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Review Article

Nocturnal Asthma: A Special Type of Asthma

Abstract

Nocturnal asthma is defined by a drop in forced expiratory volume in 1 second (FEV1) of at least 15% between bedtime and awakening in patients with clinical and physiologic evidence of asthma. Nocturnal asthma is associated with a circadian pattern in lung function, distal airway inflammation, glucocorticoid receptor affinity, pulmonary capillary blood volume, and beta-2 adrenergic receptor function may also contribute. Knowledge of these characteristics, along with an understanding of the specific therapies directed at the circadian nature of this disease, can result in significant improvements in lung function, sleep quality, and asthma related quality of life.

Introduction

Nocturnal asthma is defined by a drop in forced expiratory volume in 1 second (FEV1) of at least 15% between bedtime and awakening in patients with clinical and physiologic evidence of asthma. 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 hyper responsiveness. Nocturnal worsening of asthma is a well-described and important problem that must be considered in the management of patients with asthma [1]. In particular, nocturnal asthma symptoms are felt to be a characteristic feature of asthma that is not well-controlled [2,3].

Epidemiology

Nocturnal asthma is common and approximately 30 to 70 percent of patients with asthma report nocturnal asthma symptoms at least once a month [4,5]. The occurrence of nocturnal asthma symptoms is also reflected in mortality statistics. As an example, over a one-year period, 53 percent of asthma deaths in one report occurred at night [6]. In addition, 79 percent of these patients had premortem complaints of asthma affecting their sleep and occurring every night in 42 percent. Thus, nocturnal asthma symptoms suggested a deterioration in asthma control that had been present over several days.

Pathophysiology

Asthma is associated with a circadian pattern in lung function [7], with the best function typically occurring at approximately 4 PM, and the worst at around 4 AM. The normal population also experiences a circadian change in lung function, but the peak-to-trough swings in peak expiratory flow rate are only 5 to 8 percent compared to a variation of 15 to 50 percent or more in asthmatics [8]. Thus, nocturnal asthma appears to reflect an exaggeration of the effects of normal changes in neurohormonal activation that have time-related rhythms (chronobiology) [9,10]. Circadian changes in lung volume, distal airway inflammation, glucocorticoid receptor affinity, pulmonary capillary blood volume, and beta-2 adrenergic receptor function may also contribute.

Several hormones are secreted in a circadian pattern that can contribute to nocturnal airway inflammation and asthma in predisposed individuals. With cortisol, for example, peak levels occur upon awakening while trough levels are noted around midnight [11]. One study evaluated the effects of hypothalamic and pituitary control of the cortisol response in nocturnal asthma by measuring corticotropin-releasing hormone, corticotropin, and cortisol levels every two hours [12]. Corticotropin peak levels and the area under the 24-hour curve were significantly higher in nocturnal asthmatics, but these elevations were not accompanied by a commensurate increase in cortisol levels, which were the same in nocturnal asthmatics as in non-nocturnal asthmatics and healthy controls. These findings suggest a blunted adrenal response to corticotropin in nocturnal asthma, which may play a permissive role in the nocturnal worsening of asthma.

Melatonin, a sleep inducing hormone, has a proinflammatory effect in subjects with nocturnal asthma. At 4 PM, peripheral blood mononuclear cells (PBMCs) from nocturnal asthmatics produced significantly greater amounts of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha in response to costimulation with melatonin than non-nocturnal asthmatics or controls did [13]. However, at 4 AM, non-nocturnal asthmatics demonstrated an increased response to melatonin, whereas PBMCs from nocturnal asthmatics were unable to be stimulated further. These observations suggest that the nocturnal asthma phenotype is associated with a chronically enhanced inflammatory milieu, which blunts the ability of PBMCs to respond further to stimulation at night. A separate investigation focused on endogenous melatonin demonstrated that peak melatonin levels occurred at approximately 2 AM, and that these levels were significantly greater in nocturnal asthmatics [14]. Furthermore, in nocturnal asthmatics alone, peak melatonin level was inversely associated with overnight change in lung function, such that higher peak melatonin levels were associated with a greater overnight fall in lung function.

Epinephrine release also varies in a circadian fashion, with peak levels during the afternoon and trough levels during the early morning [11]. The infusion of physiologic doses of epinephrine has been reported to lessen but not abolish the overnight decline in lung function in patients with nocturnal asthma [11]. Cholinergic (vagal) tone is increased at night and may contribute to the circadian change in airway function. A role for cholinergic tone is suggested by improvement in the peak expiratory flow rate (PEFR) at 4 AM after administration of intravenous atropine, but not at 4 PM [15]. Studies of heart rate variations induced by deep breathing, Valsalva maneuver, and standing from the recumbent position in asthmatic and non-asthmatic subjects suggest enhanced parasympathetic neural drive to the sinoatrial node among subjects with asthma [16]. This observation is consistent with an association between increased parasympathetic activity and asthma.

During sleep, relative hypoventilation tends to cause reduced lung volumes, which interferes with one of the body's compensations for airflow limitation. Normally, increasing airways resistance in asthma leads to progressive air trapping and, thereby, an increase in lung volume. This hyperinflation is thought to decrease airway resistance by increasing circumferential traction on the airway walls. Conversely, when lung volumes decrease, airflow limitation increases due to decreased traction on the airways. In one study, patients with nocturnal asthma had reduced lung volumes during sleep, accompanied by greater than expected increases in airway resistance [17]. Airway resistance remained high even when lung volumes were normalized. The loss of the normal volume-resistance coupling of the respiratory system is thought to be due to inflammation of the distal airways.

Bronchial responsiveness to inhaled bronchoconstrictors is also markedly increased at night in asthmatic subjects [18,19]. Larger circadian changes in bronchial reactivity predict a greater overnight fall in peak expiratory flow rates [20].

In nocturnal asthma, inflammation predominantly affects the distal, smaller airways. This observation was illustrated in a study that obtained daytime and nighttime endobronchial (airway) and transbronchial (alveolar tissue) biopsies from patients with nocturnal asthma and asthmatics without nocturnal symptoms [21]. The greatest inflammation in nocturnal asthmatics occurred in the alveolar tissue area at 4 AM compared to 4 PM; only eosinophilic alveolar inflammation correlated with the overnight fall in lung function. These findings were supported by another study evaluating epithelial cell markers obtained by brushing the proximal and distal airways [22]. Only in the nocturnal asthma group was the expression of CD51 (vitronectin and fibronectin receptor) correlated to airway obstruction at 4 AM. This increase in CD51 in nocturnal asthma patients suggested a relationship to the lung inflammatory and repair processes in response to injury.

Since the CD4+ T-lymphocyte is felt to be the principal controller cell in eosinophil recruitment, lymphocyte and eosinophil influx into the alveolar tissue was evaluated at 4 AM and 4 PM [23]. At 4 AM, there were more alveolar tissue CD4+ cells in the nocturnal asthma group compared to the asthma control group. In addition, only alveolar tissue and not airway tissue CD4+ cells correlated inversely to lung function and positively with EG2+ eosinophils (activated and/or secreted) [23].

Several studies have shown increased airway eosinophils, neutrophils, CD4 lymphocytes, superoxide production, and mediators of bronchoconstriction when bronchoalveolar lavage is performed at 4 AM in subjects with nocturnal asthma [23,24]. Furthermore, nocturnal lung function significantly improves when the inflammatory process is altered. Inhaled antiinflammatory agents may have difficulty reaching the small airways and alveoli due to the relatively large particle size of most inhaled glucocorticoids. Inhaled glucocorticoid preparations with extra fine particle size (<2 microns mass medium aerodynamic diameter), such as HFA-beclomethasone dipropionate, ciclesonide, and HFA-flunisolide, may reduce peripheral lung inflammation [25,26]. Oral glucocorticoids, 50 mg oral dose of prednisone at 3 PM, significantly reduced the overnight fall in FEV_1 and produced a reduction in all cell types obtained by bronchoalveolar lavage compared with the same dose at 8 AM or 8 PM [27].

The levels of mast cell mediators such as leukotrienes, interleukins, and histamine have also been shown to be elevated at night in asthmatics with nocturnal worsening and, for certain mediators, in normal subjects as well [16,30,35,36]. Increased levels of exhaled nitric oxide (eNO) are hypothesized to reflect airway inflammation in patients with asthma [28]. In a study designed to evaluate circadian variations in exhaled NO in nocturnal asthmatics [29] showed that mean exhaled NO concentrations were significantly higher at all circadian time points in subjects with nocturnal asthma than in subjects with non-nocturnal asthma or in control subjects. Mean eNO levels correlated with variations in peak expiratory flow rates of >15% between 4 AM and 4 PM ($r = 0.61$; $P < 0.01$) but not with FEV1.

Since the inflammatory response is increased at night, the question arises if the glucocorticoid receptor functions appropriately during that time period. One investigation demonstrated that glucocorticoid receptor binding affinity as well as glucocorticoid responsiveness exhibited a circadian variation in subjects with nocturnal asthma. There was a reduced binding affinity and suppression of peripheral blood mononuclear cell proliferation at 4 AM. This was not observed in normal subjects or asthma control subjects. Thus, inhibition of the anti-inflammatory effect of glucocorticoids occurs at night and may contribute to the nocturnal inflammation discussed above [30].

In patients with nocturnal asthma, unlike asthmatics without nocturnal asthma symptoms, the capillary blood volume significantly increases during sleep by 16 percent [31]. This may be a contributing factor in recruiting additional inflammatory cells and producing more edema in the airways.

Both the number and physiologic function of beta-2 receptors are significantly decreased from 4 PM to 4 AM in asthmatics with nocturnal worsening compared to non-nocturnal asthmatics and normal controls. This phenotypic down regulation may be related to a polymorphism within the genetic coding block of the beta-2 receptor. Specifically, glycine at position 16 (Gly16) imparts an accelerated down regulation of the receptor compared to arginine at

this position [32]. In one study, the frequency of the Gly16 allele was 80 percent among nocturnal asthmatics, compared to 52 percent for non-nocturnal asthmatics (odds ratio [OR] 3.8) [33]. A subsequent meta-analysis of this study and four others noted a similarly increased frequency of the Gly16 allele among nocturnal asthmatics compared to non-nocturnal asthmatic control patients (OR 2.2; 95% CI 1.56-3.11) [32].

Clinical manifestations

The typical presentation of nocturnal asthma is the occurrence of typical asthma symptoms (eg, shortness of breath, chest tightness, wheezing, and cough) in a patient with daytime asthma symptoms. The frequency and severity of nocturnal asthma symptoms usually parallel daytime asthma symptoms and the degree of airflow limitation. For most adults with asthma, nocturnal awakenings due to asthma occurring twice a month or less often correlate with daytime asthma symptoms two or fewer days a week and normal spirometry; nocturnal awakenings occurring one to three nights a week correlate with daytime symptoms more than two days a week and mild airflow limitation on spirometry or peak flow; and nocturnal awakenings four or more nights a week correlate with asthma symptoms throughout the day and a forced expiratory volume in one second or peak flow of less than 60 percent of predicted. Similar correlations are described in children.

While some patients find nocturnal symptoms particularly bothersome, others are less troubled by the symptoms and fail to report them unless specifically questioned.

Evaluation and diagnosis

The evaluation and diagnosis of nocturnal asthma parallels that of asthma in general. The first step is confirmation of the diagnosis of asthma, which is based on a history of typical, intermittent symptoms of asthma, demonstration of reversible airflow limitation (preferably by spirometry), and exclusion of alternative diagnoses. Frequently, the diagnosis is clear, based on known underlying asthma and response to a trial of therapy. If symptoms do not respond to empiric therapy, objective confirmation may be needed.

Initial evaluation and a trial of therapy

For patients with a clear diagnosis of asthma, typical asthma symptoms occurring during the night or in the early morning are usually due to asthma. At the time of new onset nocturnal symptoms, we typically obtain office spirometry to assess daytime asthma control and to guide selection of controller medication(s) for initial therapy, as described below. If nocturnal symptoms respond to empiric treatment of asthma, further diagnostic testing is not necessary.

For patients without a prior diagnosis of asthma, we obtain spirometry before and after inhaled bronchodilator to assess for reversible airflow limitation [2,3]. If spirometry is normal, the next step can either be a trial of empiric therapy for asthma or bronchoprovocation testing, depending on the preference of the patient and physician. If spirometry shows normal airflow, but reduced lung volumes, we consider other possible explanations for symptoms, such as heart failure or hypersensitivity pneumonitis among others.

Laboratory tests such as total IgE and an eosinophil count are generally not helpful. If heart failure appears likely, a plasma brain natriuretic peptide is obtained. When hypersensitivity pneumonitis is considered, serologic tests for suspected inciting agents are sent. Bronchoscopy with bronchoalveolar lavage (BAL) may also be useful in diagnosing hypersensitivity pneumonitis.

The chest radiograph almost always shows normal or slightly hyper inflated lung parenchyma in patients with asthma. A chest radiograph is more likely to be helpful when heart failure or hypersensitivity pneumonitis are suspected.

Objective confirmation

If nocturnal symptoms do not respond to empiric asthma therapy, the next step is usually to obtain objective confirmation that the nocturnal symptoms are associated with airflow limitation. The simplest device for home measurement of airflow is the peak expiratory flow (PEF) meter. PEF is typically measured at bedtime and on arising in the morning. However, it is also useful to obtain PEF measurements if the patient awakens for any reason during the night. That is, many asthmatic patients, do not perceive bronchoconstrictive symptoms very well, particularly at night. A PEF measurement can be of value at this point for both the patient and care giver.

PEF variability of 15 percent or greater is consistent with asthma. However, the lack of PEF variability does not exclude the possibility of nocturnal asthma. It has been demonstrated that twice daily measurements of PEF fail to detect 55 to 80 percent of the maximum circadian variability [33]. This does not imply that variability in PEF measurements is not found. Additional information about peak flow monitoring is provided separately. Other devices that measure both PEF and forced expiratory volume in one second (FEV_1) can also be used and may give additional information.

Assessment of contributing factors

For patients with infrequent nocturnal asthma symptoms, the potential contribution of factors, such as environmental allergens, cigarette smoking, and gastroesophageal reflux, is assessed with a series of assessment questions such as those in the table. The need for further evaluation is based on the responses to questioning. When a particular allergen exposure is suspected (eg, animal dander), skin testing or allergen immunoassays can be used for confirmation of sensitivity.

When assessing potential allergen triggers, it is important to remember that asthmatic responses to a given allergen exposure can be circadian dependent. A late asthmatic response (LAR) from allergen exposure is generally stated to occur in approximately 40 to 50 percent of asthmatic patients and is manifest by a recurrence of asthma symptoms several hours after the initial exposure [34,35]. However, the likelihood of an LAR is dependent on the time of inhalation exposure. If the exposure occurs in the evening instead of the morning, a LAR develops in close to 100 percent of sensitive asthmatics [36]. As an example, if a sensitive asthmatic comes in contact with a cat during the daytime, both an immediate and LAR will be seen about 40 to 50 percent of the time. If the exposure occurs in the evening, close to 100 percent will develop both immediate and LAR.

For patients with refractory nocturnal symptoms, a more thorough assessment is appropriate and may include allergy skin testing, an empiric trial of anti-GERD therapy, and possibly overnight polysomnography.

Management

The goals of management of nocturnal asthma include reduction of symptoms, improvement in lung function, and reduction in risk of an exacerbation, essentially the goals of asthma care as outlined by national and international guidelines [2,3]. Therapy of nocturnal asthma is generally based on the severity and frequency of symptoms. Specific interventions include optimization of the medication regimen. Indirect therapies include control of contributing factors such as allergen exposure, rhinitis and sinusitis, gastroesophageal reflux, and sleep apnea.

Indirect therapies, such as control of rhinitis, sinusitis, gastroesophageal reflux, and obstructive sleep apnea, relieve nocturnal asthma symptoms in a small proportion of the asthmatic population. For a given patient, however, they may be of significant importance in controlling the nocturnal component of asthma. There may also be a beneficial carryover to daytime lung function and symptom control.

While nocturnal allergen exposure does not explain nocturnal asthma symptoms in general, dust mite, dog/cat, and other sensitivities must be considered in individual patients, and interventions should be taken, ranging from elimination to desensitization [37,38].

Laryngeal clearance mechanisms are decreased during sleep [39]. As a result, asthmatic patients with chronic nasal and sinus disease can aspirate the inflammatory components of "postnasal drip." One study in an animal model showed that induced sinus inflammation does not produce an increase in pulmonary resistance by itself, but airway resistance will increase if aspiration of inflammatory components occurs [40].

Gastroesophageal reflux (GER) is common in patients with asthma and has been identified as a potential trigger for asthma. However, the relationship between GER and nocturnal asthma is controversial. The treatment of GER and its role in asthma management are discussed separately.

In a cross-sectional study of 2202 subjects from the general population, subjects with nocturnal GER symptoms (eg, belching, heartburn) were more likely to report nocturnal breathlessness and to have greater peak flow variability compared with those without GER [41]. In awake asthmatics with a diagnosis of GER, acid infusion in the supine position produced a decrease in peak flows and an increase in specific airway resistance [42].

On the other hand, at least two studies suggest a lack of influence of GER in nocturnal asthma. In one study, hydrochloric acid was infused during sleep with simultaneous and continuous measurements of lower airway resistance and esophageal pH [43]. The increase in lower airway resistance over the night was not affected by the presence or absence of acid in the esophagus. Additionally, in a small double-blind crossover study in nocturnal asthmatics with gastroesophageal reflux, there were no differences in peak expiratory flow measurements, symptoms, or bronchodilator use in patients treated with placebo versus omeprazole [44].

Nonetheless, GER with aspiration could play a role in nocturnal asthma in a given patient. Treatment of GER in nocturnal asthma should be based upon symptoms of reflux, and not worsening of asthma. The possibility of reflux with aspiration should be considered if the patient complains of a sour taste in the mouth upon arising or has unexplained opacities on the chest radiograph.

Obstructive sleep apnea (OSA) is a cause of nocturnal awakening and is in the differential diagnosis of nocturnal asthma. In addition, OSA that coexists with asthma can cause worsening of nocturnal asthma [45]. Management of OSA is discussed separately.

A few case series have described improvement in nocturnal and daytime asthma symptoms with treatment of OSA. In one report, for example, all such patients treated with nasal continuous positive airway pressure (nasal CPAP) experienced a marked improvement in nocturnal and daytime asthma symptoms with an associated reduction in the use of bronchodilators and lung function [45]. The exact reason for improved lung function with treatment of OSA is not clear. Proposed mechanisms include elimination of pharyngeal/laryngeal irritation that can cause reflex bronchoconstriction [46], improvement in hypoxia, and/or decreased vagal tone. Nocturnal asthma is not improved with nasal CPAP in the absence of sleep apnea [47].

Infrequent nocturnal asthma

Most patients with asthma have occasional nocturnal symptoms that are treated with use of a short-acting beta agonist medication for quick relief. As long as these symptoms occur less than once or twice a month, additional controller medication (eg, inhaled glucocorticoids) is not needed. However, it is reasonable to determine whether nocturnal allergen exposure, allergic or nonallergic rhinosinusitis, or gastroesophageal reflux are contributing to these intermittent symptoms, as preventive measures may reduce the frequency of nocturnal asthma symptoms.

Nocturnal symptoms due to poor control of asthma

Patients who have nocturnal asthma symptoms one or more times per week meet criteria for asthma that is not-well controlled. These patients typically also have daytime symptoms consistent with suboptimal asthma control. Based on the National Heart, Blood, and Lung Institute Expert Panel Report 3, these patients are candidates for enhanced controller therapy of their asthma in addition to use of a SABA for quick relief of the nocturnal symptoms [2]. A step-wise approach to asthma management is provided separately, so the following discussion will focus on the role of these medications in nocturnal asthma.

Controller therapies include initiation of or an increase in dose of inhaled glucocorticoids, addition of a long-acting inhaled beta-2 agonist or a long-acting anticholinergic medication for patients already taking an inhaled glucocorticoid. Alternatives include a once-daily sustained theophylline preparation or a leukotriene modifier. In addition, these patients may need an initial course of oral glucocorticoids to gain control of their asthma.

As with patients who have infrequent nocturnal symptoms, environmental controls, treatment of rhinitis or sinusitis, and treatment of GER should be implemented, as described above.

Inhaled glucocorticoids: Inhaled glucocorticoids are the mainstay of controller therapy in asthma. Most inhaled glucocorticoids are dosed twice daily, but some studies have examined the effect of a single daily dose at various time points. Inhaled glucocorticoids dosed at 3 PM produce equal or better efficiency than when dosed four times daily or once daily at either 8 AM or 5:30 PM [48,49].

Attention to timing of dosing and duration of action of beta-2 agonists is often beneficial in nocturnal asthma.

Long-acting beta agonists: Long-acting inhaled beta-2 agonists (LABAs) are indicated in patients whose nocturnal asthma symptoms are not controlled with inhaled glucocorticoids alone and are always used in combination with an inhaled glucocorticoid. However, early studies evaluating the role of LABAs in nocturnal asthma used monotherapy: this practice is not recommended [50-52].

LABAs can lead to improved overnight lung function but not total elimination of the nocturnal decrement in lung function. As an example, in one double-blind, placebo-controlled study of 20 patients with nocturnal asthma, salmeterol at a dose of 50 mcg twice daily significantly improved overnight PEFR by a mean value of 69 L/min and led to an improvement in sleep quality [50]. A higher dose (100 mcg twice daily), however, may produce central stimulation and decreased slow wave sleep [50]. Other studies of salmeterol in nocturnal asthma have demonstrated its efficacy not only in improving overnight lung function but also improving both global and domain scores on the Asthma Quality of Life Questionnaire [53].

Theophylline: Controlled release theophylline preparations differ in their pharmacokinetics and, therefore, improve or stabilize nocturnal pulmonary function to a greater or lesser degree.

One dosing schedule strategy is to administer a once-daily preparation (eg, Uniphyl) in the evening at 6 to 7 PM, aiming for theophylline levels of 10 to 15 mg/mL at night in order to attenuate nocturnal symptoms and early morning bronchoconstriction. Daytime levels fall to approximately 8 mg/mL without deterioration in asthma control. Lung function is better during the day, so that comparably high drug levels are not needed at that time. This regimen has been found to be clinically superior to conventional twice daily dosing [54,55] and can improve patient compliance.

In addition to having a bronchodilator effect, theophylline is thought to have a mild anti-inflammatory effect. When administered to patients with nocturnal asthma, theophylline decreases neutrophil influx into the lung and reduces leukotriene B4 levels from alveolar macrophages measured in the early morning [56].

Comparison of inhaled salmeterol and sustained-release oral theophylline suggests that effectiveness in controlling nocturnal asthma is not significantly different between the two agents [57]. However, there may be fewer nocturnal arousals with inhaled salmeterol than with sustained release oral theophylline.

Agents affecting leukotriene synthesis or action: Studies have demonstrated that montelukast and zafirlukast (LTD4 receptor antagonists) and also zileuton (a 5-lipoxygenase inhibitor) can improve nocturnal asthma [58,59]. These agents are typically used as add-on therapy in patients whose asthma is refractory to a medium to high dose of inhaled glucocorticoids.

Oral glucocorticoids: Nocturnal asthma symptoms are often a sign of deteriorating asthma control and may warrant a brief course of oral glucocorticoids for an acute asthma exacerbation. Infrequently, oral glucocorticoids are indicated for patients with persistent asthma symptoms despite maximal inhaled medications and control of asthma triggers. Efforts are redoubled to remove any asthma triggers and to optimize the medication regimen, which may include adding anti-IgE therapy (omalizumab).

Conclusions

Nocturnal asthma is an important asthma phenotype which, if not treated appropriately, can result in significant morbidity and mortality. Unique physiologic and inflammatory characteristics form the substrate for this phenotype. Knowledge of these characteristics, along with an understanding of the specific therapies directed at the circadian nature of this disease, can result in significant improvements in lung function, sleep quality, and asthma related quality of life.

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