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Diurnal variation in airflow obstruction in chronic bronchitis

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ABSTRACT Twelve patients fulfilling strict criteria for chronic obstructive bronchitis recorded serial peak expiratory flow rates (PEFR) five times daily for a two-week period. Despite a 9·2% improvement in forced expiratory volume in one second (FEV_1) with ipratropium bromide, and an 11·3% improvement with ipratropium bromide plus salbutamol, the inherent diurnal variation in PEFR while on no medication was greater than the improvement caused by either bronchodilator. In the group as a whole, the difference between the highest and the lowest daily PEFR over the two weeks was 24% of the mean daily value. Using cosinor analysis, 10 of the 12 patients showed a significant rhythm in PEFR with a computed mean amplitude between highest and lowest readings of 8·6% of the mean daily value. This is no greater than that found in normal subjects, but is considerably less than the variation in PEFR in patients with bronchial asthma.

Patients with chronic obstructive bronchitis caused by cigarette smoking often complain that their symptoms, particularly of breathlessness, are worse on waking than they are at other times of the day, although this clinical impression has never been analysed formally. However, it is known that non-smoking asthmatics frequently suffer exacerbations in the early hours of the morning.[1 2]

The diurnal variation in airway resistance which may underlie these asthmatic exacerbations has been studied extensively both in asthmatic patients,[3–10] and in normal subjects.[4 5 9–13] It has been shown that both groups exhibit a circadian rhythm in phase with the pattern of sleep, but not dependent on sleep itself,[14] and that airway resistance usually reaches a peak between 0400-0600 hours. The amplitude of the variation in peak expiratory flow rate in normals is about 8% of the mean daily value,[9] whereas in asthmatics the amplitude is often much greater, and this is exaggerated during the acute attack.[2]

Similar patterns have been observed in two reports[5 8] which included some patients with a diagnosis of chronic bronchitis, but in neither instance were the patients studied without the complicating effects of concurrent bronchodilator or steroid therapy, nor were they shown to have no features of allergic asthma. Consequently, the magnitude and pattern of any diurnal variation in patients who have airflow obstruction caused solely by cigarette smoking remains unknown. We have investigated this by recording serial peak expiratory flow rates during a two-week period in a group of 12 chronic bronchitics with varying degrees of airflow obstruction.

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Methods

Patients fulfilling the MRC criteria for chronic bronchitis[15] were selected from a routine outpatient chest clinic. At the time of admission to the study each patient had airways obstruction defined by a reduction in forced expiratory volume in one second (FEV_1) to 80% or less of the predicted value based on age, sex, and height. All patients were smokers or ex-smokers with no past medical or family history of bronchial asthma, rhinitis, conjunctivitis, or atopy. No patient gave a history of cough, wheeze, or shortness of breath precipitated by animal contact, after exercise, or on exposure to cold air. There was no clinical evidence of other significant pulmonary or cardiovascular disease when the patients were examined at the beginning or the end of the two-week investigation period. No patient had an upper or lower respiratory tract infection during the study. At the time of the initial assessment blood was taken for a blood eosinophil count and total serum IgE concentration, sputum was examined for eosinophils, and a battery of six common allergens (cat, feathers, grasses, *Aspergillus fumigatus*, house dust, and house dust mite) were tested by skin prick test-

ing. Patients were excluded with a blood eosinophilia > 250/ul, a total serum IgE > 60 IU/ml, a significant sputum eosinophilia (> 10% cell count), or with any reaction to skin prick testing. Postero-anterior and left lateral chest radiographs showed no evidence of localised pulmonary disease.

After the initial examination, 14 patients fulfilled these strict clinical criteria, but two were subsequently found to have an elevated total serum IgE level and were withdrawn from the study. The remaining 12 patients were seen at the beginning and the end of the 14-day trial period. Between clinic visits they were at home or work going about their usual daily routine. No patient was a night shift worker. The patients were supplied with a record card and a mini-Wright peak flow meter. They were instructed to take the best of three peak expiratory flow rates (PEFR) on five occasions per day (0700, 0800,1200, 1800, 2300 hours), and to record them on the record card. The first reading of the day was recorded before the first drink or cigarette. Patients have previously been shown to be capable of accurately recording their own PEFR,[16] and the mini-Wright peak flow meter is a suitable instrument for this purpose.[17 18]

At the initial clinic visit the response to two bronchodilators—ipratropium bromide (Atrovent) 40 μgm and salbutamol (Ventolin) 200 μgm—was assessed by inhalation using a standard protocol. A baseline spirogram (FEV_1B) was recorded using a dry wedge spirometer (Vitalograph), followed immediately by inhalation of ipratropium bromide 40 μgm. Sixty minutes later a further spirogram (FEV_1A) was recorded followed immediately by inhalation of salbutamol 200 μgm. A final spirogram (FEV_1S) was recorded 15 minutes later still. Patients were seen after 14 days at a similar time of day when a further spirogram was recorded to exclude any significant baseline shift. Each recording used in the study was the best of three attempts, and all readings are expressed at BTPS.

Serum IgE levels were measured by the Phadebas IgE kit method (Pharmacia Diagnostic UB Uppsala, Sweden). With this method a level of 125 IU/ml is taken as the upper limit of normal (+2 SD).

Statistical analysis was by conventional unpaired *t* tests or multiple regression analysis as appropriate.

Results

The pre-trial data are shown in table 1. Post-study spirometry and a second chest radiograph demonstrated no change during the period of the study, and no patient was withdrawn at this time.

The response to bronchodilators at the start of the trial is shown in table 2. The percentage improvement in the baseline FEV_1 (FEV_1B) is shown after ipratropium bromide (FEV_1A-FEV_1B/FEV_1B%), and after ipratropium bromide plus salbutamol (FEV_1S-FEV_1B/FEV_1B%). In the group as a whole there was a 9·2% (SD ± 6·4% $p < 0.001$) improvement with ipratropium bromide (FEV_1B/FEV_1A), and a 11·3% (SD ± 8·4% $p < 0.001$) improvement after the two agents (FEV_1B/FEV_1S). However, the addition of salbutamol to the ipratropium bromide did not make a significant difference (mean improvement +2·1% SD ± 7·0% $p = 0.5$).

Table 1 *Pre-trial data*

Number of patients: 12 (7F, 5M)
Mean age: 64 (50-75) years
Mean FEV_1: 1·29 (SD ± 0·45) litres
Mean FEV_1 (% predicted): 53 (SD ± 18)%
Skin prick tests (× 6): negative
Mean blood eosinophils: 129 (SD ± 93)/μl
Sputum eosinophils: < 10% cell count
Sputum microscopy/culture: negative
Serum total IgE concentration: 24·6 (SD ± 18) IU/ml

Table 2 *Response to bronchodilators*

Patient	*Percentage improvement with ipratropium bromide*	*Percentage improvement with ipratropium bromide plus salbutamol*
1	+12·8	+15·0
2	+11·8	+16·7
3	+ 5·9	+ 5·9
4	+ 8·7	+16 0
5	+ 8·3	+24·0
6	+ 5·7	+ 0·0
7	+25·0	+25•0
8	+12·8	+15·0
9	+ 0·0	+ 0·0
10	+ 0·0	+ 8·3
11	+ 7·3	+ 9·5
12	+12·0	+ 0·0
Mean	+ 9·2	+11·3
SD ±	6·4	8·4

The highest and lowest PEFR were recorded for each day, and the mean readings over the two-week period are shown for each patient in table 3. The mean absolute difference in PEFR for each patient and the variation in PEFR expressed as a percentage of the mean reading are also shown. In the group as a whole the mean difference between the highest and the lowest PEFR, expressed as a percentage of the mean, was 24 (SD ± 12)% over the two weeks, and the mean absolute variation was 44 (SD ± 15) litres/min.

In order to determine whether there was a significant diurnal rhythm in PEFR, the data were analysed for each patient by regressing all the peak flow readings on $\cos(2t/24\pi)$ and $\sin(2\pi t/24)$. This regression model, usually called cosinor analysis, enables the amplitude and phase of the best fit sine curve with a period of 24 hours to be estimated. This method has been described in detail elsewhere.[9 10 19]

Table 3 *Mean high/mean low PEFR (litres/min)*

Patient	*Mean high PEFR*	*Mean low PEFR*	*Difference*	*Difference (% mean)*
1	332	280	52	17
2	299	254	41	15
3	188	168	20	11
4	175	126	49	32
5	177	128	49	32
6	417	391	26	6
7	113	70	43	47
8	338	304	34	11
9	223	175	48	24
10	165	111	54	39
11	333	256	76	26
12	148	116	32	24
Mean	242	198	44	24
SD±			15	12

A significant ($p<0.05$) rhythm was seen in 10 patients, with a computed mean variation between highest and lowest PEFR of 16·1 (SD ± 8·6) litres/min, representing 8·6 (SD ± 5·7)% of the mean daily peak flow (table 4). For the group, the computed mean low PEFR occurred at 0420 hours, with a mean high 12 hours later at 1620 (SD ± 3) hours.

Table 4 *Characteristics of patients with a significant rhythm in PEFR*

Patient	*Mean PEFR*	*High-low PEFR*	*High-low PEFR (mean %)*
1	273	16	6
2	130	16	12
3	296	36	12
6	319	10	3
7	91	17	19
8	406	8	2
9	151	15	10
10	152	22	14
11	179	5	3
12	309	16	5
Mean	220	16	8·6
SD±	97	8·5	5·7

Discussion

We have studied the diurnal variation in airflow resistance in a group of patients with airflow obstruction caused by cigarette smoking and without evidence of atopy, late onset "asthma", or bronchial hyperreactivity.

As is typical of bronchitic patients, most (10 out of 12) improved significantly ($p<0.001$) with ipratropium bromide, and although there was a tendency for further improvement with the addition of salbutamol, this was not significant. Two patients (6 and 12) actually deteriorated with salbutamol. This phenomenon is unexplained but it has been noted previously (DJ Lane, personal communication, 1979). However, in 11 patients the mean daily variation in PEFR while on no medication was greater than the improvement shown with either ipratropium bromide, or ipratropium bromide plus salbutamol. This observation has important implications when assessing the efficacy of drugs used in the treatment of airflow obstruction. Patients may well be labelled as having a "reversible" component to their airflow obstruction, when in reality the improvement noted after a bronchodilator is significantly less than their own inherent diurnal variation.

Using cosinor analysis, 10 patients in the group showed a significant daily rhythm in PEFR at the 5% level. Hetzel and colleagues[9 10 13] have shown in normal subjects a computed variation in PEFR of 8·3 (SD ± 5·2)% of the mean daily value. They suggest that a variation of over 20% might be a useful screening test for bronchial asthma. Diurnal variation in PEFR is not age-dependent, and the duration of symptoms in the bronchitic and asthmatic groups was similar (mean 22 years and 18 years respectively). The bronchitics showed a variation of 8·6 (SD ± 5·7)%, virtually identical to that found in normal subjects, suggesting that this may be an additional method of distinguishing between patients with airflow obstruction caused by cigarette smoking and airflow obstruction caused by intrinsic bronchial hyperreactivity. One of the advantages of using cosinor analysis is that, assuming enough PEFR readings are taken within a 24-hour cycle, the peak and trough values may be computed, even if an actual reading was not taken at that particular time. The computed high PEFR for the bronchitic group occurred at 1620 hours (again similar to normals of between 1500 and 1700 hours), with a trough 12 hours later at 0420 (SD ± 3) hours. This suggests that the diurnal variation in airways obstruction may well be the reason why patients with this disease often complain of being at their worst in the early morning.

The mechanism or mechanisms which underlie the circadian rhythm in airway calibre remain obscure. It has been shown to persist despite pharmacological doses of corticosteroids,[20] and of beta-agonists,[21] although vagal blockade has not been examined formally. A neurogenic cause seems likely, and the greater amplitude among asthmatics may represent the effect of a normally increased nocturnal bronchoconstrictor tone (perhaps in non-cholinergic nerves) upon airways resting at the steep portion of their stimulus/response curve.[22] We do not know whether the additional stimuli of infection or left heart failure are associated with a proportionately greater amplitude of variation in airways resistance, but this seems likely, despite our own finding that the percentage variation was not proportional to the mean peak expiratory flow rate. However, the fact that we detected no large (>20%) variation in our patient sample is further supportive evidence that the air-

ways resistance of these patients is less labile than that of other groups such as the atopic asthmatic.

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