

Comparison of circadian variations using FEV₁ and peak expiratory flow rates among normal and asthmatic subjects

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Abstract

Background – Most studies that describe circadian variations in asthma have used maximum rate of peak expiratory flow (PEF) rather than forced expiratory volume in one second (FEV₁) to assess airway calibre. This study was designed to assess circadian variations in PEF and FEV₁ measured simultaneously and to compare variations in these measurements in normal and asthmatic subjects in a stable clinical state.

Methods – Twenty nine subjects (nine asthmatic subjects on bronchodilators, 10 on inhaled steroids, and 10 normal controls) were asked to record their PEF and FEV₁ with a new portable instrument every two hours during the day and once on waking at night for two weeks. Circadian variations were examined in different ways using arithmetical indices and cosinor analysis.

Results – 78% of PEF values and 75% of FEV₁ values were considered to be reproducible and were included in the analysis. Variations obtained using PEF did not differ from those obtained using FEV₁. Significant cosinor variations were found in at least 50% of recording days for most of the subjects and showed the same features as for arithmetical indices. Daily variations in PEF and FEV₁ were significantly correlated with airway calibre and PC₂₀ methacholine ($r \sim 0.5$ to ~ 0.6).

Conclusions – PEF is as satisfactory as FEV₁ for describing circadian variations among normal subjects and stable asthmatic subjects.

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All forms of life from cells to the most complex organisms show circadian periodicity¹ and this applies to airway calibre, hyperresponsiveness, respiratory symptomatology, and the effect of respiratory medication². It has been recognised for centuries that asthma is a cyclical condition, with the typical manifestations of unstable asthma occurring during the night, as described by John Floyer in the 17th century.³ The clinical relevance of these nocturnal events has been stressed over the past 15 years and has been related to the occurrence of nocturnal or early morning deaths.⁴ Portable instruments for recording peak expiratory flow rates became available during the same period.^{5,6}

Circadian variations in airway calibre can be assessed by various arithmetical indices – for example, differences between highest and lowest values, coefficient of variation⁷ – and cosinor analysis which matches biological rhythms with sinusoidal functions by depicting the acrophase (timing of the maximum value), mesor (maximum value), and the differences between the highest and lowest values (amplitude or peak to trough value). Although the maximum rate of peak expiratory flow (PEF) can be assessed with inexpensive portable instruments as a physiological index, it reflects primarily large airway calibre and is less sensitive and specific than forced expiratory volume in one second (FEV₁). Until recently, however, it was not possible to record FEV₁ serially, so most studies of circadian variations in asthma were conducted using PEF.⁷⁻¹⁰ The studies in which FEV₁ was assessed were carried out over short intervals of one day at a time (not serially) and results were not compared with PEF.¹¹⁻¹⁵

The aim of this study was to compare circadian rhythms obtained by PEF and FEV₁ recording simultaneously in normal subjects and in asthmatic subjects in a stable clinical state.

Methods

SUBJECTS

Nineteen asthmatic subjects were recruited from a group who consecutively attended an outpatient clinic at a tertiary care hospital and 10 normal subjects were recruited from among the hospital staff. All asthmatic subjects fulfilled the criteria of the American Thoracic Society.¹⁶ The asthmatic subjects included 10 who were taking a short acting β_2 adrenergic agent only if needed, and nine who took inhaled steroids regularly with short acting inhaled β_2 adrenergic agents on an as-needed basis. Asthmatic subjects were judged to be in a stable clinical state on entry and in the course of the study (no nocturnal awakenings due to asthma symptoms, no change in asthma medication requirements in the month preceding their entry into the study, no exposure to a relevant allergen except for house dust that could affect their status). Baseline spirometric values (FEV₁, FEV₁/forced vital capacity (FVC)) were assessed according to standardised criteria¹⁷ for all subjects. Bronchial responsiveness to inhaled methacholine was assessed using a Wright's nebuliser (output 0.14 ml/min) at tidal volume breathing for two minutes.¹⁸ All subjects gave written informed consent.

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SERIAL ASSESSMENT OF AIRWAY CALIBRE

It is now possible to record PEF and FEV₁ simultaneously with a portable instrument (VM1, Clement Clarke Inc, Columbus, Ohio, USA). This consists of a slightly modified mini-Wright peak flowmeter with a pressure sensor and electronic signal processing circuitry. A pressure transducer monitors the pressure in the expired stream at a point close to the mouthpiece and supplies an electrical signal to the processing circuitry. The readings are shown on a digital display. Data obtained in our laboratory in 53 subjects with asthma showed good reproducibility in FEV₁ in comparison with data generated with the Vitalograph instrument (Vitalograph Ltd, Buckingham, UK) ($r^2=0.98$, mean (SD) of differences = 110 (110) ml), and in PEF with the Mini-Wright peak flow meter ($r^2=0.97$, mean (SD) of differences = 23 (17) l/min). Values are within 5% of the American Thoracic Society testing standards. In this study subjects were asked to record their lung function every two hours during the day (from 08:00 hours until 22:00 hours) and once at night waking up at different times (midnight, 02:00 hours, 04:00 hours and 06:00 hours in rotation). This nocturnal assessment ensured that circadian rhythms could be better described. Three forced expiratory manoeuvres were requested at each time. The best of two reproducible values (± 20 l/min for PEF and $\pm 5\%$ FEV₁^{17,19}) was kept for analysis. Recordings were done for two consecutive weeks.

ANALYSIS OF RESULTS

The concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) was obtained from individual dose-response curves drawn on a semilogarithmic scale. Reference values for FEV₁ and FEV₁/FVC were obtained from Knudson and coworkers.²⁰ A PC₂₀ ≤ 16 mg/ml reflected significant bronchial hyperresponsiveness.²¹

Study day recordings that were kept for analysis included at least four reproducible values and did not include values that were obtained within four hours of inhaling a β_2 adrenergic agent. The best discriminants of the arithmetical indices proposed by Higgins and coworkers⁷ were kept for analysis and included: (1) daily amplitude (maximum value - minimum value) expressed as a percentage of the mean daily value (amplitude % mean) and as a percentage of the lowest daily value (amplitude % lowest); (2) daily coefficient of variation. The amplitude obtained from the cosinor analysis was also kept for analysis. Cosinor analysis was performed with the S-Plus program (StatSci Division, Seattle, Washington, USA) and yielded the following results: the fit of the curve expressed by the r^2 value (which needed to be significant at the $p < 0.05$ level with [n-2] degrees of freedom), the acrophase (timing of the highest value), and the mesor (peak to trough difference). A more suitable detection of significant rhythms was obtained by adding the last half of the previous day and the first half of the

following day to the day that was kept for analysis.

The mean, maximum, and minimum values for each circadian index were obtained for each subject using both PEF and FEV₁ for the two week period of recording. These values were compared using the two functional indices (PEF and FEV₁) by the Wilcoxon test, and in the three groups of subjects (asthmatic subjects taking inhaled bronchodilator only, asthmatic subjects taking inhaled steroids, normal subjects) with the Kruskal-Wallis one way analysis of variance. Circadian indices were related to baseline airway calibre (FEV₁ % predicted) and PC₂₀ in categorical values (> 128 , 16-128, 4-16, 1-4, 0.25-1, < 0.25 mg/ml) by regression analysis.

Results

Only two subjects (in the group requiring inhaled steroids) needed inhaled β_2 adrenergic agents 2-3 times a day on average. The remaining subjects used it once a day or less (no requirement at all during the course of the study in eight of the 19 asthmatic subjects). Normal subjects were significantly younger (30 (9) years) than those in the two other groups (45(17) and 48(17) years). FEV₁ and FEV₁/FVC values were higher in normal subjects (102(9)% and 102(3)% predicted compared with 83(14)% and 93(10)%, and 77(20)% and 91(14)% in the two asthmatic groups). Nine asthmatic subjects had an FEV₁ value $< 80\%$ predicted. All asthmatic subjects had a PC₂₀ value ≤ 16 mg/ml (significant bronchial hyperresponsiveness).²⁰

Reproducibility criteria were met for 77.6% of PEF readings and for 75.2% of FEV₁ values (NS). There were no significant differences in all circadian arithmetical indices (amplitude % mean, amplitude % lowest, coefficient of variation) using FEV₁ or PEF, and in no instance was any value out of range using FEV₁ or PEF (mean (SD) results for each group shown in table 1 and individual results for mean values in fig 1). There were no significant differences between variability in each index using FEV₁ or PEF by the Wilcoxon test (z values 0.23, 0.24 and 0.35, $p > 0.05$, for mean values of amplitude % mean, amplitude % lowest, and coefficient of variation, respectively); significant differences in the mean values were seen between normal subjects on the one hand, and asthmatic subjects on inhaled β_2 adrenergic agent on an as-needed basis and those taking inhaled steroids on the other hand, by the Kruskal-Wallis test (H = 9.3, $p = 0.2$, and 9.4, $p < 0.01$ for PEF and FEV₁ for amplitude % mean; H = 9.0, $p = 0.01$, and 8.7, $p = 0.01$ for PEF and FEV₁ amplitude % lowest; H = 9.0, $p = 0.01$ and 9.1, $p = 0.01$ for coefficient of variation).

We were able to show significant circadian rhythms for slightly more than 50% of the total number of days of recording using FEV₁ and PEF. This was also seen in most of the subjects (table 2). Results for subjects who showed at least three days with significant rhythms are given. The indices derived from the cosinor analysis were examined in the same way as for

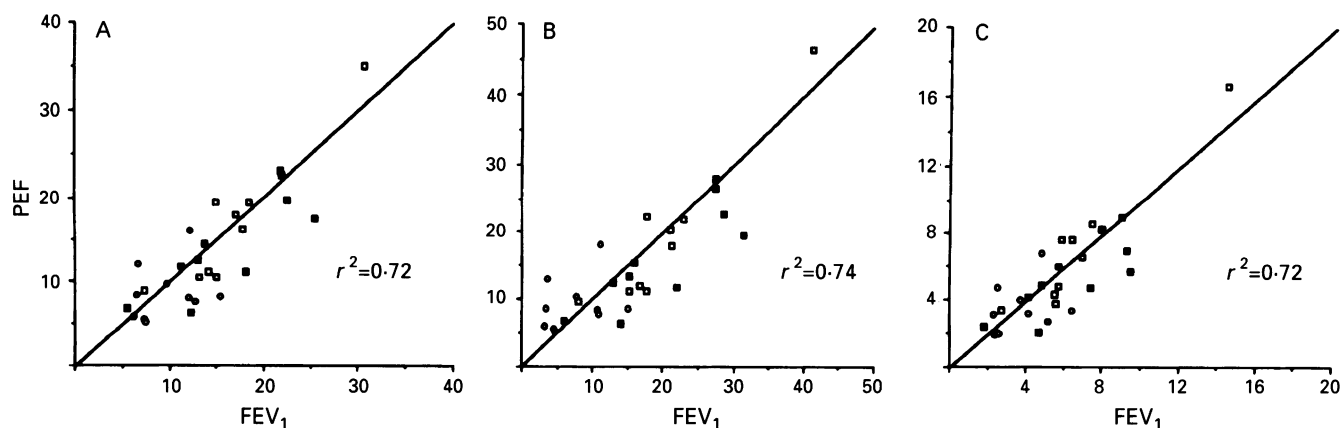


Figure 1 Individual results for the mean values of (A) amplitude % mean, (B) amplitude % lowest, and (C) coefficient of variation as obtained for each subject for the two week period of recording. No significant differences were seen in the values assessed by FEV₁ and PEF. The line of identity is shown as well as the r². ○, non-asthmatic subjects (group 1); □, asthmatic subjects taking a bronchodilator if needed (group 2); ■, asthmatic subjects on inhaled steroids (group 3).

Table 1 Mean (SD) circadian indices for FEV₁ and PEF in normal and asthmatic subjects

Group	Functional index	No. of days	Amplitude % mean			Amplitude % lowest			Coefficient of variation		
			Mean	Maximum	Minimum	Mean	Maximum	Minimum	Mean	Maximum	Minimum
Normal subjects	FEV ₁	9-15	9.6 (3.3)	18.4 (7.3)	3.5 (0.6)	10.5 (3.9)	21.7 (9.1)	3.5 (0.6)	3.6 (1.5)	7.5 (3.5)	1.5 (0.4)
	PEF	9-15	8.6 (3.4)	16.5 (6.3)	3.2 (0.7)	9.2 (3.9)	18.3 (7.8)	3.3 (0.7)	3.4 (1.5)	6.3 (3.5)	1.3 (0.3)
Asthmatic subjects on β ₂ adrenergic agents as needed	FEV ₁	9-14	16.5 (6.2)	26.9 (10.2)	7.0 (3.1)	18.8 (8.3)	34.1 (14.5)	7.3 (3.3)	6.7 (3.3)	11.6 (5.8)	3.0 (1.4)
	PEF	6-18	16.6 (8.2)	27.2 (12.2)	6.8 (3.6)	19.2 (11.5)	33.4 (19.5)	7.1 (3.8)	6.9 (4.0)	11.6 (7.1)	3.0 (1.7)
Asthmatic subjects on inhaled aerosols	FEV ₁	8-15	16.5 (6.3)	26.7 (11.9)	6.2 (2.3)	18.7 (7.8)	32.2 (16.9)	6.4 (2.4)	6.4 (2.6)	10.3 (4.7)	2.6 (1.0)
	PEF	7-15	14.6 (6.0)	22.3 (9.1)	7.1 (2.9)	16.4 (7.7)	26.5 (13.1)	7.4 (3.3)	5.4 (2.3)	8.5 (3.5)	2.8 (1.2)

FEV₁ = forced expiratory volume in one second; PEF = peak expiratory flow.

Table 2 Mean (SD) indices derived from cosinor analysis for FEV₁ and PEF in normal and asthmatic subjects

Group	Functional index	No. of significant/total days	Amplitude (%)			Acrophase (hour)		
			Mean	Maximum	Minimum	Mean	Maximum	Minimum
Normal subjects	FEV ₁	4-11/12-15	4.1 (1.9)	6.7 (3.9)	2.5 (1.6)	13:12 (1:24)	16:04 (1:47)	10:05 (2:11)
	PEF	3-9/9-15	4.2 (2.0)	5.9 (3.7)	2.5 (1.2)	13:01 (1:23)	15:46 (1:13)	9:19 (2:45)
Asthmatic subjects on β ₂ adrenergic agents as needed	FEV ₁	3-11/7-14	9.5 (6.0)	13.8 (9.6)	5.7 (3.7)	11:20 (2:30)	16:15 (2:10)	8:00 (2:38)
	PEF	3-10/11-18	8.0 (4.0)	10.7 (4.3)	6.5 (3.5)	12:36 (2:43)	15:18 (2:47)	8:51 (3:38)
Asthmatic subjects on inhaled aerosols	FEV ₁	5-10/11-15	8.1 (4.2)	10.6 (5.2)	5.5 (2.9)	13:54 (1:27)	16:30 (1:12)	10:04 (3:24)
	PEF	5-14/7-14	6.5 (3.6)	10.3 (6.7)	3.9 (2.2)	13:26 (1:36)	16:32 (1:30)	9:38 (3:31)

the arithmetical indices. The amplitudes showed the same tendency as for the indices given in table 1. There were no significant differences between variability in each index using FEV₁ or PEF by the Wilcoxon test (*z* values of 0.26 and 1.11, *p* > 0.05, for mean values of amplitude and acrophase respectively). Mean values differed significantly between normal subjects on the one hand, and asthmatic subjects on inhaled β₂ adrenergic agent on an as-needed basis and those taking inhaled steroids on the other hand, by the

Kruskal-Wallis test (*H* = 6.0, *p* = 0.05, and 7.0, *p* < 0.05 for PEF and FEV₁ for amplitude; no significant differences were recovered for acrophase). As a rule, acrophases (timing of the maximum value of the cycle) coincided around 14:00 hours with either FEV₁ or PEF.

A significant correlation was found between airway calibre and the categorical level of bronchial responsiveness on the one hand, and circadian indices on the other; the mean amplitude % mean FEV₁ is illustrated in fig 2 and the mean amplitude % mean PEF in fig 3.

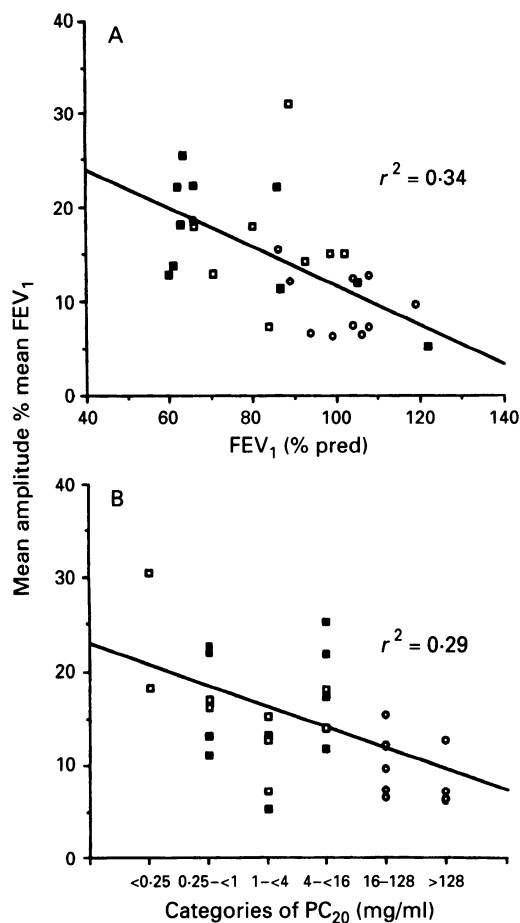


Figure 2 Relation between (A) FEV_1 (% pred) and (B) categories of PC_{20} and amplitude % mean for FEV_1 , the mean value being obtained for each subject for the two week period of recording. The r^2 values are given (significance at $p < 0.05$ level). \circ , non-asthmatic subjects (group 1); \square , asthmatic subjects taking a bronchodilator if needed (group 2); \blacksquare , asthmatic subjects on inhaled steroids (group 3).

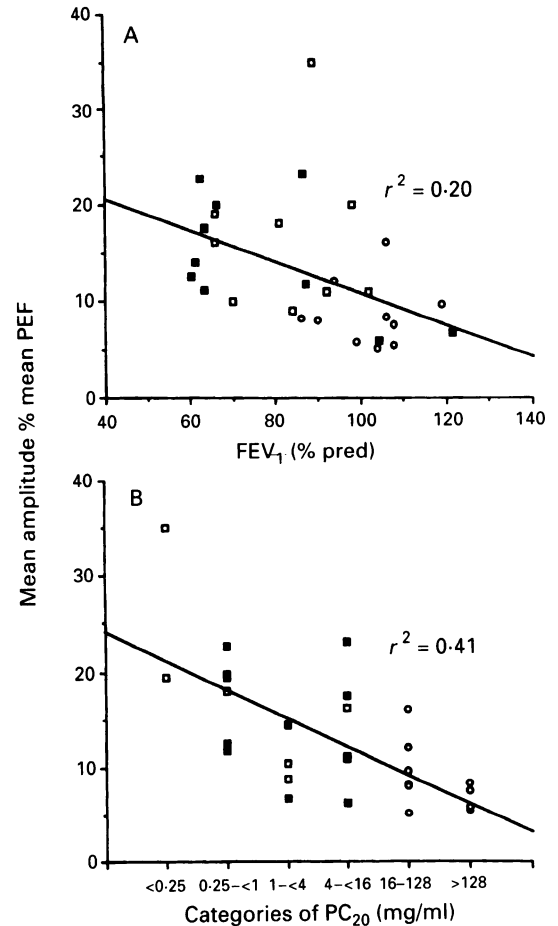


Figure 3 Relation between (A) FEV_1 (% pred) and (B) categories of PC_{20} and amplitude % mean for PEF, the mean value being obtained for each subject for the two week period of recording. The r^2 values are given (significance at $p < 0.05$ level). \circ , non-asthmatic subjects (group 1); \square , asthmatic subjects taking a bronchodilator if needed (group 2); \blacksquare , asthmatic subjects on inhaled steroids (group 3).

Discussion

Our study shows that circadian variations in airway calibre expressed by different means are similar using PEF and FEV_1 . Although FEV_1 is more sensitive than PEF in detecting changes in airway calibre in spontaneous¹³ and induced²² asthma, PEF seems to be as satisfactory as FEV_1 in describing circadian variations. In a study of 23 stable asthmatic subjects over a 24 hour period Meltzer and coworkers showed that the differences in maximum and minimum values were comparable with both PEF and FEV_1 .¹³ The reason for the sparsity of previously reported results is that portable instruments that record PEF and FEV_1 have only recently become available. Our study differed in that we compared fluctuations in PEF and FEV_1 simultaneously over a prolonged period (two weeks) with a maximum of nine assessments per day. We examined the amplitude of circadian variations first using arithmetical indices, of which the best three discriminants of subjects with and without respiratory symptoms were selected (amplitude as a percentage of mean and minimum values and coefficient of variation).⁷ Using PEF only, Higgins and coworkers found that the mean amplitude % mean was 13.3% and 8.5% in asthmatic and

non-asthmatic subjects, respectively. We found similar values – that is, 16.6% and 14.6% for the two asthmatic groups and 8.6% for the non-asthmatic subjects (table 1). Albertini and coworkers found corresponding values of 15.2% in well controlled asthmatic children and 9.9% in non-asthmatic children.²³ Brand and coworkers²⁴ and Henneberger and coworkers²⁵ studied asthmatic subjects only and found mean values of 14.5% and 17% respectively for amplitude % mean of PEF values.

We also examined the circadian variations using cosinor analysis which matches biological rhythms with sinusoidal functions. Although this means of analysis is theoretically interesting, its use can be criticised on the grounds that it seems simplistic to summarise complex intrinsic and extrinsic factors that can affect airway calibre with a sinusoidal fit using only one harmonic. Furthermore, the way cosinor analysis is applied is highly variable from one study to the next. The number of assessments per day and the degree of significance necessary for keeping the curves for analysis are variable. Furthermore, the fit of the sinusoidal function can be done for all days if the number of recordings per day is not sufficient, or for each day. In the original study by Hetzel and Clark,⁸

data from only 66% of 221 normal subjects who recorded their values four times a day for seven days were kept for analysis. Higgins and coworkers found significant fits in approximately 50% of a random sample of 346 subjects.⁷ In these instances, as well as in other reports,^{9,10} the fit of the sinusoidal function was made for all days and not for each day as in the present report. Kondo found a significant fit in 22% of 346 different study days in 125 stable asthmatic subjects,¹⁴ whereas the proportion was as high as 81% on average in eight asthmatic subjects assessed by PEF monitoring by Reinberg and coworkers.¹¹ The proportion of days in which significant rhythms were found was similar using FEV₁ (147/288; 51.0%) and PEF (172/341; 50.4%). A summary article written by Smolensky and coworkers showed that the amplitudes ("peak to trough") of variations in PEF and FEV₁ assessed by cosinor analysis varied from 2% to 20% in asthmatic subjects.²⁶ Hetzel and Clark showed that the mean amplitude was 50.9% among 56 asthmatic subjects who had just been discharged from hospital after an asthma flare-up.⁸ This is to be compared with mean daily amplitudes of 9.5% and 8.1% in the case of FEV₁ and of 8.0% and 6.5% among the stable asthmatic subjects included in our study who either required or did not require inhaled steroids. The acrophase (time of maximum value) was in the early afternoon, which corresponds to other published data,^{8,26} and did not differ using PEF or FEV₁.

The main purpose of this study was not to compare circadian variations in asthmatic subjects taking inhaled steroids on a regular basis and asthmatic subjects not taking such anti-inflammatory preparations. The design of our study did not allow for adequate comparison since this was not a randomised, double blind prospective study. We nevertheless included these two types of asthmatic subjects, the criteria for selection being the stability of asthma only. It is unlikely that the use of β_2 adrenergic agents significantly influenced our results. Only two subjects used the preparations twice or more per day and eight of the 19 asthmatic subjects used none during the course of the study. We also excluded from analysis all data that were recorded four hours or less after inhaling a short acting β_2 adrenergic agent.

Although this was not the main goal of our study, we also related circadian variations in airway calibre to baseline functional results such as spirometry and bronchial responsiveness to methacholine. Significant correlations were found between these indices, thereby confirming previous work.^{27,28}

It can be suspected, although this has not been demonstrated in a prospective way, that the use of portable instruments to record airway calibre in asthma can result in more satisfactory control of the asthmatic state, thereby reducing morbidity and mortality. This is what is recommended in international consensus reports on asthma,²⁹ although it has not been validated prospectively. It is interesting to note that only 75% of readings were kept for analysis using reproducibility criteria and that the proportion was similar for PEF and FEV₁. In this study we

had no mechanism to check compliance and honesty as the data were not stored on a computer chip. PEF data can be stored with another apparatus (VMX, Clement Clarke Inc, Columbus, Ohio, USA) but it does not record FEV₁.

In conclusion, it is widely accepted that airway calibre should be assessed repeatedly in asthma. Although absolute values recorded at one time or another are important, the variations shown by both of the indices described in our study are also relevant. Obtaining reference values for circadian variations among stable asthmatic subjects using PEF and FEV₁ – two functional indices that are widely used – can lead to useful comparisons with values obtained from asthmatic subjects who are thought to be unstable. It may well be that, in unstable asthmatic subjects, circadian variations will be more pronounced using FEV₁ than using PEF.

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