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Transit-time analysis of the forced expiratory spirogram during clinical remission in juvenile asthma

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ABSTRACT The mean transit time (MTT), coefficient of variation (CoV), and index of skewness (IoS) of transit times of the forced expiratory flow/time curve have been compared with maximal mid-expiratory flow (MMEF), flow at 75, 50, and 25% of vital capacity ($\dot{V}_{75}$, $\dot{V}_{50}$, and $\dot{V}_{25}$), and the ratio of forced expiratory volume in 1 second (FEV_1) to vital capacity (VC) in 51 asthmatic children judged on clinical grounds to be in remission. In 19 children all eight indices were normal. Of the remaining 32, MTT was normal in 5, $\dot{V}_{50}$ in 11, $\dot{V}_{75}$ in 12, and FEV_1/VC and MMEF in 13 each. MTT was significantly more sensitive in detecting abnormality when other indices were normal, and abnormalities in MTT were of significantly greater magnitude when present. In 12 patients with at least one abnormal index given salbutamol aerosol, MTT was not more sensitive than MMEF, $\dot{V}_{25}$, FEV_1/VC, or $\dot{V}_{50}$ in detecting change.

Conventional derivatives of the forced expiratory spirogram—namely, forced expiratory volume in 1 second (FEV_1), FEV_1/vital capacity (VC) ratio, maximal mid-expiratory flow (MMEF), and flow at 75, 50, and 25% of VC ($\dot{V}_{75}$, $\dot{V}_{50}$, and $\dot{V}_{25}$)—each measure only a single attribute of the spirographic curve. Much information may thereby be lost. A comprehensive description of the curve may be obtained by moment analysis of the flow/time curve that is implicit in the routine volume/time curve (Fish *et al*, 1974). The forced vital capacity (FVC) can be considered as a large number of discrete volume increments (or even gas molecules) each of which is distinguished by a transit time measured from the start of the expiration to a given point on the record. The distribution of transit times can be described mathematically by the mean transit-time (MTT), the coefficient of variation (CoV) of transit-times, and the index of skewness (IoS) of the transit-time distribution. These are derived from the first three moments of the flow/time curve (see appendix); higher moments can be derived but add little to the description.

We have compared MTT, CoV, and IoS with conventional spirographic indices in 51 asthmatic children who considered themselves free from symptoms at the time of study and in whom wheezes were not audible on auscultation. Nineteen of these children showed no abnormality of the spirogram, however analysed. In the remaining 32, abnormalities of MTT were both more frequent and of greater magnitude than those of any other index.

Methods

SUBJECTS

Thirty-five children (17 boys, 18 girls) aged between 7 and 14 years were selected from those attending a summer camp run by the Auckland Asthma Society. Sixteen children (9 boys, 7 girls) aged between 7 and 13 years were patients under the care of one of us (AL). All were Europeans and had had typical asthma since early childhood; two were not receiving any treatment at the time of study and the rest were having regular treatment with one or more of salbutamol (aerosol or tablets), disodium cromoglycate by Spinhaler, and beclomethasone aerosol. None was receiving oral steroids. Admission to the study required absence of symptoms and of clinical evidence of upper respiratory infection or wheeze. All were studied in the morning, and none had taken any medication since the previous day.

PROCEDURE

Each patient, after instruction and practice, made forced expirations from total lung capacity (TLC) to residual volume, in the standing position, into a calibrated Med Sci model 565 rolling-seal spirometer

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through a tube 60 cm long and 5 cm wide. Volume and flow signals from the spirometer were sampled every 10 minutes and stored by a PDP8-E computer. Sampling ceased 6·3 s after the first detected volume change. The computer executed the following calculations on the stored data: (1) the volume/time curve at peak flow was extrapolated back to TLC and the interval from the first detected volume change to this intercept was measured and printed. It was usually less than 0·1 s; if more than 0·3 s all data from that breath were rejected; (2) starting from the peak-flow/TLC intercept, the time scale was divided into intervals of 100 min and each corresponding volume change assigned a transit-time up to the midpoint of the interval. Computation ceased at 6 s after 60 intervals, unless an inspiratory signal appeared before then. In this case computation stopped at the beginning of the inspiratory volume change. This rescued otherwise satisfactory curves when the subject inadvertently inspired after the FVC without taking the tube from his lips; and (3) MTT, CoV, and IoS were calculated (see appendix) and printed, together with FVC, MMEF, $\dot{V}_{75}$, $\dot{V}_{50}$, and $\dot{V}_{25}$. In addition to the printed data, all volume/time curves for each patient were displayed, superimposed, on a storage oscilloscope. If one curve appeared obviously different from the others the data for that curve were rejected and an extra expiration made. Having obtained three technically satisfactory curves, the one showing the biggest FVC was used for further analysis.

All patients performed, in addition, three satisfactory slow and three forced expirations into a wet spirometer (Mijnhardt Volutest). FEV_1 and VC were measured by hand from the traces and FEV_1/VC calculated from the biggest values of each obtained.

The 16 patients of AL carried out the whole procedure both before and after an effective dose of salbutamol aerosol.

CALCULATIONS

Prediction was made of the normal value for each variable as follows. For FEV_1/VC (wet spirometer) the value 85·8 (SD 6·78)% was used for all subjects (Liang *et al*, 1975). Normal values for MMEF, $\dot{V}_{75}$, $\dot{V}_{50}$, $\dot{V}_{25}$, MTT, CoV, and IoS were derived from 107 healthy subjects aged between 6 and 15 years selected from a study by Macfie *et al* (1978). Regressions were calculated for each variable on age and height, separately and combined. The prediction equations giving significant single or partial correlations and the smallest residual standard deviations were chosen, and were as follows:

MMEF	= 0·02866 (ht) − 1·750	$sy{:}x_1$	0·4935
$\dot{V}_{75}$	= 0·1848 (age) + 0·02682 (ht) − 1·922	$sy{:}x_{12}$	0·6200
$\dot{V}_{50}$	= 0·03296 (ht) − 2·1174	$sy{:}x_1$	0·4990
$\dot{V}_{25}$	= 0·02783 (ht) − 0·09838 (age) − 1·696	$sy{:}x_{12}$	0·3392
MTT	= 0·004287 (ht) − 0·0632	$sy{:}x_1$	0·1095
CoV	= 6·572 (age) − 0·8967 (ht) + 145·9	$sy{:}x_{12}$	14·5300
IoS	= 1·704	sy	0·6976

MMEF, $\dot{V}_{75}$, $\dot{V}_{50}$, and $\dot{V}_{25}$ are given in 1 s^{-1}, MTT in s, CoV as a percentage (dimensionless), height in cm, and age in yr. IoS (dimensionless) was not significantly correlated with age and/or height. s is the residual standard deviation.

Each measured value of a variable in the present study was expressed as the difference between it and the expected mean value in standard deviation units—for instance, for $\dot{V}_{25}$ as (measured $\dot{V}_{25}$ minus predicted $\dot{V}_{25}$)/0·3392. A table of these derived values for all patients may be obtained from the authors (Dr Harris) on request.

RESULTS*

Figure 1 shows the distribution of the eight indices of the spirogram among the 51 patients; data obtained after salbutamol inhalation are not included.

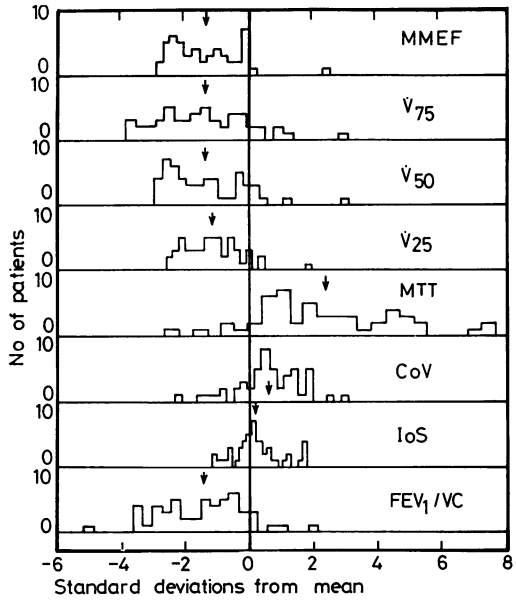

Fig 1 *Histograms showing distribution of eight spirographic indices in 51 asthmatic children in clinical remission. Each index is expressed as deviation from expected normal mean value, in standard deviation units. Range of each index is divided into 24 bins in each case.*

*Full details of individual results are obtainable from the authors (Dr Harris) on application.

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Table 1 *Mean deviations, in standard deviation units, of observed values of eight spirographic indices from the expected normal mean value in 51 asthmatic children in clinical remission*

Index	*MMEF*	$\dot{V}_{75}$	$\dot{V}_{50}$	$\dot{V}_{25}$	*MTT*	*CoV*	*IoS*	FEV_1/VC
Mean	−1·3484	−1·4051	−1·3922	−1·1647	+2·3631	+0·6026	+0·1817	−1·4538
SE	1·0972	1·4398	1·2529	0·8729	2·1985	1·1526	0·7118	1·3796
SEM	0·1536	0·2016	0·1754	0·1222	0·3079	0·1614	0·0997	0·1932
t	−8·7790	−6·9695	−7·9356	−9·5283	+7·6761	+3·7335	+1·8230	−7·5255
2P	≪0·001	≪0·001	≪0·001	≪0·001	≪0·001	<0·001	>0·05	≪0·001

SE=Standard error of deviations; SEM=Standard error of mean deviation; 2P=Two-tailed probability of chance deviation of mean from zero.

MMEF, $\dot{V}_{75}$, $\dot{V}_{50}$, $\dot{V}_{25}$, and FEV_1/VC lay predominantly below, and MTT, CoV, and IoS predominantly above, the mean normal value. Mean values for all indices save IoS (table 1) differed very significantly ($2P<0·001$) from the mean normal values, represented by deviations of zero in fig 1.

An abnormal result was arbitrarily defined as a deviation of more than 2 SD below the mean normal value for MMEF, $\dot{V}_{75}$, $\dot{V}_{50}$, $\dot{V}_{25}$, and FEV_1/VC, above this value for MTT and in either direction for CoV and IoS. By this definition, 19 patients showed normal values for all eight indices. In each of the remaining 32 patients at least one index was abnormal. The relative power of each index to show abnormality was assessed as follows. Of these 32 patients, those with a normal MMEF and an abnormal $\dot{V}_{75}$ were counted, then those with a normal MMEF and an abnormal $\dot{V}_{50}$, and so on through the indices. Next, those with a normal $\dot{V}_{75}$ but an abnormal MMEF, a normal $\dot{V}_{75}$ but an abnormal $\dot{V}_{50}$ and so on were counted. This procedure was followed for all indices, and the results are shown in table 2.

Summation of roman numbers in each column of table 2 gives a score for each index, and the possible score in each case is the sum of the normal patients (bold numbers) in all other columns. The highest fractional score (actual/possible) is that for MTT. $\dot{V}_{75}$, FEV_1/VC, and $\dot{V}_{50}$ follow, roughly equal. MMEF scores less well, $\dot{V}_{25}$ and CoV score poorly, and IoS scores nil. Exclusion of IoS (lower part of table 2) does not affect the ranking of the other indices. The numbers of actual and missed (possible minus actual) scores were analysed between pairs of indices by the χ^2 test. The yield of MTT was higher than that of any of its three closest rivals ($2P<0·0005$) while the latter ($\dot{V}_{75}$, FEV_1/VC, and $\dot{V}_{50}$) did not differ significantly from each other in yield.

Table 2 *Numbers of patients showing abnormal and normal results in pairs of indices*

	MMEF	$\dot{V}_{75}$	$\dot{V}_{50}$	$\dot{V}_{25}$	*CoV*	*MTT*	*IoS*	FEV_1/VC
	13	4	2	1	3	9	0	5
	3	**12**	3	3	2	10	0	6
	0	2	**11**	1	2	8	0	4
	10	13	12	**22**	3	17	0	13
	19	19	20	10	**29**	25	0	18
	1	3	2	0	1	**5**	0	1
	19	20	21	10	3	27	**32**	19
	5	7	6	3	2	9	0	**13**
Total abnormal	57	68	66	28	16	105	0	66
Total possible	124	125	126	115	108	132	105	124
Missed "scores"	67	57	60	87	92	27	105	58
Actual score / Possible score	0·460	0·544	0·524	0·244	0·148	0·795	0	0·532
Excluding IoS								
Total abnormal	38	48	45	18	13	78	—	47
Total possible	92	93	94	83	76	100	—	92
Missed "scores"	54	45	49	65	63	22	—	45
Actual score / Possible score	0·413	0·516	0·479	0·217	0·171	0·780	—	0·511

Only 32 patients showing at least one abnormal index are considered. Bold number in each column is number of patients showing a normal result for that index. Numbers in horizontal row corresponding to each bold number are numbers of these patients showing abnormal results in other indices. Sum of roman numbers in each vertical column is total "score" of that index; sum of bold numbers in all other columns is possible "score" for that index.

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In fig 2 MTT is plotted in SD units against $\dot{V}_{75}$, FEV_1/VC, and $\dot{V}_{50}$ respectively for all 51 patients. Counts of patients falling around ± 2 SD and ± 3 SD are shown in the upper right-hand corner of each plot. At both levels of confidence, MTT "revealed" abnormality, when the other variable did not, more often than the converse. In four of six cases this difference was significant by χ^2 test, as shown.

EFFECT OF SALBUTAMOL AEROSOL

Of the 16 patients given salbutamol aerosol, four had normal indices throughout, both before and after aerosol. Mean values and SDs for the remaining 12 patients are shown in table 3. The significance of the change in each index after inhaling salbutamol was assessed by paired *t* test. In order from highest to lowest *t*, the indices were MMEF, $\dot{V}_{25}$, FEV_1/VC, $\dot{V}_{50}$, MTT, $\dot{V}_{75}$, IoS, and CoV. The change in CoV was insignificant; that in IoS just failed to reach the 5% level of significance; the remaining changes were significant at the 1% level or better. It is worth noting that CoV once, and IoS twice, increased to abnormal values after salbutamol, having been normal before; the mean change in IoS was also an increase.

Discussion

The aim of this investigation was to compare the sensitivity of indices derived by moment analysis with that of conventional indices in distinguishing abnormality from normality. For this reason patients without overt symptoms of asthma were chosen, in the expectation that many would in fact be mildly abnormal. Such was the case. The analysis of such data involves a basic assumption—that the presence of an abnormal result means that abnormality is indeed present. We have made this assumption for the purposes of this analysis. Our conclusions do not necessarily apply to adults with chronic asthma or to asthma of greater severity.

Of 32 patients in whom one or more indices were abnormal, MTT was normal in only five, followed by $\dot{V}_{50}$ (11), $\dot{V}_{75}$ (12), FEV_1/VC, and MMEF (13 each) (table 2). MTT thus detected more abnormal patients than any other index. The value of an index

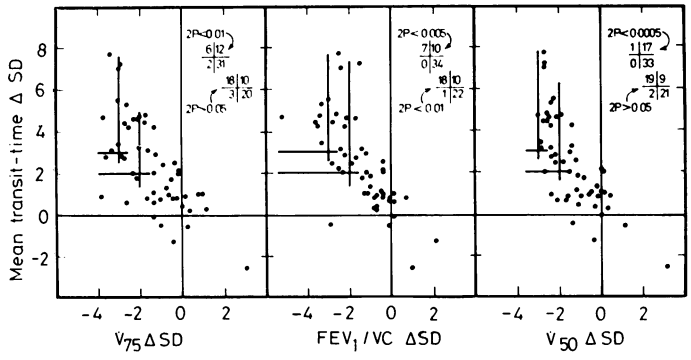

Fig 2 *MTT plotted against $\dot{V}_{75}$, FEV_1/VC, and $\dot{V}_{50}$ respectively, each as deviations from expected normal mean value in standard deviation units. Deviations of 2 SD and 3 SD in abnormal direction are marked on left of each figure. On right are shown numbers of patients in four quadrants of each division, with probability of a chance result by χ^2 test.*

Table 3 *Mean deviations, in standard deviation units, of observed values of eight spirographic indices from expected normal mean value in 12 asthmatic children, before and after salbutamol aerosol*

Index	*MMEF*		$\dot{V}_{75}$		$\dot{V}_{50}$		$\dot{V}_{25}$	
	B	*A*	*B*	*A*	*B*	*A*	*B*	*A*
Mean	−1·9674	−0·7148	−2·1007	−0·8970	−1·9459	−0·5396	−1·6303	−0·4919
SE	0·7567	1·0481	0·8532	1·1920	0·8038	1·0587	0·6000	0·9538
t	−6·5820		−3·1255		−5·2376		−6·4542	
2P	<0·001		<0·01		<0·001		<0·001	
Index	*MTT*		*CoV*		*IoS*		FEV_1/VC	
	B	*A*	*B*	*A*	*B*	*A*	*B*	*A*
Mean	3·8879	2·0096	0·8789	0·4832	0·0999	0·7164	−2·5897	−0·9182
SE	1·4126	1·6656	0·7035	1·2426	0·2975	0·9642	1·1359	0·9603
t	3·5534		1·2105		−2·1155		−5·5575	
2P	<0·005		>0·20		>0·05		<0·001	

B, A=Before and after salbutamol; SE=Standard error of deviations; *t*=Paired *t* of differences in deviations B and A; 2P=Two-tailed probability of mean difference differing by chance from zero.

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lies as well, however, in the detection of abnormality that is missed in the same patient by other tests; in this respect MTT is still superior, while the order of $\dot{V}_{75}$, FEV_1/VC, $\dot{V}_{50}$, and MMEF is slightly rearranged (table 2). Finally, the magnitude of abnormalities in MTT is greater than those in other indices. Figure 2 shows this for $\dot{V}_{75}$, FEV_1/VC, and $\dot{V}_{50}$; MTT yields significantly fewer false negatives than these indices, especially beyond 3 SD from the normal mean value.

The other indices derived by moment analysis (CoV and IoS) were conspicuously poorer than conventional indices by the above criteria. This is no doubt partly because their normal range is relatively wide, as the prediction equations above show. In the great majority of patients CoV and IoS were normal, although the means for both were increased and that for CoV was significantly greater than the normal mean (table 1). We have shown elsewhere (Macfie *et al*, 1978) that inhalation by normal adults of 80% helium, 20% oxygen greatly reduced MTT but did not increase CoV or IoS significantly. Helium, in effect, reduces resistance only in large airways, and the inference is that if change of large-airway resistance does not alter CoV and IoS, any change in these must be due to changes in small airways. The present results are consistent with this view if one supposes that in these mildly asthmatic patients mainly large airways were affected. Neuburger *et al* (1976), who studied 37 patients with cystic fibrosis, found that CoV in 20 patients (54%) and IoS in six patients (16%) were abnormal; these findings were attributed to the presence of small-airways disease, and show that CoV and IoS are often abnormal in a condition with frequent involvement of small airways. The increase to abnormal values of CoV and IoS in three of our patients after salbutamol implies that in them the aerosol dilated some small airways and not others.

The results of Fish *et al* (1974), who found that MTT increased without change of relative dispersion of transit times (analogous with CoV) in asthmatic patients exposed to bronchial challenge with antigen or metacholine, are consistent with the present findings.

Our data show that MTT, while apparently the most sensitive indicator of abnormality tested, is not necessarily the most sensitive detector of change after salbutamol aerosol. This result may be due to the small number (12) of subjects analysed for change due to salbutamol. It is difficult to see how small-airway effects of the drug could do other than reduce MTT, and this effect would presumably summate with the inferred large-airway effects.

MTT would therefore appear to be a more sensitive guide than other indices to the presence of abnormality in asymptomatic asthma, and as such would be useful in the routine management of these patients. Unfortunately MTT cannot be quickly measured without on-line computerisation, although it can be derived simply enough from the conventional forced spirogram. As shown in the appendix, MTT is the area under the FVC curve, truncated at 6 s, divided by the FVC.

Appendix

Figure 3 shows a flow/time curve and the corresponding volume/time curve, which is like the conventional spirogram upside down. The flow/time curve is shown divided into infinitesimal time-increments dt, the volume/time curve into finite volume increments ΔV. The mean transit-time J is the first moment α_1 about the origin of the flow/time curve. Let the 2nd and 3rd moments about this mean be denoted μ_2 and μ_3. Let the corresponding quantities related to finite increments be A_1, M_2, and M_3. Then:

$$t = \alpha_1 = \frac{\int F t dt}{\int F dt} \approx A_1 = \frac{\Sigma t \Delta V}{\Sigma \Delta V} = \frac{\Sigma t \Delta V}{FVC}$$

$$\mu_2 = \frac{\int F(t-\bar{t})^2 dt}{\int F dt} \approx M_2 = \frac{\Sigma (t-\bar{t})^2 \Delta V}{FVC}$$

$$\mu_3 = \frac{\int F(t-\bar{t})^3 dt}{\int F dt} \approx M_3 = \frac{\Sigma (t-\bar{t})^3 \Delta V}{FVC}$$

Derived from these parameters of the flow/time curve, we have:

Mean transit-time (J) $= \alpha_1 \approx A_1$
Standard deviation (SD) $= \mu_2^{1/2} \approx M_2^{1/2}$
Skewness (S) $= \mu_3^{1/3} \approx M_3^{1/3}$
Coefficient of variation (CoV)
$= SD/\bar{t} = \mu_2^{1/2}/\alpha_1 \approx M_2^{1/2}/A_1$
Index of skewness (IoS) $= \mu_3/SD^3 \approx M_3/SD^3$

It will be evident that $\bar{t}$, defined as $\frac{\Sigma t \Delta V}{FVC}$, is equal to

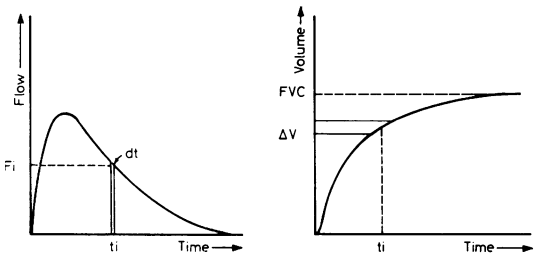

Fig 3 *Flow/time and volume/time curves from a forced expiration (diagrammatic only: arbitrary units).*

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the area above the volume/time curve (ie below the conventional spirogram) divided by the FVC.

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performed successfully and safely, lobectomy or segmental resection are the operations usually recommended (Sabiston and Wolfe, 1976). Bosher *et al* (1959) in their survey of 350 cases showed that 89 out of 110 cases (where suitable data were available) were superficial enough to allow excision without pulmonary resection. In our two cases local resection of the lesions including the feeding vessels without damaging functional lung tissue was easily and safely carried out.

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Correction

Liang, A *et al.* Transit-time analysis of the forced expiratory spirogram during clinical remission in juvenile asthma. *Thorax*, 1979, **34**, 194–199.

Line 13 page 195 should read . . . intervals of 100 ms and each corresponding volume . . .