

# Asthma and Sleep

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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.<sup>1</sup> Airway narrowing at night is a normal physiological phenomenon, more obvious in asthmatic patients because their airways are already narrowed even in day time.

Children with asthma often suffer from night coughing, wheezing and breathlessness that disturb their sleep. Nocturnal asthma is often associated with such problems as difficulty falling asleep, restless sleep, difficulty maintaining sleep, daytime sleepiness, and daytime tiredness. The increase in airflow obstruction overnight is underassessed by children as well as by their parents. Worsening of the early morning peak flow values may be an indication for an increase in airflow obstruction overnight.<sup>2</sup>

Several underlying mechanisms that may shed light on how and why nighttime seems to exacerbate asthma symptoms include the inflammation process, airway resistance, and bronchial hyper-responsiveness (all circadian factors) as well as gastro-esophageal reflux (a non-circadian factor). It is important to understand the mechanisms of nocturnal asthma and conduct sleep assessments comprehensively in order to design and implement appropriate strategies to improve the sleep quality of patients with asthma.

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Though definitive studies remain lacking, sleep itself may play a direct role in the nocturnal worsening of asthma. Potential mechanisms for such a sleep-related effect could include the supine posture, alterations in sympathetic and parasympathetic balance, sleep-associated reductions in lung volume, intrapulmonary pooling of blood, and sleep-associated upper airway narrowing, both with and without snoring and obstructive sleep apnea (OSA).<sup>7</sup> Chronic upper airway edema, and inflammation associated with OSA may further exacerbate nocturnal asthma symptoms. Allergic rhinitis may contribute to both OSA and asthma.

A hypothetical OSA-asthma relationship that has implications on the diagnosis and management of patients presenting with either condition singly has been proposed. Treatment with CPAP therapy has been shown to improve both daytime and nighttime peak expiratory flow rates in patients with concomitant OSA and asthma.<sup>3</sup> It is important for clinicians to be aware of how OSA may complicate diagnosis and treatment of asthma and allergic rhinitis. A thorough sleep history and high clinical suspicion for OSA is indicated, particularly in asthma patients who are refractory to standard pharmacotherapy.

## Mechanism and causes of nocturnal bronchoconstriction

Nocturnal bronchoconstriction in asthma appears to be an exaggeration of the normal circadian changes in airway caliber. Asthmatic patients are hyperreactive to constrictor stimuli; thus, nocturnal bronchoconstriction in asthmatic patients is probably an expression of hyperresponsiveness to the factors that produce mild nocturnal bronchoconstriction in normal subjects.

*Circadian Rhythm:* Sleep deprivation reduces, but does not abolish nocturnal airway narrowing. Overnight airway narrowing persists even if patients are kept awake

all night.

An extensive body of research shows 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 beta2-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.

*Allergens:* Findings suggest that allergic reaction and particularly, perhaps, late or delayed allergic reactions are important in the development of nocturnal wheeze in some patients.

*Airway cooling :* It has been suggested that nocturnal asthma might be caused either by breathing cooler air at night or by bronchial wall cooling as a result of the overnight decrease in body core temperature.

*Gastroesophageal reflux (GER):* GER is common in those with asthma. 77% of asthmatics complaining of heartburn, and 41% experiencing reflux-associated respiratory symptoms. 24% of those with asthma that is difficult to control have “clinically silent” GER. Esophageal dysmotility is also common, and abnormal esophageal acid contact times on 24h esophageal pH tests were found in 82% of asthmatics examined consecutively. Most asthmatics with GER also have abnormal esophageal acid contact times while in the supine position, reflecting sleep time. Endoscopic evidence of esophagitis was found in 43% of asthmatics. Two mechanisms of bronchoconstriction induced by esophageal acid have been proposed: a vagally mediated reflex, (by which esophageal acid in the distal esophagus causes reflex bronchoconstriction,) and microaspiration. Although there is conflicting evidence, distal esophageal acid causes a decrease in peak expiratory flow rates, an increase in respiratory resistance, and an increase in minute ventilation. If microaspiration is present, there is further augmentation of this airway response. One study in a pediatric population showed that esophageal acid infusions caused more airway responses at 04:00 than at 24:00. Also, asthmatic children with nocturnal asthma symptoms have a higher reflux score, with a

positive correlation between reflux score and nighttime-associated wheezing. However, a study performed in sleeping adults with nocturnal asthma noted no alterations in airflow resistance with esophageal acid, concluding that GER contributed little to the nocturnal worsening of asthma. There are also gastroesophageal circadian issues that may influence GER in asthmatics. Gastric acid secretion peaks at approximately 21:00, and gastric emptying is delayed when a meal is given at 20:00 versus 08:00. Esophageal acid clearance is delayed significantly during sleep, and acid clearance occurs during arousals. Upper esophageal sphincter (UES) pressure also decreases with sleep onset, which may predispose to microaspiration. Further research is needed to clarify what role nocturnal reflux has on nocturnal asthma and airway inflammation and whether circadian rhythm factors alter airway responses to esophageal acid.<sup>4</sup>

*Mucociliary clearance:* This is impaired during sleep and the accumulation of mucus in the airways could contribute to nocturnal airway narrowing.

*Bronchial hyperreactivity:* bronchial responsiveness to inhaled histamine and allergens increases throughout the night.

*Endogenous opioids:* A role seems unlikely as naloxone does not significantly alter overnight bronchoconstriction.

*Inflammation:* A nocturnal increase in inflammatory mediators seems to play a role of importance. Cytokines are elaborated during the hypoxemic episodes leading to inflammatory responses marked by elevated C-reactive protein (CRP). Elevated CRP levels are considered markers of the acute phase response and characterize progression of vascular injury. It is also likely that cytokines and superoxide radicals generated during hypoxemic episodes could exacerbate reactive airway disease. Patients with Cough, Obstructive sleep apnea, Rhinosinusitis, and Esophageal reflux clustered together can be categorized by the acronym, “CORE”, syndrome.<sup>5</sup> Treatment of nocturnal airflow obstruction should therefore consider on inflammatory processes in the lungs.

## Consequences of nocturnal bronchoconstriction

Nocturnal wheezing causes inconvenience and disturbed sleep and probably also contribute to hypoxemia and death. The major complaint of patients with nocturnal

wheeze is that their sleep is interrupted and that they sometimes feel tired in the daytime. This sleep disruption has been confirmed by EEG studies, which show a decreased sleep efficiency with increased intervening wakefulness and drowsiness and in some a decrease in total sleep time. Patient with acute, severe asthma often have several worsening night with little or no sleep during their attacks. Sleep deprivation for as little as 24hr can reduce ventilatory drive by as much as one third, and such a blunting of drive may be a factor, along with fatigue and continuing bronchospasm, in the subsequent development of hypoxemia and hypercapnia in some of these patients.

Patients with nocturnal asthma can undoubtedly become hypoxemic during the night, but the hypoxemia is rarely severe in stable asthmatic patients. In stable asthmatic patients there is also no correlation between the extent of hypoxemia and the degree of overnight bronchoconstriction.

## Treatment

Nocturnal bronchoconstriction is a sign of inadequate control of asthma, and the new development of nocturnal wheeze in a patient must be regarded as a dangerous sign requiring monitoring and urgent treatment. Nocturnal wheeze often responds to increasing conventional daytime maintenance treatment. Inhalation of bronchodilators immediately before sleep, repeated whenever the patient is awakened by wheeze is the initial treatment of choice. Inhaled sympathomimetics are frequently ineffective in preventing nocturnal symptoms due to their short duration of action. While corticosteroids and anticholinergics are effective, sustained-release theophylline is particularly advantageous

for controlling nocturnal symptoms. Once-daily theophylline when dosed in the evening not only controls nocturnal symptoms and improves airflow during the early morning hours, but decreases airway responsiveness to histamine as well. The close association between airway inflammation, airway hyper-responsiveness, and nocturnal asthma symptoms makes further studies of the mechanism of action of theophylline interesting.<sup>6</sup>

In a minority of asthmatic patients whose nocturnal airway narrowing relates to their snoring or obstructive apneas, continuous positive airway pressure therapy should be tried.

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