Sleep in Asthma

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KEYWORDS

• Sleep • Asthma • Nocturnal • Breathing • Dyspnea

KEY POINTS

- Understanding the mechanism of nocturnal asthma and the factors that exacerbate asthma during sleep would lead to better management of the condition.
- Normal sleep architecture changes with nocturnal asthma.
- The exact mechanisms for nocturnal exacerbation of asthma are not fully established.

EPIDEMIOLOGY

Many patients with asthma experience worsening of symptoms at night. A review of emergency room visits by Horn and colleagues[1] indicated that patients with respiratory symptoms were more likely to present to the emergency room between the hours of midnight and 8 AM That study further found that 40% of the calls to physicians from asthmatic patients occurred between 11 PM and 7 AM A greater proportion of asthma patients tend to die at night than those in the general population.[2,3] In a review of deaths related to asthma in Victoria, New Zealand, over a 1-year period, Robertson and colleagues[4] determined that 53% of the asthma exacerbations that led to death began between 6 PM and 3 AM

Understanding the mechanism of nocturnal asthma and the factors that exacerbate asthma during sleep would lead to better management of the condition.

Many patients with asthma experience nocturnal symptoms at some time in their lives and most experience them on a regular basis. In a large survey of 7729 patients with asthma,[5] 74% reported experiencing nocturnal cough and wheeze at least once a week. The most studied causes and contributing factors to exacerbations of asthma at night include circadian changes in ventilation, airway responsiveness and inflammation, mucociliary clearance, ventilatory responses to hypercapnia and hypoxia, and hormone levels. This article is an update to that of D'Ambrosio and Mohsenin and Denjean and colleagues,[6,7] and reviews the normal physiologic changes that affect the lung during sleep and how those changes may contribute to nocturnal asthma.

PATHOPHYSIOLOGY

Flow Rates and Airway Resistance

Up to 90% of patients with asthma report some wheezing or cough at night.[8] Those symptoms may well be attributable to the functional changes that occur in ventilation during sleep. Normal subjects have sleep-related decreases in functional residual capacity (FRC), peak expiratory flow rate (PEFR), minute ventilation, and tidal volume.[9]

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Asthmatics have greater loss of FRC, PEFR, and tidal volume during sleep than normal subjects.

Several studies have found circadian changes in flow rates and airway resistance (Fig. 1). Hetzel and Clark[10] found a circadian change in PEFR in normal and asthmatic subjects. The lowest values for PEFR in both the normal and asthmatic subjects occurred in the early morning hours. The asthmatic subjects had much lower values than the normal subjects, indicating more severe bronchoconstriction.

To better define the site of increased airway resistance during sleep, Bellia and colleagues[11] examined 7 asthmatic patients and compared them with 4 normal adults. Upper and lower airway resistances were measured by placing catheters in the esophagus and supraglottic areas, with the measurement of airflow at the mouth using a tight-fitting mask. The lower airway resistance was calculated as the difference between total lung resistance and supraglottic resistance at a given lung volume. An increase in lower airway resistance was responsible for the decline in PEFR. The severity of the morning decrease in PEFR in the asthmatic subjects with nocturnal symptoms closely correlated with the higher values of lower airway resistance and its duration during sleep.[11]

Those findings were confirmed by Ballard and colleagues,[12] who studied 6 asthmatic patients with nocturnal symptoms and 4 control subjects overnight on 3 separate occasions. They measured lower airway resistance during sleep using a technique similar to that of Bellia and colleagues.[12] Each patient was studied during 1 night of normal sleep, 1 night awake, and 1 night after sleep deprivation. During the night of normal sleep, asthmatic patients had much greater airway resistance than the normal subjects. During the sleep prevention night, the airway resistance in the asthmatic group was lower by a factor of 2 but still higher than that of the controls. In the normal group, airway resistance did not change significantly between normal sleep and the sleep prevention night.

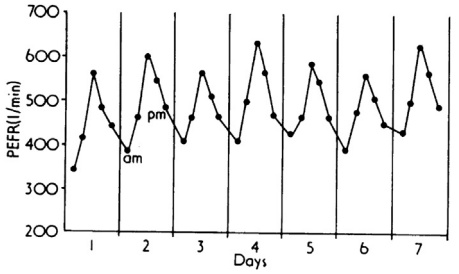

Fig. 1. Diurnal variation in peak expiratory flow rate in an asthmatic patient over four 24-hour periods. (*Adapted from* Soutar CA, Costello J, Ijaduola O, et al. Nocturnal and morning asthma. Thorax 1975;30:436; with permission.)

The studies on the effect of sleep stages on airway resistance are inconsistent, showing either no change,[12] an increase in stage N3 non–rapid eye movement (NREM) sleep,[13] or an increase in rapid eye movement (REM) sleep.[14] In a multivariate analysis of the relationship between sleep stages and sleep time and changes of airway resistance,[15] the latter part of sleep appears to be a more important determinant of increased airway resistance than the sleep stage.

The effects of sleep per se of worsening asthma and increased airway resistance are further supported by the work of Clark and Hetzel,[16] who studied asthmatic shift workers during rotating shifts with varying sleep schedules. They observed that their decline in PEFR was related to the change in sleep schedule as opposed to time of day.[16]

Spengler and Shea[17] have also addressed diurnal indices of pulmonary function. They studied 10 healthy individuals who remained awake in a semirecumbent position for 41 hours in a controlled environment with low light. They found circadian variations in forced expiratory volume in 1 second (FEV_1), cortisol, and core body temperature but not in PEFR.[17]

Bronchial Hyper-responsiveness

There is wide diurnal variation in bronchial hyperresponsiveness to histamine in asthmatic patients.[18] The variation in flow rates in a 24-hour period is related to changes in bronchial hyperresponsiveness in the subjects.[19] Several potential mechanisms exist for enhanced bronchial hyperresponsiveness in asthma, including enhanced parasympathetic tone, hormonal variations, and inflammation of the airways.

Parasympathetic System

The PEFR, specific airway conductance, and pulse rate were measured in a group of 7 asthmatic patients after an intravenous dose of atropine or placebo. The bronchoconstriction at 4 AM was almost completely reversed by atropine, suggesting a major role of the parasympathetic nervous system in nocturnal bronchoconstriction in asthma (Fig. 2).[20] The dose of atropine that completely blocked vagal activity in the bronchi was higher at 4 AM than at 4 PM. There was a strong correlation between pulse rate and PEFR at 4 AM and 4 PM, indicating increased vagal tone overnight. In the study, the changes in specific airway conductance were completely prevented at 4 AM