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Editorial

The pulmonary clock

Measurement is fundamental to modern medicine, yet few doctors appreciate the importance of analysing biological data, not only as individual results, but also as a signal related to time. Biological rhythms are predominantly circadian—so called because they have a natural period of approximately 24 hours (*circa diem*) if allowed to run freely in the absence of external stimuli. They can be further described as diurnal if the peak of the rhythm (acrophase) occurs during daylight and the nadir (bathyphase) is seen during the night. Clinicians are familiar with the rhythm in adrenal cortical function,[1] but many other rhythms—for example, in body temperature,[2] pulse rate,[3] or renal function[4]—are also relevant to medicine, particularly in the design and interpretation of experimental work. Some rhythms have such low amplitude that they are not clinically important. Chronobiology is particularly important in the lung, however, since a circadian rhythm in airway resistance is easily demonstrated and, in asthma, is sometimes of such large amplitude that it is obvious to clinican and patient alike. The implications of this rhythm are threefold. It is relevant to the diagnosis of asthma, to the design and interpretation of trials of bronchodilator drugs, and, in severe cases, nocturnal asthma remains a challenge to pharmacology.

Nocturnal asthma was described long before the birth of chronobiology. Aurelianus Caelius (fourth or fifth century AD) noted the frequent nocturnal occurrence of asthma attacks,[5] and Maimonides (1135-1204)[6] suggested that sleep was dangerous during an attack. Willis (1679)[7] attributed it to the bedclothes overheating the blood, necessitating a "more plentiful sucking in of air." Floyer (1698)[8] found that his attacks were exclusively nocturnal over seven years and Laënnec (1827)[9] described a patient whose attacks only occurred if his night light went out. Trousseau (1868)[10] described nocturnal asthma in both himself and his mother.

In the present century the aetiology of nocturnal asthma remained unknown until the rhythm in airway calibre was identified in normal subjects. Claims that it was caused by feathers in bedding and could be abolished by floss pillows[11] were disputed by other authors.[12] More obscure theories included an error of metabolism with accumulations of toxins during the night.[13] In 1951 Israels[14] demonstrated rhythms in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) in asthmatic and bronchitic patients with an acrophase at 1200 hours. Lewinsohn *et al.*[15] compared an increase in normal subjects of 2·9% in FEV_1 between 0600 and 0800 hours with an increase of 36-60% in patients with airways obstruction. More detailed studies were prompted by the need to exclude the effects of circadian variation in lung function tests in research work. In normal subjects there is a rise of about 0·15 l in FEV_1 in the morning with a subsequent fall of 0·05 l in the afternoon,[16] $FEV_{0·75}$ falls by 10% in the afternoon,[17] and a rhythm in airways resistance shows an acrophase between 0500 and 0800 hours.[18 19] Elegant studies of subjects in environmentally controlled chambers over six-day periods[20] show a normal rhythm in specific conductance (sGaw) which rises from a mean 0·202-0·285 s^{-1} cm H_2O^{-1} (2·02-2·85 s^{-1} kPa^{-1}) between 0400 and 1200 hours and mean changes of 0·305 l in functional residual capacity (FRC), 0·17 l in total lung capacity (TLC), and 0·2 l in residual volume (RV) over the 24-hour cycle. Rhythms have also been described in dynamic compliance,[21] resting ventilation,[22] ventilatory response to CO_2[23] and gas transfer factor.[24]

The normal rhythm in airway calibre may be more simply studied using a peak flow meter alone.[25-28] If a normal subject's mean peak expiratory flow rate (PEFR) is calculated from recordings made four times a day for a week, the amplitude (peak to trough) of the PEFR rhythm is of the order of 8% of this mean value (±SD 5%).[28] Comparison of asthmatics studied in the same way[28] shows that the normal and asthmatic PEFR rhythms have similar phase but asthmatics show much greater amplitudes. Nocturnal asthma therefore apparently represents an exaggeration of this normal rhythm through increased bronchial lability.

The clock driving the rhythm in airway calibre has not been identified. On shift work the PEFR rhythm shows similar behaviour to that noted in other circadian rhythms such as temperature or electrolyte excretion.[29] Within two or three days of

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changing shift the phase of the rhythm adjusts so that highest PEFR is seen around the mid-point of the awake period, irrespective of solar time.[30] Rapid changes of shift can disrupt the clock and reduce the amplitude of the PEFR rhythm.[31] This suggests that sleep may cause the nocturnal fall in PEFR but studies of sleep interruption and deprivation[32] show the rhythm to be independent of sleep, although normally closely synchronised with it. EEG studies of nocturnal asthma attacks suggest that very deep sleep in children[33] precludes nocturnal bronchospasm, although this is not seen in adults.[34] During deep, phase IV non-rapid eye movement sleep airways obstruction may be insufficient stimulus to wake patients—some asthmatics certainly wheeze loudly while asleep.[9] Asthma attacks are, nevertheless, rare in the first two hours of sleep when deep sleep predominates.[32-34] The sleeping posture does not cause nocturnal asthma.[30] Varying degrees of allergen exposure during the day are also unlikely to be an adequate explanation, since nocturnal asthma is unrelated to atopic status,[30 35] it persists in allergen-free environments,[26] and occurs in hospitalised patients with relatively mite-free bedding.[30 36] It has been suggested that the rhythm in plasma cortisol may be the pulmonary clock, since the nadir of the cortisol rhythm occurs a few hours before that of the PEFR rhythm, which would be compatible with the delayed effects of corticosteroids on the airways. This relationship has not, however, been convincingly demonstrated,[37] and abolition of the cortisol cycle by continuous hydrocortisone infusions has no significant effect on the PEFR rhythm.[38]

Soutar *et al*[39] found some correlation between the PEFR rhythm and urinary catecholamine excretion in asthmatics and also suggested that increased nocturnal vagal activity might contribute to the PEFR rhythm. Recently Barnes *et al*[40] were able to show that rhythms in plasma adrenalin, cyclic AMP, and PEFR were in phase with each other but out of phase with plasma histamine. Results were similar for asthmatic and normal subjects except that the latter did not show a nocturnal rise in plasma histamine. The nocturnal fall in PEFR in asthma may therefore relate to falling plasma adrenalin which has a permissive action on sensitised mast cells, as evidenced by the nocturnal rise in plasma histamine. Brief infusions of low dose adrenalin at 0400, 0900, and 1600 hours reduced histamine levels and improved PEFR. High dose infusions raised histamine levels, possibly through alpha-adrenergic mediated increases in mediator release. The cyclic AMP results obtained in this study suggested normal beta receptor responsiveness. Unfortunately this work only proves that the catecholamine rhythm is in phase with the PEFR rhythm. This is equally true of other rhythms—for example, body temperature.[41 42] To prove that catecholamines drive the PEFR rhythm, criteria laid down by Mills[43] must be satisfied: (1) artificial manipulation of the phase of the catecholamine rhythm would produce immediate, appropriate changes in the PEFR rhythm; (2) changes in the catecholamine rhythm would produce changes in the PEFR rhythm at any time of day; (3) constant catecholamine levels would abolish the PEFR rhythm. One hopes future studies may meet these conditions. The authors conclude that beta$_2$ agonists should prevent nocturnal asthma by stimulating mast cell beta receptors but in practice slow release preparations of sympathomimetic drugs or salbutamol infusions do not abolish the PEFR rhythm.[44]

If the catecholamine rhythm is the pulmonary clock its mechanism must be more complex than previous work suggests. There is a remarkable paradox in that, while it is virtually impossible to abolish the nocturnal fall in PEFR with oral or intravenous sympathomimetic drugs, a dramatic response to aerosol bronchodilator drugs is nevertheless seen in most patients at 0600 hours.[45] This implies the existence of a rhythm in sensitivity of the receptors to sympathomimetic drugs and is in keeping with observations of rhythms in bronchial sensitivity to histamine[46] and acetylcholine[47] which are maximal in the early morning.

A minority of patients, however, are refractory to bronchodilators at 0600 hours but improve slowly during the day.[45] This could be the result of mucus plugging of the airways developing overnight. Mucociliary clearance of ^{99m}Tc tagged polystyrene particles is reduced at night[48] but the reduction is predominantly caused by direct effects of sleep[49] rather than by a true circadian rhythm in mucociliary clearance. Finally, immunological rhythms may be relevant. Asthmatics sensitised to house dust extract show greatest response to challenge at night.[50] Similar nocturnal increased sensitivity can also be demonstrated for cutaneous response to histamine,[51] cutaneous response to house dust extract in atopic subjects,[52] and in the effectiveness of antihistamines in reducing the cutaneous response to histamine.[53]

The observed rhythm in airway calibre may therefore be the net effect of rhythms in circulating catecholamines, cortisol, vagal tone, beta$_2$ receptor responsiveness, mucociliary clearance, and immunological performance. The phases of all these rhythms seem to be so arranged that they all tend to make asthma worst at night.

Different methods of analysis of the rhythm in PEFR have led to some confusion. The most

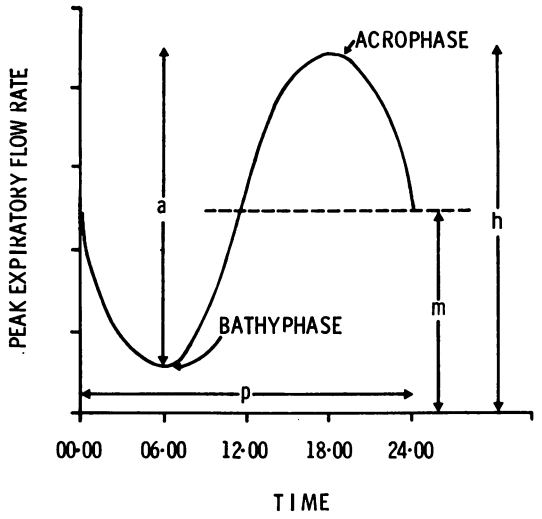

Figure *Analysis of circadian variation in PEFR. This can be simply measured as the difference between highest and lowest daily values, expressed as a percentage of highest value (a/h%). Cosinor analysis allows more detailed analysis, fitting the best sinusoidal waveform to the raw data. Amplitude is expressed as a percentage of mean value (a/m%). Phase is expressed as time of the acrophase (highest daily value). a = amplitude; p = period; m = mean; h = highest daily reading; amplitude* $\% = \frac{a}{m} \times 100$; *diurnal* $\begin{cases} swings \\ falls \end{cases} = \frac{a}{h} \times 100$.

popular methods are compared in the figure. The simplest method measures the morning fall in PEFR as a percentage of the highest daily reading (a/h%); the diurnal swing or fall in PEFR. This is a valuable approach in clinical practice since the diurnal fall can be judged accurately on simple inspection of a peak flow chart. If the PEFR amplitude is low, however, this direct approach is liable to misinterpret biological noise as a true rhythm. An analysis of variance might then be used to analyse blocks of readings at different times of day for several days but this would not provide any idea of the phase of the rhythm.

Cosinor analysis[54 55] is a more versatile computer technique which enables the phase of the rhythm to be calculated and can detect low amplitude rhythms. It is widely used in chronobiology. It considers a mathematical model of the circadian rhythm which is best approximated by a sine or cosine wave, as shown in the figure, with a peak to trough amplitude a, about a mean value m, and a period p, which is usually assumed to be 24 hours. A least squares method is used to test the goodness of fit of the raw data to this model. Unfortunately cosinor programmes are not generally available but regression programmes can be adapted for a sinusoidal regression of PEFR upon time.[28] The programme determines the significance, amplitude, and phase of the sinusoid which best fits the raw data. Phase is conventionally expressed as the timing of the acrophase. Amplitude measured by cosinor analysis is the radius which describes the sinusoid—that is, a/2 in the figure. The peak to trough amplitude a, has more clinical application and would be identical to the diurnal fall in PEFR in the example shown in the figure. This amplitude is most usefully expressed as a percentage of the mean value m, as a/m%. Measurement of circadian variation in PEFR, either as diurnal swings (a/h) or as an amplitude (a/m) is best made in these percentage terms since this allows some comparison between patients with differing degrees of airways obstruction and with normal subjects.

Cosinor analysis of normal PEFR rhythms[28] suggests that normal subjects are unlikely to exceed an amplitude of >20% of the individual's mean PEFR reading. Connolly, however, measuring circadian variation in PEFR as diurnal falls (a/h%) found that some of his patients with chronic bronchitis exceeded this limit.[35 56] This discrepancy illustrates the relative merits of the two methods of analysis. Cosinor programmes give a reliable estimate of amplitude and phase and avoid misinterpretation of noise as a true rhythm but they are time-consuming and require computer facilities. On the other hand direct assessment of diurnal swings in PEFR from raw data is biased towards the widest variations in results, overestimates circadian variation, and is susceptible to biological noise but is very convenient for clinicians. Mathematically speaking, the two methods are comparable unless the degree of circadian variation is very large.[41] Results of a cosinor analysis of the PEFR rhythm in chronic bronchitis showed amplitudes which were very similar to those observed in normal subjects.[57] Measurement of diurnal variation (a/h) in a large study of asthmatic patients in hospital suggested that diurnal falls of <25% of the highest daily reading were uncommon in asthma.[58] From the clinician's viewpoint, therefore, diurnal variation of 20-25% of the highest daily reading is a reasonable threshold for consideration of a diagnosis of asthma. Readings on waking, at around 1600-1800 hours, and at bedtime for seven days with a mini peak flow meter[59] can be performed at home by patients themselves[60] and should assess the PEFR rhythm satisfactorily.[28] This technique should be a useful screening test for asthma.

Different patterns of PEFR readings in airflow

obstruction can be usefully identified.[61] Interpretation of variation in the amplitude and mean value of the PEFR rhythm itself can further extend the value of PEFR monitoring. On recovery from an acute asthma attack, amplitude will be seen to increase as the attack resolves and mean peak flow rises, and will then subsequently reduce somewhat as maximum mean PEFR is achieved. This period of maximum amplitude during recovery apparently indicates a state of increased bronchial lability. There is little evidence that the biological clock becomes more active at this time since temperature rhythm does not show a corresponding amplitude increase.[31] A somewhat analogous pattern may be seen after allergen challenge when large amplitude variation in PEFR,[62 63] sometimes with symptoms of nocturnal asthma,[64] may be initiated and continue for several days. Thus various stimuli, including respiratory tract infection and antigen challenge, may induce increased bronchial lability which amplifies a constant rhythmic stimulus from the biological clock to produce a large amplitude rhythm in PEFR and nocturnal asthma. Diurnal swings in PEFR of $>50\%$ of the highest daily reading can be associated with increased risk of sudden asthma death.[58 65 66] Many patients have little awareness of the severity of their asthma,[67] particularly for their early morning and nocturnal airways obstruction.[45] If previous recommendations for widespread self-monitoring of PEFR[68] gain acceptance, one hopes that recognition of these warning signs in the PEFR rhythm might reduce mortality and morbidity.

The rhythm in airway calibre has considerable implications for therapy. It is clearly important that patients in bronchodilator drug trials are studied at the same time of day when comparing different agents. Care must be taken to avoid misinterpretation of the natural improvement in lung function during the day as a beneficial effect of treatment.[57] In future, assessment of drugs for the treatment of asthma should evaluate their stabilising effect on bronchial lability in reducing the amplitude of the PEFR rhythm as well as their bronchodilator effect in increasing overall PEFR values. The treatment of nocturnal asthma can be very difficult. The concept that it is an expression of increased bronchial lability is valuable in forming a rational approach to treatment, since simple regular therapy during the day with bronchodilator aerosol drugs, and in some cases sodium cromoglycate will often abolish nocturnal attacks in mild cases. Response to corticosteroids is less predictable and sometimes these agents increase the degree of circadian variation, although improving mean PEFR. Mild cases of nocturnal asthma may therefore be successfully treated without extra medication at night. On the other hand, the more severe cases may be refractory to all of the currently available slow release preparations of sympathomimetic agents, at least in doses which can be tolerated.

New drugs are needed in this area, but in the meantime studies of circadian variation in the pharmacokinetics of existing agents[69] might indicate regimens by which they might be used more effectively. An alternative approach would be to try to stop the clock but the only way in which this can be done at present is to disrupt it by rapid changes of shift.[31] This treatment is clearly as unpleasant as nocturnal asthma itself. Unfortunately professional chronobiologists seem unable to offer any better solution to this problem.

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The Third World Congress for Bronchology will be held from 4–6 March 1982 at the Town and Country Hotel, San Diego, California, USA. The purpose of this meeting is to bring together physicians around the world to share knowledge and review the advances in bronchology. The scientific programme, consisting of special lectures and panels, will be programmed around the original investigation sessions. This Congress offers a unique opportunity to be updated in the advances in bronchology. Abstracts are invited in this area. They should not exceed 250 words in length and should be typed double spaced, including title, first and last names of all authors, and the institution where the work was performed. Please designate the address for correspondence and identify who will present the paper. Abstracts should be submitted to the Scientific Program Chairman, Third World Congress for Bronchology, American College of Chest Physicians, 911 Busse Highway, Park Ridge, Illinois 60068 USA. The deadline for abstracts is 1 September 1981. Further information about the meeting can be obtained from the same address.