

Current topic

Diurnal variation in asthma

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It has been known for many hundreds of years that asthma is worse at night. Sir John Floyer in his classic 'Treatise of the Asthma' (1698) wrote: 'I have observed the fit always to happen after Sleep in the Night when Nerves are filled with windy Spirits, and the heat of the bed has rarified the Spirits and Humours'.¹ Although these exacerbations are a well established clinical phenomenon, the precise reasons for them and an entirely satisfactory method of treating many of them are still unknown.

Circadian rhythm

In the early years of the century nocturnal asthma was variously thought to be due to cold air, allergy to feathers, or allergy to house dust; more recent research, however, has shown that it does not seem to depend upon external stimuli but upon an endogenous physiological rhythm. Most biological variables measurable in man (for example body temperature, hormone concentrations, and blood pressure), exhibit oscillations which in a free-running state have a periodicity of about 25 hours, and are therefore referred to as circadian ('about a day'). Oscillations which have a daytime peak and a night-time trough are referred to as 'diurnal' (Fig. 1). It has been proposed that this fundamental rhythmicity in man is a property of two complementary neuronal 'pacemakers' the X or temperature-driving pacemaker and the Y or rest-activity pacemaker which is sited within the suprachiasmatic nuclei of the brain.² The signals generated by these endogenous pacemakers are thought to be modulated by a number of other inputs, notably the light-dark cycle acting via the optic pathways, so that the body's circadian rhythms have a precise 24 hour periodicity under normal conditions of sleep and wakefulness.

Diurnal rhythms in lung function

There is ample evidence of low amplitude diurnal variation in lung mechanics.³ These studies have

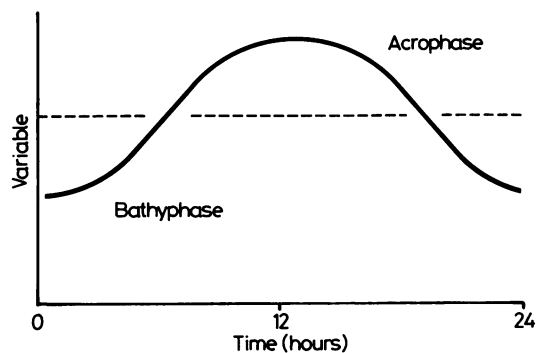


Fig. 1 Diurnal circadian rhythm.

A diurnal circadian rhythm has its peak during waking hours (in this example at noon) and its trough during sleep (in this example at midnight). Asthmatics have larger diurnal rhythms in airway calibre than normal subjects.

consistently shown that airway resistance is higher at night. Therefore, the commonly measured variables such as specific airway conductance, the forced expiratory volume in one second, the forced expiratory volume in one second: forced vital capacity ratio, or the more simply measured peak expiratory flow rate are *lower* at night. If a number of measurements (for example, five) are made at intervals spread across each 24 hour period and are repeated for a week or more, the statistical technique of cosinor analysis may be applied and can give accurate figures for the periodicity and amplitude (mean high minus mean low or average value) for any biological variable. It has been shown by this technique that the results obtained by measuring the peak expiratory flow rate at home using the mini peak flow meter give reproducible results, and that the rhythms found are comparable in wave form with those detected in the laboratory using more elaborate equipment. Thus, in a series of normal subjects Hetzel and Clark⁴ showed that the trough for peak expiratory flow rate was at 3.26 am and the amplitude was mean (SD) 8.3% (5.2%). One should note at this point, however, that as with all

biological variables, there seems to be a distribution of individual values about the mean both in respect of phase (see Fig. 2) and amplitude.

Diurnal rhythm of asthma

In asthmatics the phase of the changes in airways resistance is identical to normal subjects (Fig. 2), but they are characteristically different in that the amplitude of their oscillations is much larger. For example, in the study just quoted it was found that the peak expiratory flow rate amplitude of 56 asthmatics was mean (SD) 50.9% (41.7%). We can therefore conclude that nocturnal asthma is an exaggeration of the normal diurnal rhythm in airway calibre. In this sense it may be regarded as an example of the bronchial hyperreactivity which is evident as a quantitative distinction between asthmatics and normal subjects in other ways—for example by their greater bronchoconstrictor response to cold air, exercise, or inhaled histamine challenges.

Mechanisms of the diurnal rhythm

If one accepts the hypothesis that the fundamental 'clock' driving these oscillations in airway calibre is the same as for other diurnal rhythms, the next problem is to identify the 'effector' mechanisms (themselves subject to the influence of the clock) which directly cause alterations in the calibre of the bronchial tree.

Sleep. The most intensively investigated modulator has been sleep. The diurnal rhythm of airway resistance depends on a regular wake-sleep pattern, and studies of shift workers (for example nurses) have shown that abrupt changes of sleep pattern are

followed by an adjustment of the peak expiratory flow rate rhythm which is complete after two or three days so that the acrophase (peak) is approximately in the middle of the wake period.⁵ Sleep deprivation studies have shown, however, that sleep is not a necessary prerequisite for a nocturnal drop in peak expiratory flow rate, although persistent sleep disruption does cause a decrease in the amplitude of the rhythm. Likewise, and contrary to what might have been supposed there is no evidence that the stage or type of sleep (rapid eye movement or non-rapid eye movement sleep) is particularly associated with a sharp decrease in peak expiratory flow rate. For example Montplaisir *et al.*,⁶ in a study of 12 asthmatic children, showed that their episodes of nocturnal asthma were concentrated in the last third of the natural sleep period, and that the number of episodes during particular stages of sleep were proportional to the duration of these stages during the night. It also seems that asthmatics, unlike some adults with chronic bronchitis and type II respiratory failure, are not particularly susceptible to 'dips' of low arterial oxygen saturation during hypopnoea in rapid eye movement sleep when the ventilatory response to P_{CO_2} may be blunted. Smaller dips of approximately 9% saturation have, however, been measured in a group of untreated children with moderately severe asthma; these were significantly bigger than in a control group and when the asthma was treated.⁷

Endocrine effects. Since corticosteroids bronchodilate, a tempting hypothesis to explain nocturnal asthma would be that it is the consequence of the diurnal fall in the plasma cortisol concentration which precedes the peak expiratory flow rate bathyphase (trough) by four to five hours. This cannot, however, be the only explanation since maintaining a high cortisol concentration artificially by intravenous infusion failed to modify the rhythm.⁸

More recently the association between changes in concentrations of circulating catecholamines and the peak expiratory flow rate rhythm has been studied. Barnes and his colleagues⁹ were able to show in a group of five asthmatics that diurnal swings in peak expiratory flow rate, plasma adrenaline concentration, and plasma cyclic adenosine monophosphate concentration were in phase, and that 'plasma' histamine concentration (which may have included a component from basophils) showed an inverse pattern. Infusions of adrenaline did not, however, abolish the diurnal rhythm, although the oscillation amplitudes were smaller from a higher peak expiratory flow rate baseline.

Thus, although the changes in plasma cortisol,

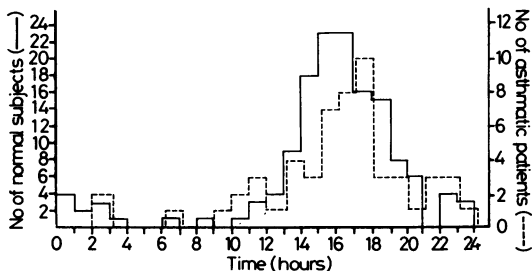


Fig. 2 Histograms showing the phase of peak expiratory flow rate rhythms in 145 normal subjects and 56 asthmatic patients.

The numbers of subjects whose acrophase (peak) occurred at each hour of the day are shown. The similarity of phase distribution in the two populations is clear. (Taken from Hetzel and Clark⁴).

plasma adrenaline and possibly plasma histamine concentrations would together tend to amplify the peak expiratory flow rate rhythm in asthmatics, there is insufficient evidence to indicate that any single substance is the major determinant.

Immunology. Studies of the type I reactions to skin prick tests in atopic subjects have suggested a large diurnal rhythm if erythema is measured,¹⁰ but a very much smaller amplitude if only the weal areas are considered (Muers and Currie—personal observations). Although these oscillations are in phase with the peak expiratory flow rate rhythm this is seen also in non-atopic asthmatics, and a rhythm is present in non-atopic subjects with chronic obstructive lung disease.¹¹ Therefore, oscillations in mast cell reactivity can only be a minor influence on the peak expiratory flow rate rhythm. The seemingly greater sensitivity of asthmatics to allergen challenge in the early hours of the morning is almost certainly a geometric effect and a consequence of the greater baseline bronchoconstriction present at this time (Fig. 3).

Airway cooling, mucus, and oesophageal reflux. Exercise induced asthma is prominent among children and the major cause for this would seem to be airway cooling and a negative respiratory heat exchange across bronchial walls. In sleep in children, Chen and his collaborators have shown that nocturnal asthma coincides with a diurnal body temperature drop of 0.7°C and that this asthma can be partially prevented by breathing fully humidified air at 37°C.¹²

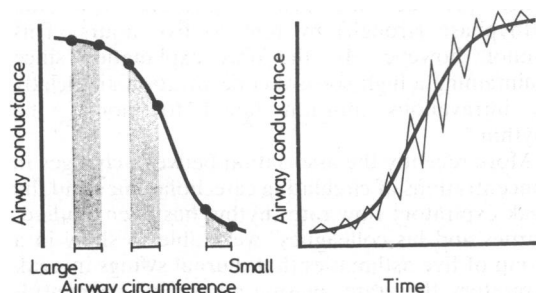


Fig. 3 Relation between airway conductance and circumference and airway conductance and time during recovery from acute severe asthma.

Maximal diurnal swings in airway conductance (or resistance) are seen during the recovery phase from acute episodes. These swings are sometimes not seen when the asthma is very severe and are not usually seen when the asthma is well controlled. One of the reasons for this is that the relation between airway conductance and airway circumference is sigmoid, so that when airways are moderately bronchoconstricted, small changes in airways circumference produce large changes in airway conductance. The signal causing diurnal variation is therefore amplified at this time.

Mucociliary clearance is known to be suppressed by sleep, but does not seem to be affected by sleep deprivation in the same way as the peak expiratory flow rate rhythm. Small airway plugging by mucus may be the reason, however, why some subjects with nocturnal asthma do not bronchodilate with an inhaled beta agonist in the early morning.

There is suggestive evidence from many clinical studies that some attacks of nocturnal asthma in children are due to gastro-oesophageal reflux. Recently Davis *et al*¹³ have shown in four asthmatic children with reflux and a positive Bernstein test, that acid infusion could provoke asthma at 4 to 5 am, but not at midnight. This implies that reflux is a rather weak stimulus for bronchoconstriction and is more likely to provoke an attack during that part of the night when airways resistance is already raised because of the diurnal rhythm.

One may summarise this evidence by saying that the diurnal rhythm of airways resistance is probably a basic, ill defined 'tissue' rhythm driven by the neurological clocks, and that this is amplified by a number of separate rhythms such as cortisol, adrenaline, histamine, mast cell sensitivity, and body temperature. In asthmatics these rhythms may combine to resonate and produce abnormally large oscillations in the hyperactive airways. The solution to the problem of nocturnal asthma would therefore seem to be to reduce the hyperreactivity—that is to improve the degree of asthma control—rather than to seek to manipulate a single contributing variable.

Clinical implications

Diagnosis. In a population of 145 non-asthmatic subjects studied by serial peak expiratory flow rate measurements, the mean amplitude +2 SD of the diurnal variation was 18.7% (8.3+10.4).⁴ The authors therefore suggested that the finding of a 20% or greater swing in serial peak expiratory flow rate measurements could be used as evidence that a subject might be asthmatic. Although this 20% figure is now being applied to many studies of adult asthmatics, there are reasons for advising caution in using this figure in paediatrics. Firstly, there has been no large study of diurnal variation in normal and asthmatic children, and it is possible that the normal diurnal rhythm in childhood is greater in amplitude than 8% and that the scatter of amplitudes is greater also. Secondly, the values quoted above were derived from cosinor analysis, whereas for clinical work it is usually necessary to rely on a mean value from a week's recording of peak expiratory flow rate. This method will accentuate rhythm as it will misinterpret signal 'noise'. Thirdly, it seems likely to the author that in only a few cases

would the use of this criterion pick out asthmatic children who have not been diagnosed either by spirometry before and after a bronchodilator aerosol, or by a simple exercise test. No correlations have been established either in adult or paediatric practice between the diurnal variation and other criteria of asthma such as the PC₂₀ for histamine.¹⁴

Treatment. It is important to recognise that large diurnal variations in asthma may be present in both mild and severe disease. Accordingly, in some patients the variations can be reduced to normal by regular use of a beta agonist aerosol, whereas in others these may persist despite large doses of oral corticosteroid. It follows that if nocturnal asthma is a problem there is no *single* optimum treatment. Mild disease will respond to simple bronchodilator treatment at night, and because of the better formulations there is probably a case for preferring in children, although not in adults, the use of a slow release theophylline preparation given at bedtime. More severe disease would clearly require treatment on a 24 hour basis rather than just at night, although in these cases thought should be given to the possibility of allergy to house dust mite. Since there is evidence from studies in adults that nocturnal asthma responds better to aerosol than oral or systemic beta agonists, it would seem logical to recommend inhaler or dry powder treatment of recurrent waking episodes in children. The timing of medication during the day may affect its efficacy because of the way it synchronises or is contrary to diurnal rhythms, and Reinberg¹⁵, for example, has shown that better asthma control results from giving oral corticosteroid treatment as a split dose at 8 am and 3 pm rather than at 3 pm and 8 pm. No systematic study of dose timing for other bronchodilator drugs has been done.

Asthma deaths. Deaths from many causes are more common at night than during the day but even when an allowance is made for this, the pooled data from four studies of asthma deaths in the United Kingdom have shown a 28% excess between the hours of midnight and 8 am compared with an expected 5% excess.¹⁶ Furthermore, a study of ventilatory arrests in a specialist chest hospital has shown that many episodes were associated with very noticeable preceding diurnal swings in peak expiratory flow rate.¹⁷

This evidence suggests that no asthmatic child with severe night-time symptoms should remain untreated and that children with diurnal swings of greater than 50% of the daily mean peak expiratory flow rate during recovery from acute severe episodes (see Fig. 3) should not normally be discharged from hospital until these oscillations have decreased.

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