Neural Respiratory Drive and Ventilation in Patients with Chronic Obstructive Pulmonary Disease during Sleep

To the Editor:

Patients with chronic obstructive pulmonary disease (COPD) experience sleep-related hypoventilation (1, 2). However, there is controversy as to whether this occurs due to an increase in upper airway resistance or a reduction in neural respiratory drive. Elevated neural respiratory drive in wakefulness is well documented in COPD (3). O'Donoghue and coworkers (4) reported in patients with COPD that a sleep-related hypoventilation was due to increased upper airway resistance, and Ballard and coworkers (5) reported an increase in upper airway resistance moving from wakefulness to sleep, although upper airway resistance was not consistently greater during sleep (*see* Figure 3 of their article [5]). Moreover, in healthy young adults, a poor correlation was observed between changes in ventilation and upper airway resistance (6). Morrell and coworkers (7) addressed the question directly in tracheotomized subjects, confirming hypoventilation during sleep, thus excluding an obligate contribution from upper airway resistance. To further address the question, we performed diaphragm electromyography (EMG_{di}) using a multipair esophageal electrode as an index of neural respiratory drive (8–11). Some of the data have been previously reported in abstract form (12).

A total of 17 stable patients with moderate to very severe COPD and 14 age-matched normal subjects participated. All subjects were free from obstructive sleep apnea (OSA; apnea–hypopnea index $<$ 5.0 events/h) and snoring confirmed by prior overnight polysomnography, and were free from clinically significant coexisting diseases, including neuromuscular disorders. The study was approved by the Ethics Committee of the Chinese State Key Laboratory of Respiratory Disease, and all patients gave their informed consent to participate.

A multipair esophageal electrode catheter (Yinghui Medical Technology Co., Ltd, Guangzhou, China) was used as previously described (8) to record the EMG_{di} during overnight polysomnography (9–11). Airflow was recorded with a pneumotachograph connected to a full facemask. Maximal EMG_{di} was recorded from maximal voluntary inspiratory maneuvers. Polysomnography was manually analyzed based on standard criteria (13). The root mean square (RMS) of the EMG_{di} ($RMS_{EMG_{di}}$) was calculated by computer with a time constant of 100 milliseconds. Efficacy of neural respiratory drive was defined as the ratio of minute ventilation to peak $RMS_{EMG_{di}}$ of each breath. Data were selected during stable breathing without respiratory events. Data collected for 10 minutes before sleep and for at least 15 minutes during non–rapid eye movement (NREM) and REM in the supine position were selected for analysis. Two-way ANOVA was used to test differences between wakefulness, NREM, and REM sleep; data are presented as means ($\pm$SD), and statistical significance was determined as a *P* value of less than 0.05.

Some subjects could not tolerate the full facemask, and satisfactory measurements were therefore obtained in 10 male patients with COPD (age, 59.3 $\pm$ 11.5 yr; body mass index, 20.8 $\pm$ 3.1 kg/m^2; FEV_1, 34.2 $\pm$ 15.8% predicted; FEV_1/FVC, 37.8 $\pm$ 11.6%; oxygen saturation $<$90%, 2.0 $\pm$ 4.0% of total sleep time) and 10 control subjects (nine males and one female, age, 58.1 $\pm$ 9.0 yr; body mass index, 22.8 $\pm$ 2.8 kg/m^2; FEV_1 97.8 $\pm$ 9.5% predicted). The maximal $RMS_{EMG_{di}}$ measured from patients with COPD was similar to control subjects (180.7 $\pm$ 92.0 μV vs. 161.7 $\pm$ 53.6 μV). $RMS_{EMG_{di}}$, as a percent maximal, in patients with COPD was significantly higher than that in normal subjects during wakefulness, NREM, and REM (Table 1). Compared with wakefulness, the $RMS_{EMG_{di}}$ decreased by 31 ($\pm$12)% in NREM, and further decreased by 49 ($\pm$12)% in REM sleep in patients with COPD. Similarly, ventilation decreased by 30 ($\pm$14)% in NREM and 44 ($\pm$11)% in REM. As shown in Table 1, the reduction in ventilation was principally mediated by tidal volume. The reductions in the $RMS_{EMG_{di}}$ and ventilation were of smaller magnitude in normal subjects. The efficacy of neural respiratory drive in normal subjects was significantly higher than that in patients with COPD during both wakefulness and sleep. However, sleep did not change the efficacy of neural respiratory drive in either patients with COPD or normal subjects (Table 1 and Figure 1).

This is the first study to simultaneously accurately record ventilation with a pneumotachograph connected to a full facemask and EMG_{di}, during wakefulness, NREM, and REM sleep, in patients with COPD without coexisting OSA. The efficacy of neural respiratory drive reflects upper airway resistance if lung mechanics and lower airway resistance remain the same. Because this is considered to be the case (4, 5), we speculate that the unchanged efficacy of neural respiratory drive between wakefulness and sleep argues against a substantial increase in upper airway resistance during sleep in either nonobese patients with COPD or normal subjects. This result is consistent with the work of Meurice and coworkers (14), who reported that upper airway resistance changed little in some patients with COPD during sleep. Although O'Donoghue and colleagues (4) concluded that sleep-related hypoventilation in patients with COPD was because of a threefold increase in upper airway resistance, the subjects they studied may have had mild OSA, because an apnea–hypopnea index up to 10 events/h was permitted.

Our results are consistent with the results reported by Morrell and coworkers (7), who showed that the development of sleep-related hypoventilation is independent of upper airway resistance, because the reduction of ventilation from wakefulness to NREM sleep in subjects who were breathing through the upper airway was similar to that in laryngectomized subjects who were breathing through a tracheal stoma. Our conclusions are also consistent with other data supporting the case that reduction of neural respiratory drive is important in sleep-related hypoventilation. For example, when continuous positive airway pressure is applied in patients with COPD to eliminate upper airway resistance (1), or to normalize upper airway resistance to waking levels in normal subjects (15), sleep-related hypoventilation is still evident.

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Table 1. The Root Mean Square of the Diaphragm Electromyography and Ventilation during Wakefulness and Sleep and Their Change Compared with Wakefulness

Characteristics	Patients with COPD			Normal Subjects		
	Wakefulness	NREM	REM	Wakefulness	NREM	REM
$RMS_{EMG_{di}}$ %max	41.0 ± 14.7	27.2 ± 7.4	20.8 ± 8.8	12.4 ± 4.1	11.4 ± 2.7	9.8 ± 2.8
$RMS_{EMG_{di}}$ Δ%	—	31 ± 12	49 ± 12	—	3 ± 21	17 ± 21
$\dot{V}_E$, L/min	8.74 ± 1.81	6.05 ± 1.56	4.80 ± 0.95	8.62 ± 1.66	7.80 ± 1.19	6.93 ± 1.16
$\dot{V}_E$ Δ%	—	30 ± 14	44 ± 11	—	8 ± 13	19 ± 11
V_T, L	0.49 ± 0.08	0.35 ± 0.08	0.27 ± 0.05	0.50 ± 0.10	0.50 ± 0.11	0.44 ± 0.08
V_T Δ%	—	28 ± 15	45 ± 11	—	0 ± 16	12 ± 12
Efficacy	0.20 ± 0.12	0.25 ± 0.07	0.29 ± 0.10	0.79 ± 0.37	0.74 ± 0.32	0.77 ± 0.29
Sa_{O_2}	96.0 ± 1.6	95.3 ± 1.8	92.8 ± 3.9	98.1 ± 0.9	97.8 ± 0.9	97.3 ± 1.1
ET-CO_2, %	4.8 ± 0.5	4.8 ± 0.6	5.0 ± 0.7	4.75 ± 0.26	5.01 ± 0.32	5.02 ± 0.26
RR, b/min	17.6 ± 1.7	17.1 ± 1.6	18.0 ± 2.6	17.2 ± 2.1	15.9 ± 2.2	15.9 ± 2.5

Definition of abbreviations: Δ% = percentage change compared with wakefulness; COPD = chronic obstructive pulmonary disease; ET-CO_2 = end-tidal CO_2; % max = percent of maximal; NREM = non–rapid eye movement; REM = rapid eye movement; $RMS_{EMG_{di}}$ = root mean square of the diaphragm electromyogram; RR = respiratory rate; Sa_{O_2} = oxygen satuation; $\dot{V}_E$ = minute ventilation; V_T = tidal volume.
Efficacy refers to the efficacy of neural respiratory drive; values presented are means (±SD).

Naturally, our study has some limitations. We had a relatively small sample size, and all patients were from one ethnic group and were not in respiratory failure, which could modify pharyngeal behavior (15). Our data are only representative of those who could sleep while instrumented. Thus, our findings should not be extended uncritically to all patients with COPD. However, in contrast to the previous hypothesis that hypoventilation is principally due to upper airway resistance, our study suggests that sleep-associated hypoventilation in patients with COPD is mainly related to reduction of neural respiratory drive. This observation suggests that noninvasive positive-pressure ventilation is a more logical

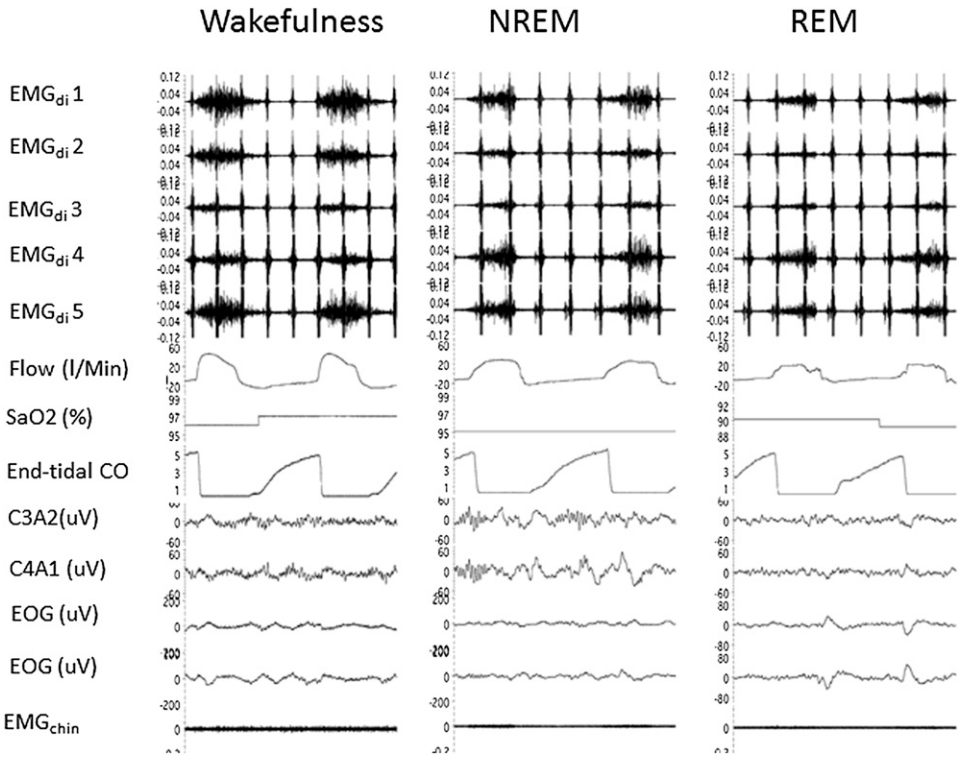

Figure 1. Polysomnography including five-channel diaphragm electromyography (EMG_{di}; 1–5) from a multipair esophageal electrode, airflow from pneumotachograph, end-tidal CO_2, electroencephalogram (EEG; C3A2 and C4A1), and left and right electrooculograms (EOGs). Compared with wakefulness, EMG_{di} and airflow decrease in non–rapid eye movement (NREM), and further decrease in REM. Data are from a patient with chronic obstructive pulmonary disease.

approach than continuous positive airway pressure to the treatment of nocturnal hypoventilation in COPD. ■

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Nuclear Magnetic Resonance–based Metabolomics Discriminates Primary Ciliary Dyskinesia from Cystic Fibrosis

To the Editor:

The respiratory phenotypes of cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) are different, with PCD showing much slower progression (1, 2). Nuclear magnetic resonance (NMR)-based metabolomics of exhaled breath condensate (EBC) recognizes markers separating children with asthma or adults with chronic obstructive pulmonary disease from healthy subjects (3–5) and unstable from stable CF (6). No NMR studies in PCD have been reported, and whether EBC metabolic profiles in PCD differ from CF is unknown. We hypothesized that stable PCD, stable CF, and healthy subjects have different EBC metabolic profiles. In this cross-sectional study we aimed to determine if NMR might be useful in discriminating between PCD and CF and possibly identify selective metabolites accounting for their differing prognoses.

After Institutional Review Boards approval, 20 patients with stable PCD, 21 patients with stable CF, and 21 age-matched control subjects were enrolled for the primary analysis (Table 1). There are no data in the literature for a sample size calculation in a NMR-based metabolomic study of patients with PCD versus patients with CF versus control subjects. Because no *a priori* analysis was possible, we could only evaluate the adequacy of our sample size *a posteriori*. Even assuming a value of 99.9% for 1-α and 1-β, a sample size of 17 $\pm$ 2 patients with PCD, 17 $\pm$ 3 patients with CF, and 17 $\pm$ 3 healthy control subjects was estimated to be adequate. PCD and CF were diagnosed according to published criteria (1, 2). To validate the model, a sample set defined as "validation subjects" (20 patients with PCD, 25 patients with CF, and 25 healthy control subjects) not included in the primary analysis was tested blindly (Table 2). Pharmacological treatment, cilia ultrastructural defects from patients with PCD, and cystic fibrosis transmembrane conductance regulator genotype from patients with CF were obtained from clinical records audit. Anthropometric measurements, sputum collection, and lung function testing were performed on the same day of EBC sampling.

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