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Nocturnal asthma

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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

DEFINITION AND EPIDEMIOLOGY OF NOCTURNAL ASTHMA

Nocturnal asthma is marked by a decrease in FEV₁ 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

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

airway hyperresponsiveness² and airway inflammation³ 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 FEV₁ 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

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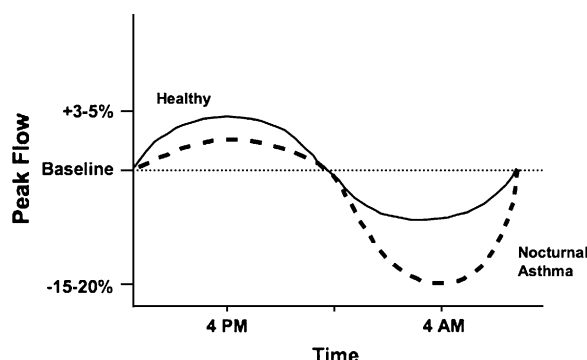


FIG 1. Both healthy individuals (solid line) and subjects with nocturnal asthma (dotted line) have circadian alterations in lung function, with nadirs occurring at approximately 4 AM. The circadian variation in lung function is increased in subjects with nocturnal asthma and might exceed 20% over the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

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 al⁹ 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 absence of hyperinflation despite increases in airflow limitation stands in contrast to the accepted relationship between airway resistance and lung volumes¹¹ and might indicate disruption of normal resistance-volume

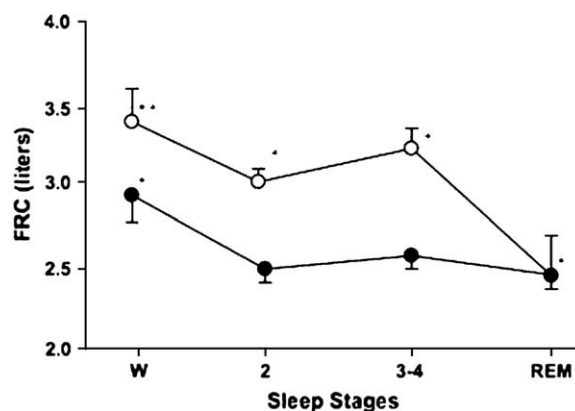


FIG 2. Changes in functional residual capacity (FRC) during sleep stages in subjects with nocturnal asthma (open circles) and healthy control subjects (filled circles). $+P < .05$ for comparison between subjects with nocturnal asthma and control subjects, $*P < .05$ for comparisons between wakefulness (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

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 al¹² 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 H₂O/L/s during early sleep to 29.8 ± 9.6 cm H₂O/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 H₂O/L/s versus 14.9 ± 1.6 cm H₂O/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 H₂O/L to 0.035 ± 0.002 cm H₂O/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

patients with nocturnal asthma, ten Hacken et al¹³ reported that mean exhaled NO concentrations were significantly higher at all circadian time points in subjects with nocturnal asthma than in subjects with nonnocturnal asthma or in control subjects but that they did not vary over the 24-hour period. Mean exhaled NO levels correlated with variations in PEFs of greater than 15% between 4 AM and 4 PM ($r = 0.61$, $P < .01$) but did not correlate with FEV₁. Although a trend toward higher NO levels at 4 AM versus 4 PM was observed, the authors were unable to demonstrate a true circadian rhythm in exhaled NO levels in patients with nocturnal asthma.¹³

A subsequent study by Georges et al¹⁴ did find a circadian variation in exhaled NO levels in patients with nocturnal asthma, but patients with nocturnal asthma demonstrated a paradoxical decrease in exhaled NO levels at night, with mean levels of 77.2 ± 8.2 ppb at 4 PM, 68.4 ± 8.7 ppb at 10 PM ($P < .003$), and 66.0 ± 8.5 ppb at 4 AM ($P < .001$). Previous studies had demonstrated that exhaled NO could decrease in the setting of bronchoconstriction,¹⁵ but when the authors adjusted for changes in FEV₁ in a mixed-model analysis, only a portion of the decrease in exhaled NO could be attributed to bronchoconstriction. The authors concluded that there is a nighttime decrease in exhaled NO levels in subjects with nocturnal asthma and speculated that decreased levels of exhaled NO at night might in fact be pathogenic in nocturnal asthma because of either a loss of NO's endogenous bronchodilatory effect or the proinflammatory activities of the conversion product peroxynitrite.¹⁴

β_2 - AND GLUCOCORTICOID RECEPTOR FUNCTION IN NOCTURNAL ASTHMA

As noted above, the bronchodilator response to β_2 -receptor agonists is reduced in nocturnal asthma,⁹ possibly due in part to the fact that both the number and physiologic function of β_2 -adrenergic receptors decrease significantly between 4 PM and 4 AM in patients with the nocturnal asthma phenotype.¹⁶ Szefer et al¹⁶ measured leukocyte β -adrenergic receptors in 7 subjects with nocturnal asthma, 10 subjects with nonnocturnal asthma, and 10 healthy control subjects. In subjects with nocturnal asthma, significant circadian differences in leukocyte β -adrenergic receptor density and function were demonstrated, with subjects with nocturnal asthma manifesting a 33% decrease in leukocyte β -adrenergic receptor density between 4 PM (294 ± 65 receptors per cell) and 4 AM (182 ± 46 receptors per cell, $P < .05$ for the comparison). This phenomenon was not observed in the other group. Additionally, although the investigators did not observe circadian differences in leukocyte β -adrenergic receptor binding affinity, in nocturnal asthma at 4 AM there was significantly lower cyclic AMP production in response to isoproterenol stimulation, with a $17\% \pm 7.3\%$ increase in leukocyte cellular cyclic AMP versus a $69.4\% \pm 13.7\%$ increase in subjects with nonnocturnal asthma ($P < .05$) and an $80.2\% \pm 21.3\%$ increase in healthy subjects. The

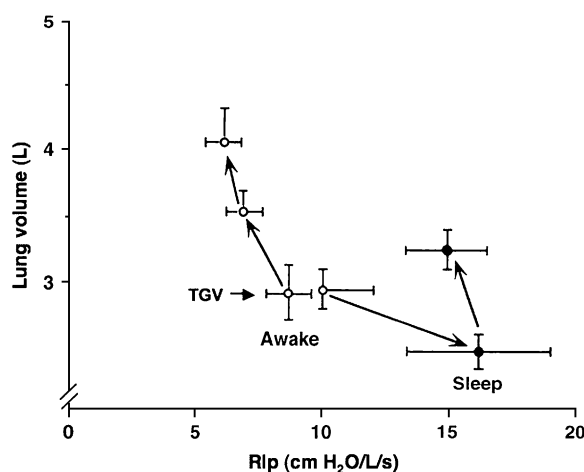


FIG 3. The effect of sleep on volume-resistance relationships in nocturnal asthma. During wakefulness (open circles), the volume-resistance relationship is intact, with increasing TGV producing a decrease in lower airway resistance (Rlp). During sleep (filled circles), lower airway resistance is increased versus wakefulness, but increases in lung volume do not result in a significant change in lower airway resistance.¹²

authors concluded that this diminished response to isoproterenol was due either to the change in leukocyte β -adrenergic receptor density or to a postreceptor abnormality.¹⁶

Subsequently, in a study investigating β -receptor polymorphisms in 23 subjects with nocturnal asthma and 22 subjects with nonnocturnal asthma, Turki et al¹⁷ demonstrated that the prevalence of the Gly16 allele was 80.4% in subjects with nocturnal asthma versus 52.2% in subjects with nonnocturnal asthma ($P = .007$). The Gly16 allele conferred a 3.8 times increased odds of nocturnal asthma, suggesting that this allele is an important factor in determining the nocturnal asthma phenotype. Although recent studies¹⁸ have suggested that adverse effects in response to long-term albuterol use might occur in patients who are homozygous for arginine (Arg/Arg) at the 16th amino acid residue of the β_2 -adrenergic receptor, the overall prevalence and effect of this genotype in subjects with nocturnal asthma is not known.

Glucocorticoid receptor (GR) binding characteristics and steroid responsiveness are also altered in patients with nocturnal asthma,¹⁹ with a significantly lower GR binding affinity at 4 AM versus 4 PM, as measured by an increased dissociation constant (Kd) at 4 AM (22.2 ± 1.6 nmol/L) when compared with that at 4 PM (10.9 ± 0.7 nmol/L, $P = .0001$ for the comparison). GR Kd, which is inversely related to receptor binding, did not change over the 24-hour period in either subjects with nonnocturnal asthma or healthy subjects. Within the group with nocturnal asthma, there was a significant inverse correlation ($r = -0.65$, $P = .04$) between the GR Kd and FEV₁ at 4 AM. This decreased affinity of the GR for corticosteroids might form the basis for nocturnal airway inflammation by decreasing the anti-inflammatory effects of both endogenous and therapeutically administered corticosteroids.¹⁹

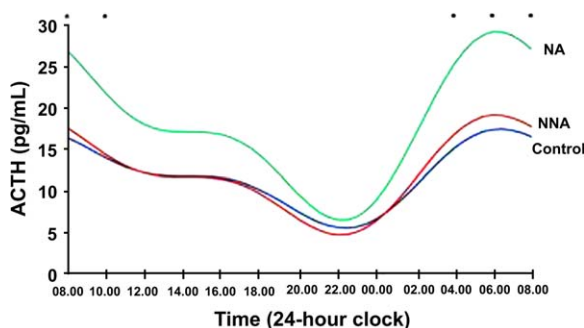


FIG 4. Modeled 24-hour corticotropin (ACTH) levels in subjects with nocturnal asthma (green), subjects with nonnocturnal asthma (red), and healthy control subjects (blue). *Subjects with nocturnal asthma > subjects with nonnocturnal asthma and control subjects ($P < .05$ at 2, 4, 6, 8, and 10 AM).²³

Alternative splicing of the GR pre-mRNA generates an isoform of the GR (GR- β), which antagonizes the transactivating activity of the classic GR. In subjects with nocturnal asthma, the expression of GR- β is significantly increased in lung macrophages ($P = .001$) when compared with that seen in subjects with nonnocturnal asthma, and this increased expression of GR- β in lung macrophages of subjects with nocturnal asthma might play a role in the decreased steroid responsiveness seen at night in nocturnal asthma.²⁰

HYPOTHALAMIC-PITUITARY-ADRENAL INTERACTIONS IN NOCTURNAL ASTHMA

In 2002, Landstra et al²¹ reported that children with nocturnal asthma demonstrated significantly reduced serum cortisol levels at 12 AM, 8 AM, and 12 PM when compared with those seen in healthy control subjects. Furthermore, the investigators identified a significant positive correlation between 24-hour mean cortisol levels and lung function at 4 AM, 8 AM, and 8 PM and an inverse correlation between FEV₁ percent predicted at all time points and the magnitude of the circadian variation in serum cortisol. When subjects with low serum cortisol levels were treated with intravenous hydrocortisone, an increase in lung function and a decrease in blood eosinophils were observed.²²

In a study designed to evaluate pituitary-adrenal axis function in nocturnal asthma, Sutherland et al²³ measured plasma corticotropin and serum cortisol levels every 2 hours over a 24-hour period in subjects with nocturnal ($n = 7$) and nonnocturnal ($n = 13$) asthma, as well as in healthy control subjects ($n = 11$). In subjects with nocturnal asthma, both peak levels of corticotropin and the area under the 24-hour corticotropin curve were significantly increased in subjects with nocturnal asthma versus levels seen in the other 2 groups (Fig 4).²³ However, a commensurate increase in cortisol levels was not observed in subjects with nocturnal asthma, suggesting that adrenal responsiveness to corticotropin is blunted in nocturnal asthma (Fig 5).²³

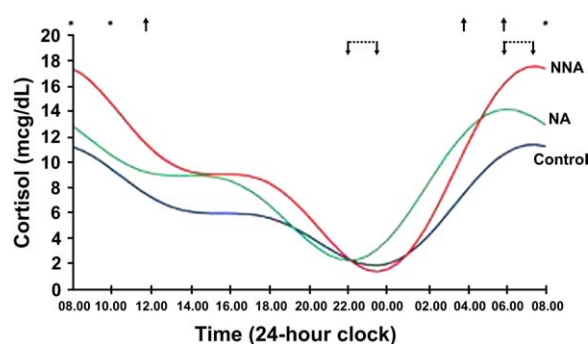


FIG 5. Modeled 24-hour cortisol levels in subjects with nocturnal asthma (green), subjects with nonnocturnal asthma (red), and healthy control subjects (blue). Connected arrows indicate a phase difference in peak and trough cortisol times in subjects with nocturnal asthma versus subjects with nonnocturnal asthma and control subjects (see text). *Subjects with nonnocturnal asthma > subjects with nocturnal asthma and control subjects ($P < .05$ for both comparisons at 8 and 10 AM). †Subjects with nonnocturnal asthma > control subjects ($P < .05$ at 4, 6, and 12 AM).²³

MELATONIN, INFLAMMATION, AND LUNG FUNCTION IN NOCTURNAL ASTHMA

Another recent development in understanding the role of the hormonal environment in nocturnal asthma is the observation that melatonin might play a role in circadian variations in lung function and inflammation. In both subjects with nocturnal asthma and those with nonnocturnal asthma, melatonin costimulation of PBMCs results in increased production of IL-1, IL-6, and TNF- α when compared with that seen in cells stimulated with zymosan alone, suggesting that although melatonin is proinflammatory, this might be independent of asthma phenotype.²⁴ When studied *in vivo*, however, melatonin levels are higher in patients with nocturnal asthma than in both patients with nonnocturnal asthma and healthy control subjects. In subjects with nocturnal asthma, there is an inverse correlation between melatonin level and overnight decrease in lung function ($r = -0.79$ [$P = .04$] vs $r = -0.24$ [$P = .44$] in subjects with nonnocturnal asthma and $r = 0.43$ [$P = .19$] in healthy control subjects, Fig 6).²⁵

AIRWAY INFLAMMATION IN NOCTURNAL ASTHMA

Biopsy studies of patients with nocturnal asthma have provided insights into small airway inflammation in asthma. In 1996, Kraft et al³ reported that both small airway (diameter <2 mm) and alveolar tissue inflammation could be observed in subjects with nocturnal asthma and that circadian variations in alveolar tissue inflammation might play an important role in the pathogenesis of nocturnal asthma. The investigators evaluated 21 subjects, 11 of whom had nocturnal asthma and 10 of whom had nonnocturnal asthma. All participants underwent bronchoscopy

with endobronchial and transbronchial biopsy at both 4 PM (the time of peak lung function) and 4 AM, when airflow limitation was at its worst.

In those with nocturnal asthma, a significant increase in the number of eosinophils per unit volume was observed in transbronchial biopsy specimens at 4 AM when compared with those of subjects with nonnocturnal asthma (median of 40.2×10^3 and interquartile range [IQR] of $26.4\text{--}57.1 \times 10^3$ cells/mm³ vs median of 15.7×10^3 and IQR of $2.1\text{--}35.2 \times 10^3$ cells/mm³, $P = .05$ for the comparison). However, comparisons of eosinophilic inflammation in the larger airway specimens obtained by means of endobronchial biopsy did not demonstrate significant differences between the nocturnal and nonnocturnal phenotypes, suggesting that a circadian difference in distal lung (small airway and alveolar) inflammation could be occurring. Thus further analysis comparing transbronchial biopsy specimens obtained at the 2 different time points was performed. This revealed that in tissue from subjects with nocturnal asthma, there was a circadian variation in the number per unit volume of alveolar eosinophils, with a significantly greater number present at 4 AM versus 4 PM ($41.4 \pm 8.6 \times 10^3$ vs $12.9 \pm 4.3 \times 10^3$ cells/mm³, $P = .005$). Increases in alveolar eosinophils in subjects with nocturnal asthma correlated with nocturnal decrements in FEV₁ ($r = -0.54$, $P = .03$).³

A circadian increase in tissue macrophages was also observed in alveolar tissue from subjects with nocturnal asthma, but similar circadian differences in inflammatory phenotype were not observed in the endobronchial (larger airway) biopsy specimens of subjects with nocturnal asthma. In asthmatic subjects who did not have the nocturnal phenotype, no significant difference in either alveolar or larger airway inflammation could be demonstrated.

A subsequent study by Kraft et al²⁶ evaluated the role of T lymphocytes in alveolar tissue inflammation in patients with nocturnal asthma. At 4 AM, subjects with nocturnal asthma had significantly greater numbers of CD4⁺ lymphocytes in alveolar tissue than did subjects with nonnocturnal asthma (median of 9.8/mm² and IQR of 5.6–30.8/mm² vs median of 1.5/mm² and IQR of 0–6.3/mm², $P = .04$ for the comparison). Alveolar CD4⁺ cells correlated positively with the number of EG2⁺ eosinophils ($r = 0.66$, $P = .01$) and inversely with FEV₁ ($r = -0.68$, $P = .0018$) at 4 AM.²⁶

Although patients with nocturnal asthma typically meet criteria for moderate or severe persistent asthma, circadian changes in lung function can be seen in patients with more mild asthma. In 2004, Kelly et al²⁷ investigated circadian changes in airway inflammation in patients with mild atopic asthma (mean FEV₁ of $93\% \pm 4\%$ of predicted value). In this patient population bronchoalveolar lavage fluid contained increased numbers of macrophages, neutrophils, and CD4⁺ T lymphocytes at 4 AM versus 4 PM. Additionally, the percentage of CD4⁺ T lymphocytes in the 4 AM lavage fluid was inversely correlated with 4 AM FEV₁.

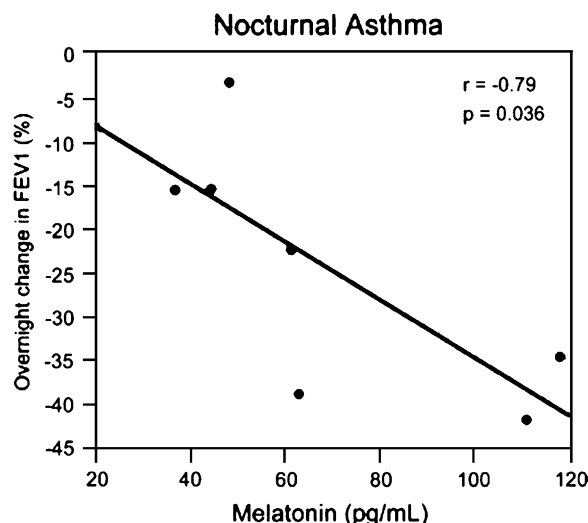


FIG 6. Inverse correlation between peak serum melatonin level and percentage overnight change in FEV₁ in subjects with nocturnal asthma.²⁵

TREATMENT OF NOCTURNAL ASTHMA

The majority of patients with significant nocturnal symptoms will meet diagnostic criteria for moderate or severe persistent asthma and should be treated according to national and international guidelines.²⁸ Many of the agents recommended for the treatment of persistent asthma have been specifically evaluated in patients with nocturnal asthma, with a focus on dosing strategies that optimize therapeutic drug effect during periods of nocturnal worsening.

Pincus et al²⁹ compared the efficacy of chronotherapeutic dosing of 800 µg of inhaled triamcinolone once daily at 3 PM versus the traditional dose of 200 µg 4 times daily in a cohort of 30 asthmatic subjects, 17 of whom (8 in the once-daily group and 9 in the 4-times-daily group) had nocturnal asthma. The authors showed that once-daily dosing at 3 PM was equally efficacious and did not increase side effects versus traditional 4-times-daily dosing. When these authors compared the effects of more convenient once-daily dosing schedules (8 AM or 5:30 PM) with those of traditional 4-times-daily dosing, they showed that early evening (5:30 PM) dosing was preferable to morning (8 AM) dosing, which did not produce comparable effects to 4-times-daily dosing with regard to morning or evening peak flow.³⁰

When oral corticosteroid therapy is required, chronotherapy can be particularly useful. Beam et al³¹ used a double-blind, placebo-controlled, crossover design to evaluate the effect of a variably timed 50-mg oral dose of prednisone given at 8 AM, 3 PM, or 8 PM on overnight spirometry, blood eosinophil counts, and bronchoalveolar lavage cytology in 7 subjects with nocturnal asthma. Compared with placebo, a single prednisone dose at 3 PM resulted in a reduction in the overnight percentage

decrease in FEV₁ ($28.2\% \pm 7.3\%$ decrease vs $10.4\% \pm 4.5\%$ decrease, $P = .04$) and improvement in the 4 AM FEV₁ (2.53 ± 0.38 L vs 3.43 ± 0.38 L, $P = .03$), an improvement not seen when prednisone was given at 8 AM or 8 PM. Additionally, the 3 PM prednisone dose significantly reduced peripheral blood eosinophil counts at both 8 PM and 4 AM. The authors concluded that a chronopharmacologic strategy for prednisone dosing could alter the inflammatory milieu and spirometric decrease associated with nocturnal worsening of asthma.³¹

Long-acting β -agonists have been evaluated in nocturnal asthma, although current recommendations dictate that these not be used as monotherapy for the control of asthma but rather as an additional controller agent in conjunction with inhaled corticosteroids. In 1999, Lockey et al³² evaluated salmeterol's effects on spirometric indices and asthma-specific quality of life in 474 patients with symptomatic nocturnal asthma. Patients were allowed to continue the use of theophylline if previously prescribed and were stratified on the basis of serum theophylline level. As-needed albuterol was continued, and patients received either 42 μ g of salmeterol twice daily or placebo in a double-blind, placebo-controlled fashion. Throughout the study there was a significant improvement in asthma-specific quality of life ($P \leq .005$) in the salmeterol group compared with baseline values. Morning PEF and mean FEV₁ were both significantly improved in the treatment group ($P \leq .002$ and $P \leq .004$, respectively). The effect on morning PEF was seen independent of subjects' theophylline use. Salmeterol significantly increased the percentage of nights uninterrupted by awakenings caused by asthma symptoms from 28% to 77% by the end of the treatment periods versus 28% to 49% in those subjects receiving placebo ($P < .001$). Rescue albuterol use was also significantly decreased in the salmeterol treatment group.³²

Inhaled anticholinergics have little effect on the overnight decrease in pulmonary function seen in patients with nocturnal asthma. Much of this lack of effect is due to the short half-life of currently available inhaled anticholinergic drugs. Coe and Barnes³³ studied the effect of the anticholinergic oxitropium bromide in a low-dose regimen (0.2 mg) administered at bedtime. They were able to identify a group of subjects with improvements in overnight lung function but could not identify features that differentiated responders from nonresponders.

Theophylline is an effective treatment for nocturnal asthma. Barnes et al³⁴ conducted a study in 12 subjects with nocturnal asthma to determine whether theophylline, administered as a single nighttime dose, could achieve therapeutic drug levels and ameliorate nocturnal symptoms. They used a slow-release preparation of theophylline and targeted therapeutic levels of 8 to 15 mg/L (mean, 10.9 mg/L) 10 hours after administration. With this dosing strategy, they showed significant improvements in morning PEF, with PEF of 332 ± 31 L/min during treatment versus 283 ± 32 L/min during placebo ($P < .001$). There was also a significant decrease in rescue salbutamol (albuterol) use during treatment with

theophylline. Many other studies³⁵⁻³⁷ of sustained-release theophylline in nocturnal asthma have shown similar results, with improved morning peak flow rates, decreased awakenings, decreased use of rescue inhalers, and subjective improvement in symptoms.

Control of nocturnal asthma appears to depend on the type and dosing schedule of sustained-release theophylline preparations.³⁶ Theophylline can be administered according to a chronopharmacologic strategy, timing the dose to achieve therapeutic efficacy at the nadir of lung function in nocturnal asthma. Martin et al³⁶ compared twice-daily sustained-release theophylline versus once-daily sustained-release theophylline in subjects with nocturnal asthma and demonstrated that administration of the once-daily preparation at 7 PM resulted in higher serum theophylline concentration at night than did an equivalent dose of the twice-daily preparation given at 7 PM and 7 AM. The 7 AM FEV₁ was higher in subjects who received the once-daily preparation. These findings suggest that if theophylline is to be used, subjects with nocturnal asthma derive benefit from a therapeutic regimen designed to achieve peak serum theophylline concentrations at the time of night when airflow limitation is greatest (ie, approximately 4 AM).

TREATMENT OF COMORBID CONDITIONS

Reflux of gastric acid, which can occur during sleep because of a combination of increased gastric acid secretion and supine posture, might result in reflex bronchospasm from increased vagal tone,³⁸ leading to increased airflow limitation and symptoms at night. A cross-sectional population survey of 2661 subjects from Iceland, Belgium, and Sweden indicated that patients with nocturnal gastroesophageal reflux (as measured by means of patient self-report) were more likely to report wheezing, breathlessness at rest, and nocturnal breathlessness and to demonstrate greater peak flow variability than were patients without reflux symptoms.³⁹ However, a small study by Tan et al⁴⁰ failed to demonstrate an association between periods of spontaneous or induced acid reflux and either increases in lower airway resistance or decreases in lung function. These authors did not examine concurrent aspiration, and therefore although reflux of gastric acid did not appear to be a direct trigger of bronchoconstriction, aspiration as a potential trigger was not excluded.

The Cochrane Collaboration⁴¹ has reviewed clinical trials of the treatment of gastroesophageal reflux in patients with nocturnal asthma, reporting that although a number of individual trials of both H₂-receptor antagonists and proton-pump inhibitors have been shown to reduce nocturnal symptoms in asthmatic subjects,⁴²⁻⁴⁴ at least 3 other trials have failed to show an improvement.⁴⁵⁻⁴⁷ Given the lack of a clear understanding of the association between gastroesophageal reflux and nocturnal asthma, empiric treatment of gastroesophageal reflux in asthma should be considered in patients with significant nocturnal symptoms who respond suboptimally to therapies described above.

Nasal continuous positive airway pressure (CPAP) has a role in patients with nocturnal asthma and comorbid obstructive sleep apnea. Chan et al⁴⁸ showed that nasal CPAP resulted in significant improvements in both morning and evening PEF, symptoms, and medication use in patients with nocturnal asthma and obstructive sleep apnea. Nasal CPAP does not improve the overnight decrease in FEV₁ in patients with nocturnal asthma in the absence of obstructive sleep apnea, however.⁴⁹ In addition to increasing the risk for obstructive sleep apnea, obesity has also been reported to be associated with nocturnal asthma.⁵⁰ In obese asthmatic subjects significant weight loss can reduce peak flow variability and improve FEV₁, midexpiratory flow rates, and airway resistance reported in response to weight loss.⁵¹

CONCLUSION

In conclusion, nocturnal asthma is a frequently encountered asthma phenotype that is characterized by circadian variations in inflammation and physiology. Awareness of these characteristics, along with an understanding of appropriate therapeutic strategies, can result in significant improvements in lung function, sleep quality, and asthma-related quality of life.

REFERENCES

- Martin RJ. Location of airway inflammation in asthma and the relationship to circadian change in lung function. *Chronobiol Int* 1999;16: 623-30.
- Martin RJ, Cicutto LC, Ballard RD. Factors related to the nocturnal worsening of asthma. *Am Rev Respir Dis* 1990;141:33-8.
- Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. *Am J Respir Crit Care Med* 1996;154: 1505-10.
- Van Keimpema AR, Ariansz M, Tamminga JJ, Nauta JJ, Postmus PE. Nocturnal waking and morning dip of peak expiratory flow in clinically stable asthma patients during treatment. Occurrence and patient characteristics. *Respiration* 1997;64:29-34.
- Turner-Warwick M. Epidemiology of nocturnal asthma. *Am J Med* 1988;85:6-8.
- Dethlefsen U, Reppas R. Ein neues Therapieprinzip bei Nachtlichen Asthma. *Klin Med* 1985;80:44-7.
- Hetzel MR, Clark TJ, Branthwaite MA. Asthma: analysis of sudden deaths and ventilatory arrests in hospital. *BMJ* 1977;1:808-11.
- Cochrane GM, Clark JH. A survey of asthma mortality in patients between ages 35 and 64 in the Greater London hospitals in 1971. *Thorax* 1975;30:300-5.
- Hendeles L, Beaty R, Ahrens R, Stevens G, Harman EM. Response to inhaled albuterol during nocturnal asthma. *J Allergy Clin Immunol* 2004;113:1058-62.
- Ballard RD, Irvin CG, Martin RJ, Pak J, Pandey R, White DP. Influence of sleep on lung volume in asthmatic patients and normal subjects. *J Appl Physiol* 1990;68:2034-41.
- Briscoe WA, Dubois AB. The relationship between airways resistance, airways conductance and lung volume in subjects of different age and body size. *J Clin Invest* 1958;37:1279-85.
- Irvin CG, Pak J, Martin RJ. Airway-parenchyma uncoupling in nocturnal asthma. *Am J Respir Crit Care Med* 2000;161:50-6.
- ten Hacken NH, van der Vaart H, van der Mark TW, Koeter GH, Postma DS. Exhaled nitric oxide is higher both at day and night in subjects with nocturnal asthma. *Am J Respir Crit Care Med* 1998;158:902-7.
- Georges G, Bartelson BB, Martin RJ, Silkoff PE. Circadian variation in exhaled nitric oxide in nocturnal asthma. *J Asthma* 1999;36:467-73.
- Silkoff PE, McClean PA, Slutsky AS, Caramori M, Chapman KR, Gutierrez C, et al. Exhaled nitric oxide and bronchial reactivity during and after inhaled beclomethasone in mild asthma. *J Asthma* 1998;35: 473-9.
- Szeffler SJ, Ando R, Cicutto LC, Surs W, Hill MR, Martin RJ. Plasma histamine, epinephrine, cortisol, and leukocyte beta-adrenergic receptors in nocturnal asthma. *Clin Pharmacol Ther* 1991;49:59-68.
- Turki J, Pak J, Green SA, Martin RJ, Liggett SB. Genetic polymorphisms of the beta 2-adrenergic receptor in nocturnal and nonnocturnal asthma. Evidence that Gly16 correlates with the nocturnal phenotype. *J Clin Invest* 1995;95:1635-41.
- Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniack R, Craig TJ, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 2004; 364:1505-12.
- Kraft M, Vianna E, Martin RJ, Leung DYM. Nocturnal asthma is associated with reduced glucocorticoid receptor binding affinity and decreased steroid responsiveness at night. *J Allergy Clin Immunol* 1999;103:66-71.
- Kraft M, Leung DYM, Martin RJ, Hamid QA. Reduced steroid responsiveness at night in asthma is due to increased glucocorticoid receptor beta expression in lung macrophages [abstract]. *Am J Respir Crit Care Med* 1999;159:A632.
- Landstra AM, Postma DS, Boezen HM, van Aalderen WM. Role of serum cortisol levels in children with asthma. *Am J Respir Crit Care Med* 2002;165:708-12.
- Landstra AM, Boezen HM, Postma DS, van Aalderen WM. Effect of intravenous hydrocortisone on nocturnal airflow limitation in childhood asthma. *Eur Respir J* 2003;21:627-32.
- Sutherland ER, Ellison MC, Kraft M, Martin RJ. Altered pituitary-adrenal interaction in nocturnal asthma. *J Allergy Clin Immunol* 2003; 112:52-7.
- Sutherland ER, Martin RJ, Ellison MC, Kraft M. Immunomodulatory effects of melatonin in asthma. *Am J Respir Crit Care Med* 2002;166: 1055-61.
- Sutherland ER, Ellison MC, Kraft M, Martin RJ. Elevated serum melatonin is associated with the nocturnal worsening of asthma. *J Allergy Clin Immunol* 2003;112:513-7.
- Kraft M, Martin RJ, Wilson S, Djukanovic R, Holgate ST. Lymphocyte and eosinophil influx into alveolar tissue in nocturnal asthma. *Am J Respir Crit Care Med* 1999;159:228-34.
- Kelly EA, Houtman JJ, Jarjour NN. Inflammatory changes associated with circadian variation in pulmonary function in subjects with mild asthma. *Clin Exp Allergy* 2004;34:227-33.
- Guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 1997.
- Pincus DJ, Szeffler SJ, Ackerson LM, Martin RJ. Chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. *J Allergy Clin Immunol* 1995;95:1172-8.
- Pincus DJ, Humeston TR, Martin RJ. Further studies on the chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. *J Allergy Clin Immunol* 1997;100:771-4.
- Beam WR, Weiner DE, Martin RJ. Timing of prednisone and alterations of airways inflammation in nocturnal asthma. *Am Rev Respir Dis* 1992; 146:1524-30.
- Lockey RF, DuBuske LM, Friedman B, Petrocella V, Cox F, Rickard K. Nocturnal asthma: effect of salmeterol on quality of life and clinical outcomes. *Chest* 1999;115:666-73.
- Coe CI, Barnes PJ. Reduction of nocturnal asthma by an inhaled anticholinergic drug. *Chest* 1986;90:485-8.
- Barnes PJ, Greening AP, Neville L, Timmers J, Poole GW. Single-dose slow-release aminophylline at night prevents nocturnal asthma. *Lancet* 1982;1:299-301.
- Goldenheim PD, Conrad EA, Schein LK. Treatment of asthma by a controlled-release theophylline tablet formulation: a review of the North American experience with nocturnal dosing. *Chronobiol Int* 1987;4: 397-408.
- Martin RJ, Cicutto LC, Ballard RD, Goldenheim PD, Cherniack RM. Circadian variations in theophylline concentrations and the treatment of nocturnal asthma. *Am Rev Respir Dis* 1989;139:475-8.
- Elias-Jones AC, Higenbottam TW, Barnes ND, Godden DJ. Sustained release theophylline in nocturnal asthma. *Arch Dis Child* 1984;59:1159-61.

38. Martin RJ, Kraft M. Nocturnal asthma: therapeutic considerations. *Clin Immunother* 1996;6:443-53.
39. Gislason T, Janson C, Vermeire P, Plaschke P, Bjornsson E, Gislason D, et al. Respiratory symptoms and nocturnal gastroesophageal reflux: a population-based study of young adults in three European countries. *Chest* 2002;121:158-63.
40. Tan WC, Martin RJ, Pandey R, Ballard RD. Effects of spontaneous and simulated gastroesophageal reflux on sleeping asthmatics. *Am Rev Respir Dis* 1990;141:1394-9.
41. Gibson PG, Henry RL, Coughlan JL. Gastro-oesophageal reflux treatment for asthma in adults and children. *The Cochrane Library* 2005;3.
42. Ekstrom T, Lindgren BR, Tibbling L. Effects of ranitidine treatment on patients with asthma and a history of gastro-oesophageal reflux: a double blind crossover study. *Thorax* 1989;44:19-23.
43. Goodall RJ, Earis JE, Cooper DN, Bernstein A, Temple JG. Relationship between asthma and gastro-oesophageal reflux. *Thorax* 1981;36:116-21.
44. Kiljander TO, Salomaa ER, Hietanen EK, Terho EO. Gastroesophageal reflux in asthmatics: a double-blind, placebo-controlled crossover study with omeprazole. *Chest* 1999;116:1257-64.
45. Boeree MJ, Peters FT, Postma DS, Kleibeuker JH. No effects of high-dose omeprazole in patients with severe airway hyperresponsiveness and (a)symptomatic gastro-oesophageal reflux. *Eur Respir J* 1998;11:1070-4.
46. Ford GA, Oliver PS, Prior JS, Butland RJ, Wilkinson SP. Omeprazole in the treatment of asthmatics with nocturnal symptoms and gastro-oesophageal reflux: a placebo-controlled cross-over study. *Postgrad Med J* 1994;70:350-4.
47. Gustafsson PM, Kjellman NI, Tibbling L. A trial of ranitidine in asthmatic children and adolescents with or without pathological gastro-oesophageal reflux. *Eur Respir J* 1992;5:201-6.
48. Chan CS, Woolcock AJ, Sullivan CE. Nocturnal asthma: role of snoring and obstructive sleep apnea. *Am Rev Respir Dis* 1988;137:1502-4.
49. Martin RJ, Pak J. Nasal CPAP in nonapneic nocturnal asthma. *Chest* 1991;100:1024-7.
50. Calhoun WJ. Nocturnal asthma. *Chest* 2003;123(suppl):399S-405S.
51. Hakala K, Stenius-Aarniala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. *Chest* 2000;118:1315-21.