

Nocturnal asthma

Over 80% of people with asthma experience nocturnal asthma. Cough, wheeze, and breathlessness at night are occasional problems for most asthmatic individuals^{1,2} but are regular events that interfere with the quality of life in some of those with the most severe asthma. This editorial concentrates on important recent advances in our understanding of the neurological and inflammatory mechanisms, daytime consequences, and management of nocturnal asthma.

Control system

Sleep is the main stimulus to nocturnal airway narrowing. The airways of both normal³ and asthmatic subjects narrow during sleep; the time of this narrowing changes rapidly with change of sleep time⁴ and the extent of overnight airway narrowing is reduced when asthmatic subjects are kept awake overnight.⁵ Some nocturnal airway narrowing persists during a single night of sleep deprivation⁵ and thus sleep does not directly cause all of the nocturnal airway narrowing.

Mechanisms

AUTONOMIC TONE

Both cardiac⁶ and bronchomotor⁷ parasympathetic tone increase during sleep. In patients with nocturnal asthma atropinic blockade greatly decreases nocturnal airway narrowing, but does not abolish it.⁸⁻¹⁰ Thus increased parasympathetic tone is a major factor in the pathogenesis of nocturnal asthma.

The only other direct innervation of the bronchial smooth muscle is the non-adrenergic, non-cholinergic (NANC) system, for which nitric oxide is the likely neurotransmitter. Recent evidence acquired by attempting to stimulate the NANC system with inhaled capsaicin indicates that NANC bronchodilator activity is inhibited in the early morning.⁷ Thus the balance of neural bronchomotor tone is swung in favour of bronchoconstriction overnight, with increased parasympathetic bronchoconstriction and decreased NANC bronchodilatation.

AIRWAYS INFLAMMATION

The suggestion that plasma histamine concentrations rise at night and cause nocturnal asthma was based on a study¹¹ with methodological problems.¹² A more recent study on larger numbers of patients with nocturnal asthma showed no rise in plasma histamine concentration despite a substantial fall in overnight peak flow.¹² Considerable attention has been focused on the more direct assessment of airway inflammation by bronchoalveolar lavage and bronchial biopsy in patients with nocturnal asthma. Martin and colleagues reported an increase in total white cells, neutrophils, and eosinophils in lavage fluid at 04 00 hours in comparison with 16 00 hours in patients with nocturnal asthma.¹³ Mackay *et al*¹⁴ similarly found significant increases in eosinophil numbers in lavage fluid at 04 00 hours in patients with nocturnal asthma and also found an increase in lymphocyte numbers, but no change in total white cell or neutrophil numbers. Jarjour *et al*¹⁵ found no change in cell numbers in lavage fluid between these two times in patients with nocturnal asthma, though only five patients were studied. Mackey *et al* found not only an increase in eosinophil

numbers in lavage fluid but also an increase in eosinophil cationic protein in lavage fluid at 0400 hours in patients with nocturnal asthma.¹⁴ Neither Mackay *et al*¹⁴ nor Jarjour *et al*¹⁵ found any change in histamine concentrations in lavage fluid between the two times. Jarjour *et al*¹⁵ reported an early morning increase in superoxide production from lavage cells in their patients with nocturnal asthma.

These studies suggest that inflammatory activity in the airways is increased in the early morning in patients with nocturnal asthma. The trigger for this is not clear. It is tempting to invoke the sleep synchronised circadian falls in catechols and corticosteroids in the early morning.^{16,17} Studies which have found persisting nocturnal asthma after catechol¹⁶ or corticosteroid¹⁷ replacement and after adrenalectomy¹⁹ do not prove that the falls in these are not important in the pathogenesis of the inflammatory component of nocturnal asthma—the observed persistence could reflect persisting neural bronchoconstriction. Another factor that could be implicated in the pathogenesis of the nocturnal inflammatory response is the change in autonomic tone, which will alter bronchial blood flow and possibly the permeability of the endothelium to influx of inflammatory cells into the airway.

REDUCED LUNG VOLUME

Functional residual capacity (FRC) falls during sleep.^{20,21} This will passively narrow the bronchial tree. Recent evidence suggests that the reduction in FRC in patients with asthma may result in bronchoconstriction that persists after awakening^{21,22} and thus will contribute to the overnight airway narrowing seen in patients with nocturnal asthma.

SNORING

Snoring is more common in people with asthma than in the general population,² perhaps because asthmatic patients often have rhinitis, which will increase nasal resistance and thus cause a more negative pressure to be generated in the pharynx during inspiration. There is evidence that some patients with asthma who snore loudly develop overnight airway narrowing as a direct consequence of their snoring.^{23,24} In these patients the application of continuous positive airway pressure will substantially reduce their nocturnal airway narrowing,^{23,24} whether or not they have episodes of coexisting obstructive apnoea. Although a history of snoring should be sought in all patients with nocturnal asthma and appropriate treatment tried if standard measures do not suffice, in my own experience this is an unusual cause of nocturnal asthma.

Factors unimportant in the aetiology of nocturnal asthma include the supine posture,²⁵ gastro-oesophageal reflux,^{26,27} allergens in bedding,²⁸ and increased intervals between doses of bronchodilator due to sleep.²⁹

Thus the causes of nocturnal airway narrowing are multifactorial (figure). These factors cause nocturnal airway narrowing in everyone, whether normal or asthmatic; but, as with other stimuli, patients with asthma show a more obvious response in terms both of decrement in lung function and of symptoms. Indeed, there is a linear relationship between a subject's reactivity to histamine and the overnight decrease in peak flow,³⁰ and thus the

twitchier the airways the greater the overnight drop in peak flow. Similarly, any factor that will increase reactivity, such as exposure to a known allergen at whatever time of day, will increase the nocturnal drop in peak flow and may induce symptoms of nocturnal asthma.³¹

Consequences

ASTHMATIC ATTACKS

Most patients with asthma experience worsening of their asthma at night or in the early morning, at least from time to time. In some, however, this is a nightly occurrence, significantly impairing their own quality of life and that of their close family. Patients with asthma present to general practitioners and accident and emergency departments more frequently by night than by day,³² to the inconvenience of both the patient and the medical staff.

Ventilatory arrests in asthmatic patients are more common by night than by day,³³ as are deaths from asthma.³⁴ Although many causes may contribute to the excess of deaths at night in asthmatic patients, nocturnal airway narrowing is probably the most important.

SLEEP DISRUPTION AND ITS CONSEQUENCES

Patients with nocturnal asthma sleep poorly, with an increase in wakefulness and drowsiness during the night and a decrease in deep (slow wave) sleep.^{35 36} Recent evidence indicates that asthmatic are more likely than the rest of the population to report that they get too little sleep and that they find nocturnal sleep unrefreshing.² They may have slightly more irregular breathing at night than the general population³⁵ but this would not be sufficient to account for their sleep related symptoms and sleep disruption, which seem more likely to be related directly to the effects of their airway narrowing. Some patients with nocturnal asthma complain of impaired work performance. Daytime cognitive function appears to be worse in patients with nocturnal asthma than in age, sex, and education matched normal subjects.³⁷ This deficit is likely to be due to sleep disturbance, and certainly in the study of Fitzpatrick *et al*³⁷ seemed not to be due to the drugs used to treat the asthma.

Treatment

The essential element in the treatment of nocturnal asthma is to regard it as a marker of inadequate control of asthma. Thus treatment must be aimed at maximising prophylaxis before specific bronchodilator treatment is introduced. Inhaled corticosteroids will reduce nocturnal

asthma³⁸ and only if high dose inhaled steroids do not control the nocturnal asthma should long acting bronchodilators be introduced. I believe that inhaled long acting β agonists such as salmeterol and formoterol are the current long acting bronchodilators of choice. They are effective over the whole duration of a night's sleep,^{39 40} improve symptoms in patients with nocturnal asthma,^{41 42} and improve overnight peak flow;^{41 42} and at least salmeterol has been shown to improve objective sleep quality in patients with nocturnal asthma as judged by electroencephalography.⁴¹ In contrast, oral sustained release bronchodilators have a relatively high frequency of side effects and, although they may be effective bronchodilators, they do not improve objective sleep quality^{43 44}—indeed, theophyllines may actually impair sleep.⁴³

Conclusions

Nocturnal worsening of cough, wheeze, and breathlessness are common problems for many patients with asthma, disrupting their sleep and impairing their daytime performance. Recent studies have identified that alterations of cholinergic and NANC function at night, in combination with increased airway inflammation, are major factors in the pathogenesis of nocturnal airway narrowing. The development of long acting inhaled bronchodilators has improved management of those patients who do not respond to standard asthma treatment.

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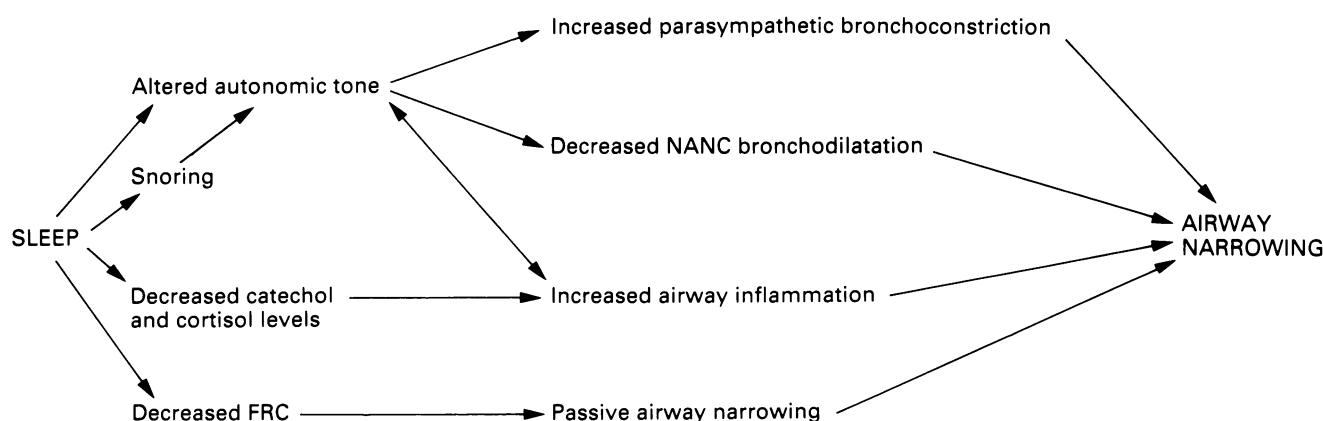


Diagram showing the causes and mechanisms of nocturnal airway narrowing. FRC—functional residual capacity; NANC—non-adrenergic, non-cholinergic.

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