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Nocturnal asthma

E. Rand Sutherland, MD, MPH *Denver, Colo*

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Nocturnal symptoms and overnight decrements in lung function are a common part of the asthma clinical syndrome. As many as 75% of asthmatic subjects are awakened by asthma symptoms at least once per week, with approximately 40% experiencing nocturnal symptoms on a nightly basis. An extensive body of research has demonstrated that nocturnal symptoms of cough and dyspnea are accompanied by circadian variations in airway inflammation and physiologic variables, including airflow limitation and airways hyperresponsiveness. Alterations in β_2-adrenergic and glucocorticoid receptors and hypothalamic-pituitary-adrenal axis function might play a role in modulating the nocturnal asthma phenotype, and recent studies have suggested that melatonin, a neurohormonal controller of circadian rhythms, might be important as well. Treatment strategies in nocturnal asthma are similar to those used in persistent asthma, although dosing of medications to target optimum effect during periods of nocturnal worsening is beneficial. (J Allergy Clin Immunol 2005;116:1179-86.)

Key words: *Inflammation, chronobiology, chronotherapy, melatonin, cortisol*

Abbreviations used
CPAP: Continuous positive airway pressure
GR: Glucocorticoid receptor
IQR: Interquartile range
Kd: Dissociation constant
NO: Nitric oxide
PEFR: Peak expiratory flow rate
TGV: Thoracic gas volume

DEFINITION AND EPIDEMIOLOGY OF NOCTURNAL ASTHMA

Nocturnal asthma is marked by a decrease in FEV_1 of at least 15% between bedtime and awakening in patients with clinical and physiologic evidence of asthma; in some patients, the variation in lung function between these 2 time points can exceed 20%.[1] This overnight decrement in lung function occurs in association with increased airway hyperresponsiveness[2] and airway inflammation[3] versus the awake baseline and leads to nocturnal symptoms,[4] such as cough and dyspnea, which disrupt sleep.

The largest study of the prevalence of nocturnal asthma symptoms was reported by Turner-Warwick in 1988.[5] Her survey of 7729 patients with asthma revealed that 74% awoke at least once per week with asthma symptoms. Sixty-four percent reported nocturnal asthma symptoms at least 3 times per week, and approximately 40% of patients experience symptoms nightly. Among the 3015 patients who rated their asthma severity as ''mild,'' 26% reported being awakened by symptoms nightly, suggesting inadequate recognition of nocturnal symptoms as an important determinant of disease severity.[5] A separate study of 3129 patients with nocturnal asthma reported that approximately 94% of dyspneic episodes occurred between the hours of 10 PM and 7 AM, with 4 AM the time of peak symptom frequency.[6] Nocturnal symptoms also appear to be associated with mortality from asthma in that the majority of respiratory arrests and sudden deaths in subjects with asthma occur between midnight and 8 AM.[7,8]

PHYSIOLOGIC MANIFESTATIONS OF NOCTURNAL ASTHMA

Although lung function has been shown to fluctuate over the 24-hour period in healthy individuals, these fluctuations are far more pronounced in patients with nocturnal asthma, with the difference in FEV_1 between wakefulness and sleep exceeding 15% (Fig 1). In patients with nocturnal asthma, the overnight decrease in lung function (as measured by changes in peak expiratory

From the National Jewish Medical and Research Center and the University of Colorado Health Sciences Center.

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Reprint requests: E. Rand Sutherland, MD, MPH, National Jewish Medical and Research Center and the University of Colorado Health Sciences Center, 1400 Jackson St, Room J-217, Denver, CO 80206. E-mail: sutherlande@njc.org.

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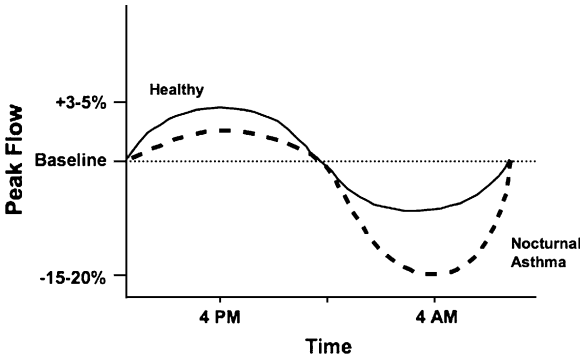

FIG 1. Both healthy individuals *(solid line)* and subjects with nocturnal asthma *(dotted line)* have circadian alterations in lung function, with nadirs occurring at approximately 4 AM. The circadian variation in lung function is increased in subjects with nocturnal asthma and might exceed 20% over the course of the 24-hour period.

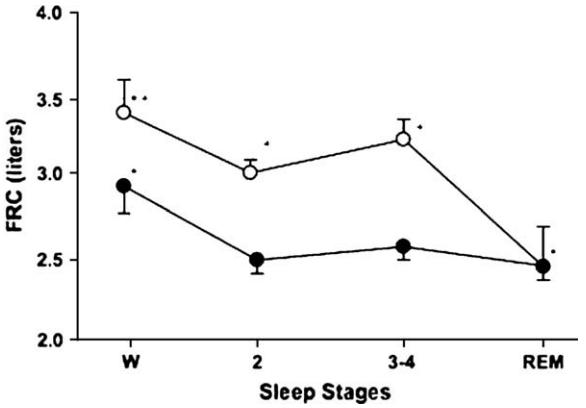

FIG 2. Changes in functional residual capacity *(FRC)* during sleep stages in subjects with nocturnal asthma *(open circles)* and healthy control subjects *(filled circles)*. $+P < .05$ for comparison between subjects with nocturnal asthma and control subjects, $*P < .05$ for comparisons between wakefulness *(W)* and rapid eye movement *(REM)* sleep in subjects with nocturnal asthma and between wakefulness and all other sleep stages in healthy control subjects.[10]

flow rate [PEFR]) has been shown to correlate not only with nocturnal symptoms ($r = 0.85$, $P < .001$)[2] but also with the percentage change in FEV_1 between 4 PM and 4 AM ($r = 0.75$, $P < .001$) and the FEV_1 percent predicted at both 4 PM ($r = 0.73$, $P < .001$) and 4 AM ($r = 0.84$, $P < .001$).[2] In addition to demonstrating that increases in airway obstruction underlie the development of nocturnal symptoms, these observations suggest that patients with more severe nocturnal decrements in lung function have more severe physiologic impairment during the daytime as well.

Although airflow limitation at 4 AM improves with inhaled bronchodilators in many patients with nocturnal asthma, this response is somewhat attenuated. Evaluation by Hendeles et al[9] of the albuterol dose-response curve at night in patients with nocturnal asthma has demonstrated a slower response to albuterol, with a greater cumulative dose required to achieve equivalent bronchodilation to that observed during the day. Patients with nocturnal asthma also manifest increased airway hyperresponsiveness at 4 AM when compared with an awake daytime baseline, as demonstrated in one study by a decrease in the methacholine PC_{20} FEV_1 (concentration required to induce a 20% decrease in FEV_1) from 1.80 ± 0.75 mg/mL at 4 PM to 0.47 ± 0.16 mg/mL at 4 AM ($P < .002$).[2]

Finally, changes in lung volumes have been reported during sleep in both healthy control subjects and patients with nocturnal asthma. In healthy control subjects functional residual capacity decreases between wakefulness and sleep, with the lowest values observed during rapid eye movement sleep.[10] Despite typically demonstrating hyperinflation during the day, patients with nocturnal asthma demonstrate marked reductions in functional residual capacity during sleep, with values during rapid eye movement sleep nearly identical to those seen in healthy control subjects (Fig 2).[10] This paradoxical abscence of hyperinflation despite increases in airflow limitation stands in contrast to the accepted relationship between airway resistance and lung volumes[11] and might indicate disruption of normal resistance-volume relationships during sleep in nocturnal asthma,[10] a phenomenon later investigated by Irvin et al.[12]

Inflammation in the small airways and alveoli might in part explain the altered physiologic interaction between airways and lung parenchyma that has been reported in nocturnal asthma.[12] In a study designed to evaluate parenchymal and airway interdependence, Irvin et al[12] studied 5 subjects with nocturnal asthma using whole-body plethysmography during sleep and wakefulness to assess volume-resistance relationships. They demonstrated that lower airway resistance increased during sleep in subjects with nocturnal asthma, from 16.2 ± 2.8 cm H_2O/L/s during early sleep to 29.8 ± 9.6 cm H_2O/L/s during late sleep ($P < .001$). The investigators then applied continuous negative thoracic pressure during sleep to increase sleeping thoracic gas volume (TGV) to a value similar to the TGV while awake. Despite the induced increase in lung volume, airway resistance failed to decrease significantly, with lower airway resistance at sleeping TGV of 16.2 ± 2.8 cm H_2O/L/s versus 14.9 ± 1.6 cm H_2O/L/s at awake TGV (Fig 3).[12] Respiratory system compliance was derived from these data, and from early to late sleep, respiratory system compliance decreased from 0.079 ± 0.02 cm H_2O/L to 0.035 ± 0.002 cm H_2O/L, indicating that nocturnal asthma might be associated with up to a 50% change in the normal lung volume–airway resistance relationship.[12]

EXHALED NITRIC OXIDE IN NOCTURNAL ASTHMA

Although airway inflammation does vary over the 24-hour period in nocturnal asthma, a similar circadian variation in nitric oxide (NO), with increases at night as airway inflammation increases, has not been reported. After evaluating circadian variations in exhaled NO in