, against an occluded airway.[13] The best value of 3 reproducible measurements was recorded. The same investigator performed the tests with a given patient.

Nighttime Sleep Studies

Standard sleep variables were recorded (Hypnotrace Pocket, Tyco Healthcare, Plaisir, France) from 22:00 to 08:00.[14] Sleep stages were scored manually on 30-second periods, according to established criteria.[15] We used standard criteria to identify transient cortical arousal, arousal index, total sleep time, awake time, and sleep efficiency.[14] Apnea was defined as a complete cessation of airflow for ≥ 10 seconds. Hypopnea was defined as an airflow decrease of ≥ 50% for ≥ 10 seconds, accompanied by an S_{pO_2} decrease of ≥ 4%. Obstructive apnea-hypopnea was defined as the absence/reduction of airflow in the presence of rib-cage and abdominal excursions. Central apnea was defined as absence of rib-cage and abdominal excursions with absence/reduction of airflow. Apnea and hypopnea episodes were counted according to apnea and hypopnea

type, and the apnea-hypopnea index was defined as the number of apneas and hypopneas per hour of sleep. The nocturnal hypoxemia index was defined as the number of S_{pO_2} decreases $\geq 4\%$ that lasted > 10 seconds but < 3 minutes per hour of total sleep time. We also recorded the lowest nocturnal S_{pO_2} and percent of total sleep time spent with $S_{pO_2} < 90\%$. All the sleep studies were scored by the same investigator (TP).

Study Protocol

First, the subject was admitted to the hospital for baseline assessment in the sleep laboratory, which included a sleep study while on NIV, then next-morning pulmonary function tests.

Second, the subject went home with the instruction to not use NIV. The informed consent explicitly stated that stopping NIV might be hazardous. For patient safety, one of us visited the subject at her/his home twice daily and was on call 24 hours a day. At the evening visit the clinician set up the sleep study with the same equipment we used in the sleep laboratory. Set-up required approximately 1 hour, and time was given for the patient to minimize the effect of equipment or stress. The patient went to bed as usual and noted the lights-off and awakening times. The quality of signals was controlled, recording was started, and the investigator left the patient's home. The next morning the clinician returned, removed the equipment, downloaded the sleep-study data to a computer, and recorded S_{pO_2} and P_{ETCO_2} values for at least 5 min, with the patient seated. These same steps were performed daily until the subject had what we defined as respiratory decompensation, which was $S_{pO_2} < 88\%$ or $P_{ETCO_2} > 50$ mm Hg, with or without headaches, fatigue, or worsening dyspnea.

Third, once in respiratory decompensation, the patient was readmitted to the hospital for a second sleep assessment, which was the same as the baseline assessment except without NIV.

Fourth, the patient went home and restarted using NIV with his or her pre-study settings.

Fifth, after the number of nights back on NIV matched the number of nights the patient had been off NIV, the patient returned to the hospital for a third assessment.

This study design (Fig. 1) was selected to have 2 symmetrical arms with each patient, and each patient acted as his or her own control.

Statistical Analysis

Results are expressed as mean ± SD. The data from the baseline, second, and third in-hospital assessments were compared with 1-way analysis of variance for repeated measures, and significance of difference between individual means was tested if required. We used the Pearson coefficient to assess correlation between variables. Because we performed numerous statistical tests on data from a small number of subjects, the usual statistical-significance threshold of $P < .05$ was corrected by applying the Bonferroni rule (0.05/number of tests), so for this study the significance level was $P < .0005$. The analysis was done with statistics software (SigmaPlot 9.0 and SigmaStat 3.1, Systat Software, San Jose, California).

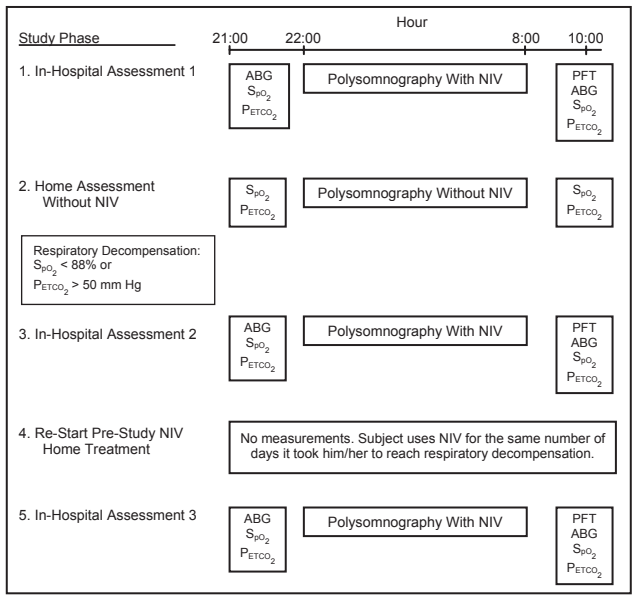

Fig. 1. Study design. ABG = arterial blood gases. S_{pO_2} = oxygen saturation measured via pulse oximetry. P_{ETCO_2} = end-tidal carbon dioxide pressure. NIV = noninvasive ventilation. PFT = pulmonary function test.

Results

We enrolled 4 female and 2 male patients (Table 2). NIV had originally been commenced because of progressive worsening of respiratory failure in 5 patients and an acute hypoventilation episode in one patient. NIV was delivered in a volume-controlled mode with all patients but one, with either standard commercially available or custom-made nasal mask. Two of the patients were receiving supplemental oxygen.

The mean baseline values were: maximum inspiratory pressure 63 ± 32% of predicted, maximum expiratory pressure 79 ± 39% of predicted, tidal volume 0.48 ± 0.25 L, respiratory frequency 15 ± 5 breaths/min, minute volume 7.8 ± 2.9 L/min, ratio of inspiratory time to total respiratory cycle time 0.36 ± 0.81, and ratio of tidal volume to inspiratory time 0.33 ± 0.12 L/s. None of those mean values were significantly different at the second and third in-hospital assessments. The same was true for the gas-exchange and metabolic rate data (Table 3) and the sleep-study data (Table 4).

Table 2. Subjects and Baseline Values

Subject	Age (y)	Diagnosis	Sex	BMI (kg/m^2)	Months on NIV	Ventilator Model	Supplemental Oxygen	I:E	Respiratory Frequency (breaths/min)	V_T (mL/kg)	P_{aO_2} (mm Hg)*	P_{aCO_2} (mm Hg)*	pH*	FVC (L, % predicted)†	TLC (L, % predicted)†	FRC (L, % predicted)†
1	57	Kyphoscoliosis	Male	26	4.6	Eole 3	Yes (1 L/min)	1/1	14	12	59	58	7.40	2.06 (42)	3.58 (48)	1.81 (49)
2	70	Post-poliomyelitis syndrome	Male	26	12.6	Eole 3	Yes (2 L/min)	1/1	16	12	56	51	7.41	2.80 (65)	4.76 (65)	2.76 (73)
3	37	Kyphoscoliosis	Female	20	27.4	Eole 3	No	1/1.5	16	14	42	54	7.37	0.89 (34)	1.17 (30)	0.51 (21)
4	61	Kyphoscoliosis	Female	27	14.6	Eole 3	No	1/1.5	13	14	73	52	7.38	1.11 (50)	1.93 (50)	1.11 (35)
5	69	Kyphoscoliosis	Female	29	72.1	Helia	No	‡	14§	ND‖	66	53	7.38	1.34 (49)	2.04 (42)	0.84 (39)
6	60	Kyphoscoliosis	Female	26	90.9	Eole 3	No	1/1	15	12	69	53	7.41	0.99 (55)	1.59 (57)	0.89 (56)

* Value at enrollment in the home NIV program
† Value at first in-hospital assessment
‡ Inspiratory to expiratory switching automatically adjusted by the patient during the breathing cycle; positive end-expiratory pressure was set at zero in all cases.
§ Backup rate
‖ No data available: V_T unknown; pressure support of 19 cm H_2O
BMI = body mass index
NIV = noninvasive ventilation
I:E = ratio of inspiratory time to expiratory time
V_T = tidal volume
FVC = forced vital capacity
TLC = total lung capacity
FRC = functional residual capacity

Patients 1 through 6 had been off of NIV for 4, 4, 7, 15, 7, and 4 nights, respectively, when respiratory decompensation occurred (Fig. 2). In addition to gas-exchange impairment, 5 patients had headaches, 6 had unrefreshing sleep, and 4 had increased dyspnea. Nocturnal hypoxemia occurred after 1–3 days off NIV, except in patient 4, in whom nocturnal hypoxemia did not occur until 14 days off NIV. Nocturnal apnea-hypopnea appeared after only one night off NIV. The subjects' sleep structure did not change markedly from baseline.

At the second in-hospital assessment, relative to the baseline assessment, nocturnal and diurnal gas exchange was significantly impaired (see Table 3 and Fig. 3), and there were nocturnal respiratory events (obstructive hypopnea), though lung volumes, respiratory muscle strength, breathing pattern, and sleep structure were not significantly changed. There was a positive correlation between apnea-hypopnea index and arousal index ($r = 0.91$, $P = .01$).

At the third in-hospital assessment the subjects were free of symptoms, they had recovered their baseline respiratory and sleep conditions (Table 3 and Fig. 3C), and there were no respiratory events.

Discussion

Some methodological considerations have to be acknowledged. First, the study was limited by the small number of subjects. A type II error is possible when statistically analyzing such a small group, so none of the differences were significant with the Bonferroni-corrected P value.

Second, we did not use the esophageal balloon method to identify obstructive hypopnea, because we did not want to conduct invasive investigations on these patients, who were receiving noninvasive therapy. Therefore, our interpretation of the obstruction mechanism might be inaccurate, because the technology of naso-buccal thermistance is not sufficient.[16]

Third, though we were concerned about withdrawing NIV, the protocol was cleared by our ethics committee, the subjects gave informed consent, the home visits provided an adequate safeguard, and other authors have used similar approaches.[8,9] Moreover, none of subjects was ventilator-dependent.

Fourth, the daytime NIV settings may not be always appropriate for nocturnal NIV, as has been observed in patients with neuromuscular disease.[17] The strength of this study was the repeated daytime and nighttime respiratory and sleep assessments performed at the subjects' homes, which shows that home sleep studies are feasible, and we believe a home sleep study assesses the adequacy of NIV settings better than does a sleep-laboratory study.

Table 3. Gas Exchange and Metabolism

	Baseline (mean ± SD)	At Time of Respiratory Decompensation After NIV Withdrawal (mean ± SD)	After Resumption of NIV (mean ± SD)
S_{pO_2}			
Morning (%)	96 ± 2	93 ± 2	96 ± 2
Evening (%)	95 ± 0	93 ± 2	96 ± 2
P_{ETCO_2}			
Morning (mm Hg)	41 ± 2	53 ± 2	40 ± 2
Evening (mm Hg)	41 ± 2	53 ± 2	41 ± 2
P_{aO_2}			
Morning (mm Hg)	75 ± 7	73 ± 10	76 ± 7
Evening (mm Hg)	74 ± 15	70 ± 12	78 ± 10
P_{aCO_2}			
Morning (mm Hg)	41 ± 5	51 ± 2	43 ± 2
Evening (mm Hg)	40 ± 10	52 ± 2	43 ± 2
pH			
Morning	7.40 ± 0.02	7.39 ± 0.05	7.40 ± 0.02
Evening	7.40 ± 0.02	7.39 ± 0.05	7.40 ± 0.02
Oxygen consumption (L/min)	0.22 ± 0.07	0.23 ± 0.07	0.23 ± 0.05
Carbon dioxide production (L/min)	0.16 ± 0.05	0.17 ± 0.05	0.16 ± 0.05

NIV = noninvasive ventilation
S_{pO_2} = oxygen saturation measured via pulse oximetry
P_{ETCO_2} = end-tidal carbon dioxide pressure

Table 4. Sleep-Study Data

	Baseline (mean ± SD)	At Time of Respiratory Decompensation After NIV Withdrawal (mean ± SD)	After Resumption of NIV (mean ± SD)
Total sleep time (min)	392 ± 93	398 ± 32	397 ± 103
Awake time within sleep (min)	98 ± 59	113 ± 64	82 ± 69
Sleep efficiency index (%)	81 ± 12	78 ± 10	82 ± 15
Cortical arousal index	17 ± 5	25 ± 12	14 ± 5
Non-REM sleep (%)	81 ± 5	78 ± 10	84 ± 10
REM sleep (%)	19 ± 5	22 ± 10	16 ± 10
Apnea-hypopnea index	0 ± 0	9 ± 5	0 ± 0
Hypopnea index	0 ± 0	8 ± 5	0 ± 0
Obstructive hypopnea index	0 ± 0	7 ± 2	0 ± 0
Central apnea index	0 ± 0	0.5 ± 1.2	0 ± 0
Obstructive apnea index	0 ± 0	0.4 ± 0.7	0 ± 0
Obstructive apnea and hypopnea	0 ± 0	6 ± 2	0 ± 0
Obstructive apnea and hypopnea index during REM sleep	0 ± 0	14 ± 17	0 ± 0
Nocturnal desaturation index	3 ± 2	23 ± 32	5 ± 5
Lowest nocturnal S_{pO_2} (%)	84 ± 5	64 ± 10	83 ± 5
Total sleep time with $S_{pO_2} < 90\%$ (min)	13 ± 17	129 ± 169	20 ± 20

NIV = noninvasive ventilation
REM = rapid eye movement
S_{pO_2} = oxygen saturation measured via pulse oximetry

Improvement of respiratory muscle strength was suggested as a contributing factor of the benefit of NIV.[18] However, as has been found by others, the present results suggest that the effect of NIV cannot be explained by increased lung volume, relief of fatigue, or increased respiratory-muscle endurance.[16,19,20]

It is still unclear how long a period of NIV discontinuation is needed before there is a daytime deterioration in

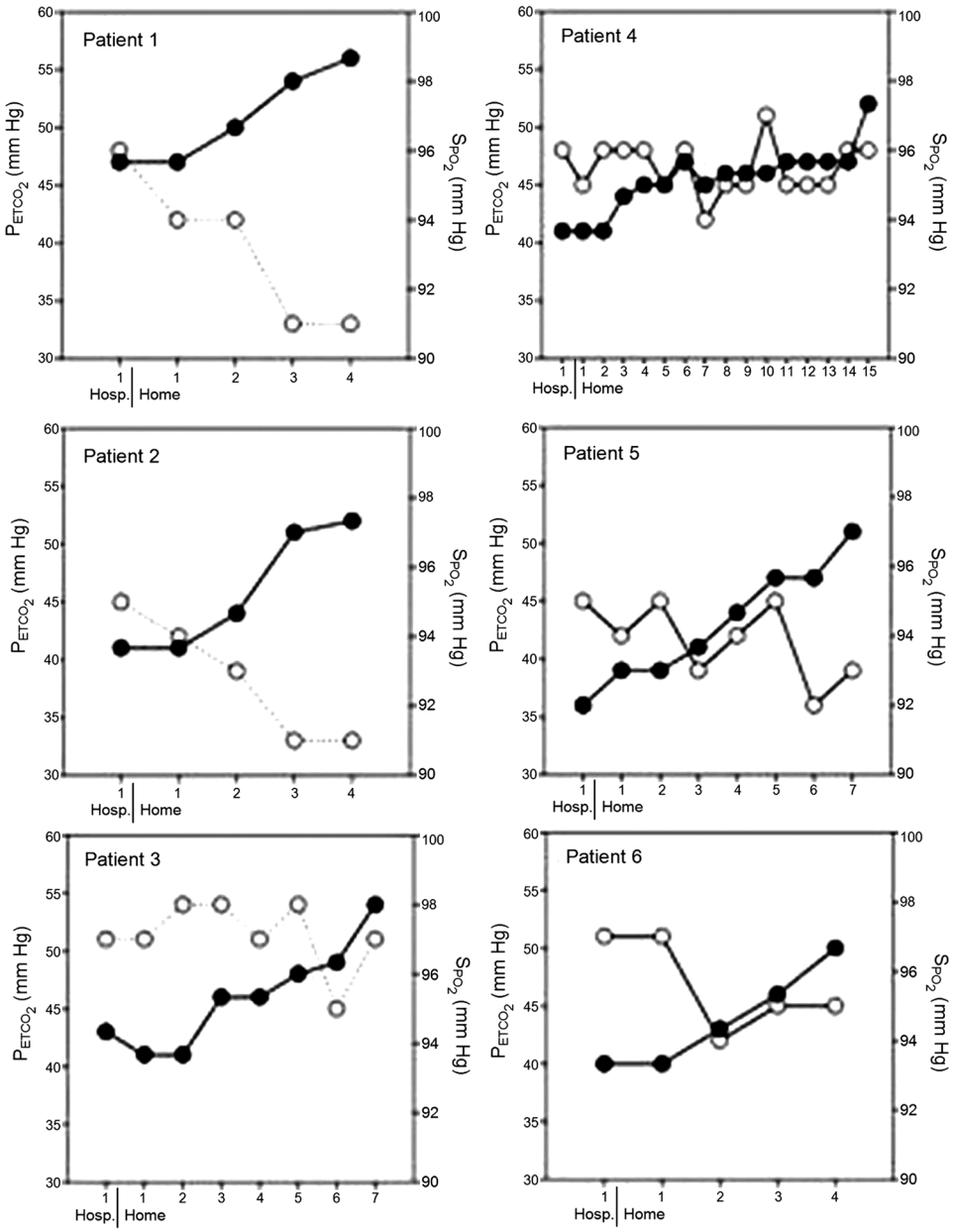

Fig. 2. End-tidal carbon dioxide pressure (P_{ETCO_2}) (closed circles) and oxygen saturation measured via pulse oximetry (S_{pO_2}) (open circles), starting at in-hospital baseline study and then each morning at home, up to the point of respiratory decompensation, in patients 1 through 6.

gas exchange. We found considerable variability in the time to respiratory decompensation. This might relate to the severity of underlying pulmonary dysfunction, respiratory-muscle deconditioning, impairment of central respiratory drive, or other factors. Piper and Sullivan[18] studied 14 patients with restrictive thoracic disease treated successfully with NIV for at least 6 months, and studied those patients on and off NIV for 24 hours. Spontaneous breathing and gas exchange during sleep were markedly improved after long-term NIV, although still abnormal. Hill et al[9] and Masa Jímenez et al[8] stopped NIV for 7 days and 15 days, respectively, and found no significant changes in daytime blood gases, despite significant worsening of nocturnal gas exchange. Masa Jímenez et al[8] found no major clinical deterioration, whereas Hill et al[9] did.

Karakurt et al[7] studied 11 patients (5 with restrictive thoracic disease) withdrawn from NIV for up to 6 days. Around half the patients needed to get back on NIV before the scheduled 6 days, due to deterioration in arterial blood gases, although none reported severe worsening of symptoms. The present study suggests that NIV discontinuation of 4–15 days (mean 6.8 d, median 5.5 d) is required to

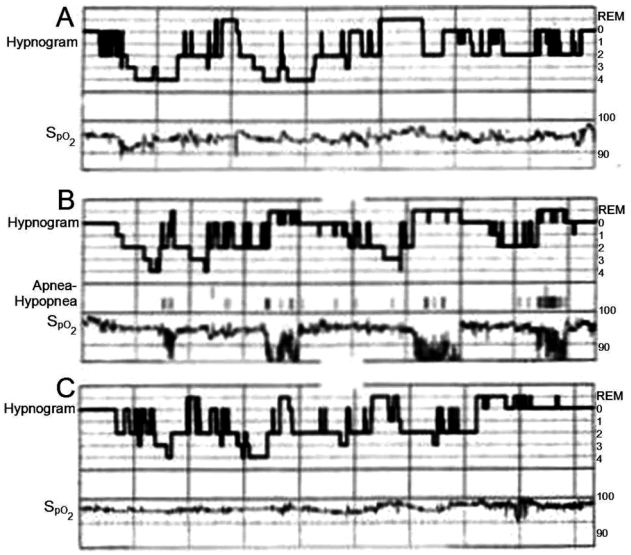

Fig. 3. Hypnogram and oxygen saturation measured via pulse oximetry (S_{pO_2}) from patient 3 (A) at baseline, (B) at time of respiratory decompensation after stopping noninvasive ventilation, and (C) after recovery with noninvasive ventilation. The vertical bars below panel B indicate apneas and hypopneas. REM = rapid eye movement.

worsen daytime gas exchange and cause symptoms. We found a mean P_{aCO_2} change between the baseline assessment and the second in-hospital assessment of 10 mm Hg, for similar CO_2 production, which is quite different from that found by Hill et al[9] and Masa Jímenez et al.[8] That difference might be explained by the fact that we waited for a P_{aCO_2} increase before resuming NIV, whereas they did not. Moreover, since all of these studies were small, considerable differences should be expected between the patients enrolled.

Our close monitoring of sleep in the present study disclosed nocturnal respiratory events (mostly obstructive) after only one night off NIV. This finding was not due to a first-night effect, because the total sleep time was not decreased. Furthermore, a first-night effect would have resulted in just the opposite (ie, worsened sleep, so fewer respiratory events). Obstructive events during sleep were reported many years ago in patients with severe kyphoscoliosis.[1,3] The positive pressure delivered by NIV is high enough to promote upper-airway patency. The fact that nocturnal respiratory events occurred as early as the first night off NIV and did not further increase suggests that the upper airway is prone to narrowing or collapse in these patients.

In the present study, respiratory events mostly occurred during rapid-eye-movement sleep in 3 patients, as has been reported by others.[1,3] Respiratory events promote nocturnal hypoventilation and may worsen respiratory condition up to chronic respiratory failure.[21] Those findings support the use of NIV mostly at night.[22] However, a converse view is possible, that respiratory dysfunction may lead to nighttime disturbances, as shown by reversal of hypoventilation for several hours per day, irrespective of whether NIV is used during the night asleep or during the day awake.[16] Furthermore, the mechanism by which NIV is effective is caused by other factors, such as respiratory-center resetting.[9]

Our clear finding of nocturnal respiratory events after NIV discontinuation contrasts with the absence of change in sleep macroarchitecture. Ellis et al[19] found significant sleep improvement with NIV in patients with severe kyphoscoliosis, but they studied previously untreated patients who were starting on NIV for the first time. Therefore, the present study compares more appropriately to investigations with patients who were are already using NIV. Masa Jímenez et al[8] observed, contrary to the present study, that daytime gas exchange did not worsen off NIV, and they found more arousals and awakenings when their subjects were off NIV than on NIV.[8] The discrepancy between those findings and our results may be due to differences in baseline sleep conditions. The baseline average number of arousals was 65 in the Masa Jímenez et al study, but it was 110 in our study.

Conclusions

NIV discontinuation in patients with restrictive chronic respiratory failure previously stabilized on NIV leads promptly to nocturnal respiratory failure and within days to diurnal respiratory failure. Stopping NIV for more than a day or 2 is not recommended.

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