Intrasubject variability of maximal expiratory flow volume curve[1]

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Cochrane, G. M., Prieto, F., and Clark, T. J. H. (1977). *Thorax*, **32**, 171–176. **Intrasubject variability of maximal expiratory flow volume curve.** Analysis of airflow in the terminal portion of the maximal expiratory flow volume curve has been suggested as a useful test for the early diagnosis of chronic airways obstruction. Whether such an analysis can identify early disease, and whether any subsequent action can prevent the progress of chronic airways obstruction, is unknown and will require prospective studies. As a precursor of such a study we have tried to establish the intrasubject variability of those tests of forced expiration which may be used for screening. We therefore measured expiratory flow volume curves of five healthy males and five healthy females aged 20–30 years as this is an age-group in which early detection of airways obstruction may be of value. Flow volume curves were obtained on the same day of the week for six weeks, and on three separate days during this period we carried out three flow volume curves every hour from 9 am to 6 pm. The data were subjected to analysis of variance to determine the variability of each measurement. Data were collected from forced expired volume in one second (FEV_1), forced vital capacity (FVC), maximum expiratory flow rates at 50% and 75% of expired vital capacity, and forced expiratory time (FET). The results showed no consistent pattern of diurnal variation over the working day.

The variation in any subject for FEV_1 and FVC over the study period was considerably less than variations detected in the maximal expiratory flow rates at 50% and 75% of the expired vital capacity and FET. Our results suggest that the intrasubject variation found in flow rates of the terminal portion of the maximal expiratory flow volume curve and forced expiratory time may limit the usefulness of these tests in detecting early airways obstruction.

FEV_1 and FVC are more reproducible tests and are therefore particularly suited for cross-sectional screening. The more sensitive maximal expiratory flow volume curve may, however, be more useful for long-term studies in individuals when the onset of disease is sought, or for short-term challenge studies requiring the most sensitive index of change in airway characteristics.

Assessment of flow rates in the terminal portion of the maximal expiratory flow volume curve (MEFVC) and of the forced expiratory time (FET) have been suggested as useful tests in detecting early airflow obstruction and thus detecting patients at risk of developing chronic airways obstruction at an early stage (McFadden and Linden, 1972; McFadden and DeGroot, 1973; Cochrane *et al.*, 1974a and b).

However, the prognostic implications of an abnormally reduced maximal expiratory flow rate after expiring 75% of the vital capacity ($MEF_{75\%}$) or an increased FET in the presence of a normal forced expiratory volume in one second (FEV_1) are not known, although these abnormalities can be found in asymptomatic smokers in the presence of a normal FEV_1 (Abboud and Morton, 1975). The significance of an abnormal flow rate or FET depends in part on the predicted values for healthy subjects being used but these vary from study to

study, are derived from relatively small populations, and show considerable interstudy variation (Cherniack and Raber, 1972; McFadden and Linden, 1972; Bass, 1973; Cochrane *et al.*, 1974b). Whether abnormalities of $MEF_{75\%}$ and FET do in fact identify early disease or chronic obstructive bronchitis is not known and may be determined only by prospective population studies (Macklem *et al.*, 1974). As a precursor of such a study it is essential to establish not only the normal range for the given population to be studied but also to investigate the variability of the tests considered, to look at small airway behaviour to determine both the size of diurnal variations and the variability in healthy subjects in order to determine intrasubject variation. This information can then be added to our present knowledge of intersubject variation (Black *et al.*, 1974).

The aim of this study was to determine the blow-to-blow, day-to-day, and week-to-week variation in a small population of healthy subjects, both male and female, in the age-group approximately 20–30 years old as this is an age at which detection may be of value.

Subjects and methods

Five healthy women aged 19–24 (mean 21·5) years, height 160–168 (mean 165) cm, and five healthy men aged 20–30 (mean 26·6) years, height 151–190 (mean 172) cm, were studied. One woman and three men gave a smoking history (mean, one pack year) (Table 1). No subject had suffered an upper respiratory tract infection in the previous three months, but unfortunately one male subject suffered a severe respiratory tract infection with sputum production during the study and dropped out. All the subjects were healthy with no history of past chest illness apart from one woman who had been a 'wheezy child' but had no history of asthma as an adult.

Two parallel studies were conducted. Subjects made three MEFVC at hourly intervals throughout the day, starting at approximately 9 am and continuing through to 5 or 6 pm, and during the intervals between testing they carried out their normal activities; this study was repeated on three days approximately one week apart (and is termed '10-hourly[3] study' from here on). The smokers were asked not to smoke during study days. In the other study, subjects performed three MEFVC at the same time of the day on one day of the week over six weeks (termed 'weekly[6] study' from here on) and these data were analysed independently. All subjects were familiar with the manoeuvre, were highly motivated, and

Table 1 *Anthropometric data and smoking history of subjects*

Subject	Height (cm)	Age (yr)	Cigarettes smoked (pack years[1])
Males			
FP	151	30	2; none for 5 yr
GMC	172	29	4—occasional cigar for 2 yr
KM	175	30	Never
DQ	190	20	2
PS	174	24	Never
Mean	172	26·6	1·6
Females			
JL	160	24	Never
AB	166	23	Never
MM	166	23	Never
CM	168	19	2
PO	165	19	Occasional
Mean	165	21·5	0·4

[1]Pack years=(cigarettes per day/20)×years smoked.

carried out the manoeuvres on each occasion with one of two operators. On each occasion three MEFVC were performed and this is termed a triad.

MAXIMAL EXPIRATORY FLOW VOLUME CURVE
A differential spirometer (Ohio 840 spirometer) was used to provide volume and flow signals during the forced expiratory manoeuvres; the flow volume signals were simultaneously recorded on a storage oscilloscope (Telequipment DM64) and a multichannel ink jet recorder (Mingograph EM801). Flow rate signals were recorded at two levels of attenuation so that accuracy could be obtained in both the high and low flow rate measurements. Calibration of the flow signal was checked using a hot bead pneumotachygraph and integrator which had first been calibrated with a constant flow rate signal from a calibrated flow source, recording multiple flow-volume loops simultaneously on an ink jet recorder and oscilloscope. All MEFVC were recorded measuring exhaled volume and differentiating this volume to obtain simultaneous flow rates. The storage oscilloscope was used to store each curve so that each triad was observed for reproducibility (by eye) by both the operator and the subject. On one 10-hour study day the MEFVC were photographed on a 35 mm Edixa camera and the curves were superimposed at one magnification to demonstrate the variability of the curves (see Fig. 1). The curves were analysed for forced vital capacity (FVC), FEV_1, peak expiratory flow rate (PEFR), maximal expiratory flow rate at 25% ($MEF_{25\%}$), at 50% ($MEF_{50\%}$), and 75% ($MEF_{75\%}$) of the vital capacity, taking total lung capacity as zero volume.
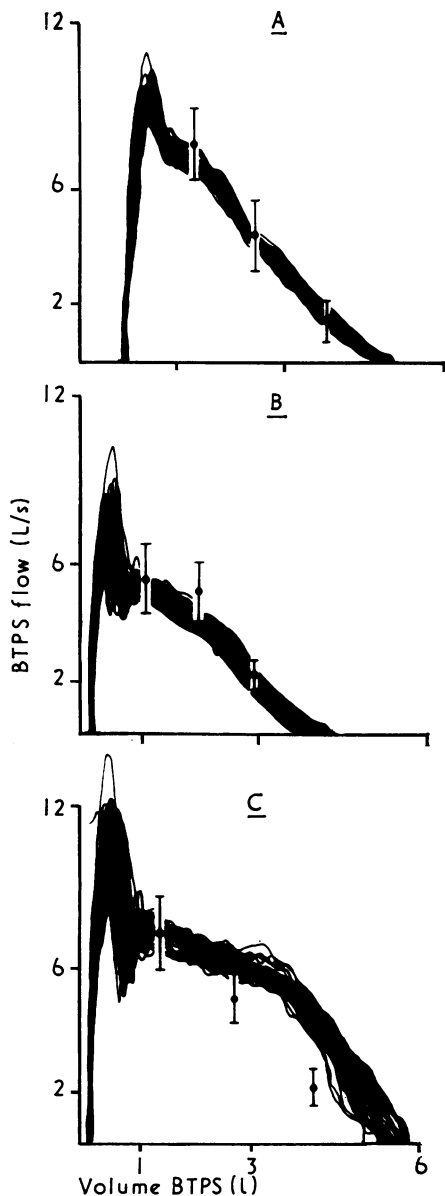
Fig. 1 *Superimposed flow volume curves obtained on one day in three subjects assuming a fixed total lung capacity:* (A) *above average reproducibility;* (B) *average reproducibility; and* (C) *below average reproducibility. The mean and 95% intersubject confidence limits obtained from Bass (1973) are shown.*

Mean expiratory flow rates were determined for 25% to 75% and 40% to 80% of the vital capacity. The zero time point for the FEV_1 and FET were determined by the method described by Dayman

(1967) as the point where a line drawn from the steepest portion of the volume curve crosses the zero volume line.

The results were calculated from the time base traced by one observer. Ten per cent of the data was randomly selected and independently analysed by a second observer, and no significant observer error was found.

STATISTICAL ANALYSIS
Every measurement obtained from the MEFVC over the 10-hourly[3] study was analysed by hierarchial analysis of variance (Davies, 1967) to obtain the intersubject variation and intrasubject variation related to the changes from blow-to-blow (triad variance), hour-to-hour (hourly variance), day-to-day (daily variance), and the change from subject-to-subject (subject variance). The data were analysed for each subject as absolute measurements and were not related to the predicted values for their age, height or sex.

The weekly[6] study was also analysed in the same way but the variation was related only to triad and days over the six weeks.

Results

COEFFICIENT OF VARIATION OF TRIADS
The coefficient of variation of triads is shown in Table 2 and for FVC and FEV_1 was 2·7% for the 10-hourly[3] study and 1·8% for the weekly[6] study compared with the considerably greater coefficient of variation, 9·5% and 11·8% for $MEF_{75\%}$ and FET in the 10-hourly[3] study and 7·3% and 13% respectively for the weekly[6] study. The coefficient of variation for the triads contains the variations associated with accuracy and reproducibility of the recorder trace, the variability of the spirometer and its calibration, the reading and observer error in obtaining the data from the trace, the reproducibility of each subject over a short period of time, and any training effect on

Table 2 *Analysis of variance for 10-hourly[3] study and weekly[6] study*

	Coefficient of variation				
	FVC	*FEV₁*	*MEF₅₀%*	*MEF₇₅%*	*FET*
10-hourly[3] study					
Triad	2·7	2·7	5·5	9·5	11·8
Hourly	1·8	2·3	3·7	6·2	9·4
Daily	2·9	2·9	5·1	8·2	12·0
Subject	14	18·5	25	34	18
Weekly[6] study					
Triad	1·8	1·85	4·7	7·3	13
Weekly	2·9	3·35	5·8	8·9	13
Subject	9·0	18·0	25·0	34·0	19·7

the subjects by repeating the manoeuvre over 80 times during the study. The similarity of the coefficients of variation for each measurement between the 10-hourly[3] study (90 MEFVC) and the weekly[6] study (18 MEFVC) suggests that there is little training effect.

HOURLY VARIATION
There appeared to be no consistent pattern of diurnal variation between the hours 9 am to 6 pm, but the different measurements varied in the same direction, ie, if FEV_1 was reduced the flow rates in the terminal portion of the curve were also reduced. The intraday variation is also shown in Fig. 1 where three subjects are shown, one who is highly variable throughout the day (2C), another showing the pattern we found in most subjects (2B), and one with remarkably little variation (2A) compared with the remaining subjects. For illustrative purposes it is assumed that the subjects always reached total lung capacity, and any variation occurs at residual volume. Throughout we have made this an assumption.

The coefficients of variation for the hourly change (Table 2 and Fig. 2) show a similar pattern and magnitude to the triad changes with little variation with FVC and FEV_1 but a larger coefficient of variation for $MEF_{75\%}$ and FET.
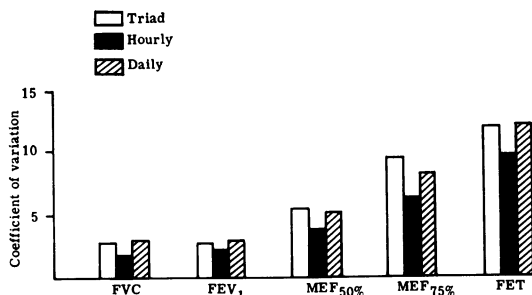

Fig. 2 Results of the analysis of variance for the 10-hourly[3] study.

DAILY VARIATION
The day-to-day variation of FVC and FEV_1 were small for both the 10-hourly[3] study and the weekly[6] study (Table 2), and $MEF_{75\%}$ and FET again showed greater variation and the magnitude was similar in both studies.

The coefficients of variation given by the hierarchial analysis are mean values, and individual differences can be considerable. Figure 3 shows the coefficient of variation for the mean of three blows over the hours and days of the 10-hourly[3] study. The measurements with least
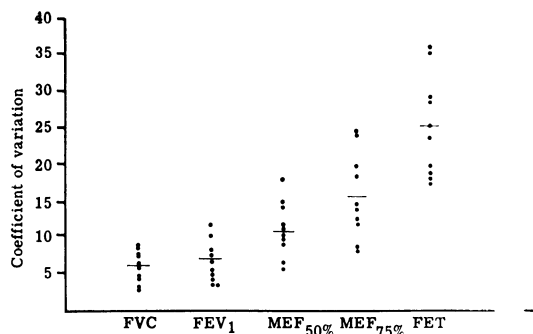

Fig. 3 Coefficients of variation for components of the maximal expiratory flow volume curve derived from the mean of triads of blows throughout hours and days of the study.

variation between individuals as well as least variation over the hour or day of study were FVC and FEV_1.

INTERSUBJECT VARIATION
The mean intrasubject variation and intersubject variation for all the data are shown in Fig. 4. The large intersubject variation in FVC, FEV_1, $MEF_{50\%}$ and $MEF_{75\%}$ was shown to be related to sex and height, and slightly to age of the individuals studied. Our age range (19–30 years) was comparatively small, and therefore age has only a minor effect on the large intersubject variation. FET, however, has a comparatively small intersubject variation and was not in our study significantly related to sex, height or age. This comparatively small intersubject variation with a large intrasubject variation almost certainly
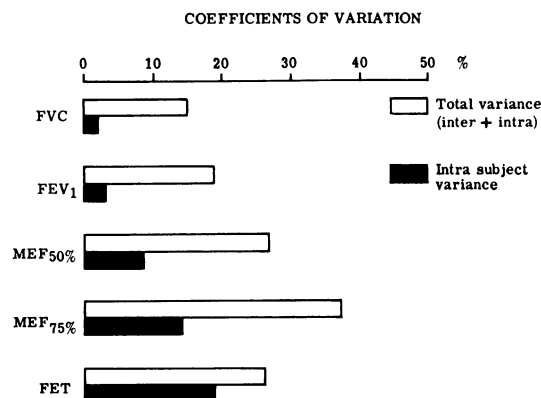

Fig. 4 Coefficients of variation for components of the maximal expiratory flow volume curve for intrasubject and intersubject variation.

precludes FET from being a sensitive discriminatory test, unlike the other measurements which, when corrected for height, age, and sex, have a small intrasubject variation. The mean flow rate measurements had coefficients of variation for both studies in the same order as $MEF_{75\%}$, while FEV_1/FVC had a coefficient of similar magnitude to FVC.

Discussion

Data on the reproducibility and intrasubject variation of the tests which are thought to detect abnormalities of small airway functions are few (Becklake *et al.*, 1975; McCarthy *et al.*, 1975; McFadden *et al.*, 1975) and the variability of the forced expiratory manoeuvre in non-smokers is poorly documented (Dawson, 1966; Stebbings, 1971).

Berry (1974) has delineated three sources of variation found within the forced expiratory manoeuvre: (*a*) variations associated with the transducer, recording the trace and obtaining the data from the tracing; (*b*) variations within the subjects without a known change in physiological state; and (*c*) intersubject variations, allowing for relevant individual characteristics.

The results of this study show that in a highly selected small group of subjects the 'error standard deviation' (square root of the triad variance) (Table 2) is small for FVC and FEV_1 and thus the variation associated with their actual measurement is small if suitable equipment and recording apparatus is used. However, for measurements such as FET significant variation can be expected because of the blow-to-blow repeatability and the limitations of measuring techniques (Macdonald *et al.*, 1975).

Examination of the coefficient of variation for the triads allows two conclusions to be drawn. The first is that reasonable accuracy for FVC and FEV_1 can be obtained from a single blow in a trained subject as the coefficient of variation when examined for triad, hourly, and daily variance is very small (Table 2). However, even in trained subjects, for $MEF_{75\%}$ and FET more than three blows would be required to provide sufficient information for an acceptable standard error of the mean (SEM) (eg, six blows are required for $MEF_{75\%}$ to provide SEM ±5%).

Based on our data we can predict that in the experimental situation (for example, in challenge tests where the individual is used as his own control) a change of ±6% of the initial value for FVC or FEV_1 will be significant but changes of ±19% or ±23·6% are needed for $MEF_{75\%}$ and

FET measurements to provide a similar degree of confidence that the challenge caused a significant change. Using the intersubject coefficient of variation we can also calculate the number of subjects needed to obtain a reliable estimate of normal values for each of the derivatives of the forced expirogram; for example, the sample population for $MEF_{75\%}$ would have to be four or five times the size of the sample necessary to provide normal values for FEV_1.

We could detect no consistent pattern of diurnal variation in any given individual; there was a tendency for the results of all measurements obtained from the forced expiratory manoeuvre to be lower after a large meal but this was never significant and was not investigated further.

The weekly[6] study showed significantly higher values for FVC (mean 4·7 1 compared with a mean of 4·35 1 for 10-hourly[3] study), suggesting that an informed subject faced with a complete study day tended to 'pace' his performance despite apparently performing the maximal forced expiratory manoeuvres in a fashion that satisfied the investigators. This did not, however, appear to introduce additional variation. As there was no consistent fall over the day this was not likely to have been fatigue but rather an intellectual 'marathon' effect.

The variation over both study periods did not show any correlation with activity of the previous day or morning before testing. No meteorological or pollution data were obtained, but the climate in our laboratory was constant throughout the testing period. The possibility that physiological fluid retention would cause consistent alteration in the tests of small airway function (Collins *et al.*, 1973) was not supported by the results in the female subjects when related to their menstrual cycle. The within-subject variation for smokers was not significantly different from that of non-smokers.

In conclusion, the data show that the more sensitive tests of airflow obstruction have a large intrasubject variation. For FET measurements, the intrasubject variation is nearly as great as the intersubject variation, and this suggests that FET is unlikely to be a suitable test for the detection of subjects with early airways disease in epidemiological surveys. The relatively poor reproducibility of $MEF_{50\%}$ and $MEF_{75\%}$ may also limit the usefulness of these tests. The absence of diurnal variation allows testing to take place throughout the working day but the well-documented effects of colds and respiratory tract infections may increase seasonal variation, and this may limit screening to certain times of the year.

The considerably smaller coefficients of variation for FEV_1, FVC, and FEV_1/FVC suggest that these measurements may be the most suitable for screening, and further work is required to determine more precisely their normal values and their natural history in healthy smokers and non-smokers. The prognostic implications of those abnormalities detected by more sensitive tests such as closing volume and $MEF_{75\%}$ are unknown. The added sensitivity of the tests is compromised by their lack of reproducibility which makes them less suitable for cross-sectional population screening than FEV_1 and FVC. The greater sensitivity of tests such as $MEF_{75\%}$ probably can be best deployed in longitudinal studies when subjects act as their own controls, and this has already been used to show the benefits of stopping smoking (Bode et al., 1975).

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