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The short-term repeatability of histamine bronchial testing in young males. The SUS study

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We have measured bronchial responsiveness (BR) to histamine on two occasions between 5 and 24 h apart, to determine if conventional and new indices of BR are repeatable. A random sample of 29 healthy male subjects with a mean age of 19 (SD 3·44) years from a larger study repeated a Yan method test of BR, recording both partial and maximal expiratory flow–volume (PEFV and MEFV) curves.

From the MEFV curves log-dose slopes (LDS) for forced expiratory volume in 1 sec (FEV_1), forced expiratory flow between 25% and 75% of forced vital capacity (FVC) ($FEF_{25-75\%}$), mean expiratory flow at 30% and 40% of FVC (MEF_{30}, MEF_{40}), and the first moment of the spirogram (α_1) truncated at 75% and 90% of FVC were calculated, as well as the provocative dose that induces a 20% fall in FEV_1 ($PD_{20}FEV_1$). From the PEFV curves LDS for $\alpha_1 75\%$ and $\alpha_1 90\%$, and MEF_{30} and MEF_{40} were derived.

Apart from MEF_{30} and $\alpha_1 90\%$ the second test was significantly lower ($P<0{\cdot}05$) than the first when measuring the repeatability of spirometric indices, whereas the LDS of the indices showed no significant change. The repeatability expressed as intra-class correlation coefficient (ICC) was highest for LDS FEV_1 (0·87), second highest for LDS MEF_{40} (0·67) and LDS MEF_{30} (0·65).

The LDS for moment indices were much less repeatable and the lowest ICC was found in all LDS indices derived from PEFV curves. Within-subject variance was not influenced by atopic status, smoking habits or recordable $PD_{20}FEV_1$. As tests for bronchial hyper-responsiveness (BHR) the LDS of FEV_1, MEF_{40} and MEF_{30} seem to be acceptable for use in population studies.

Key words: repeatability; short term; flow–volume curve; log–dose slope.

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Introduction

In epidemiological studies of respiratory health a test of bronchial hyper-responsiveness (BHR) to either histamine or methacholine is often used as a physiological marker for effects on bronchii. The commonest measure of BHR is the provocative dose that induces a 20% fall in forced expiratory volume in 1 sec ($PD_{20}FEV_1$). However, only about 10–15% of subjects will have a measurable value for PD_{20} and so the majority of subjects have censored data. An alternative is to calculate a two-point slope of change in FEV_1 against dose, of which the log dose slope (LDS) (1) has been proposed as a suitable index that is normally distributed (2), with only few subjects having censored data.

It is possible that more information may be available from testing BHR by using additional indices. The first moment of the truncated forced expiratory spirogram contains information from the whole manoeuvre up to a given point and is more size-standardized than other indices (3). Moment analysis is therefore worth considering in the context of testing BHR. The use of indices from partial curves, where the bronchodilator effect of a deep inhalation (DI) is avoided, may also offer additional information about effects on bronchii (4,5), mainly increased sensitivity without lower repeatability.

Since the utility of conventional and other indices of BHR depends on their repeatability and reproducibility we have measured conventional tests and other short-term tests of BHR in a group of normal non-asthmatic male subjects on two separate occasions and in addition examined the influence of smoking and atopic status.

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Material and methods

MATERIALS

As part of a larger study on 2478 farming students and 967 control subjects in Denmark on the effect of farming on lung function (6), we invited a random sample of 29 male healthy subjects to have their bronchial responsiveness (BR) measured twice within the space of between 5 and 24 h. The study was approved by the Danish Medical Ethics Committee and all participants gave written consent.

METHODS

BR was measured using the Yan method (7) with calibrated DeVilbiss No 40 nebulizers (Pennsylvania, U.S.A.) delivering a cumulative dose of 1·43 mg histamine. There were six provocation doses of histamine with a starting dose of 0·01 mg histamine and the last dose given was 0·72 mg histamine. Partial and maximal expiratory flow–volume (PEFV and MEFV) curves were obtained by a trained operator with the subjects in a sitting position and nostrils closed by a clip. The subjects blew into a 200-mm long plastic upstream assembly which accepts standard 28 mm internal diameter cardboard mouthpieces connected to a pneumotachograph head (Vitalograph, Buckingham, U.K.) with a differential capacitance transducer (FC040, Furness Controls, Bexley, U.K.). The temperature and humidity of the pneumotachograph was stabilized by use of a fan (8). Subjects were instructed to hold their head in a neutral position. The manoeuvre was initiated from a little above functional residual capacity by a forced expiration to residual volume, followed immediately by a maximum inspiration to total lung capacity, followed without hesitation by a forced expiration for as long as possible to residual volume again. An on-line signal was shown on the screen through the whole manoeuvre for both the operator and the subject to help ensure that technically acceptable blows were recorded. The blows were repeated until acceptable, aiming to have the start of the partial expiratory blow below 80% forced vital capacity (FVC) but above 50% FVC. Subjects rested for at least 30 sec between blows. The following indices were derived from the blows: forced expiratory volume in 1 sec (FEV_1), forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75\%}$), maximum expiratory flow at 30% and 40% of the largest FVC recorded prehistamine (MEF_{30} and MEF_{40}, respectively), and the first moment of the spirogram truncated at 75% and 90% of FVC (4) which are termed $\alpha_1$75% and $\alpha_1$90%, respectively. From the partial curves the moments were derived MEF_{30} and MEF_{40}. The first moment α_1 of the manoeuvre is derived by considering the volume time (spirogram) of the manoeuvre as a succession of transit time. Transit time is the duration of equal volume increments expired. The data must be timed from a new start time zero defined by back-extrapolation (9). The moments of the spirogram are standardized by truncation with respect to volume (3) and following this previous work truncation at 75% and 90% of expired volume was performed.

BHR was measured using the method of PD_{20} and LDS (1) following the formula below:

LDS $FEV_1 = \log_{10}(((FEV_1\text{start} - FEV_1\text{end})*100/(FEV_1\text{start}*\text{final dose})) + 1)$.

LDS were calculated as above for all indices from MEFV curves. LDS were also calculated for indices derived from the PEFV curves from subjects whose start position for the partial manoeuvre was below 80% of FVC and above 50% FVC for MEF_{40}, and above 40% FVC for MEF_{30}.

Data were censored if there was an increase of an index of more than 5% when ending challenge compared to the prechallenge value. Indices derived from the PEFV curve data were also censored if the start position was outside 80–50%/40% FVC.

All subjects had skin-prick tests performed to 10 common inhalant allergens (Soluprick ALK, ALJ-Abello, Copenhagen, Denmark) extended with allergens from storage mites (*Tyrophagus putrescentia, Accarus siro* and *Lepidiglyphus destructor*), moulds, cows, pigs and horses. Subjects were deemed atopic if they had a wheal response more than 2 mm greater than the control for any one of these allergens.

STATISTICS

Comparisons between the indices on the two test sessions were by Wilcoxon sign-rank test, since the differences were not normally distributed. Differences from the mean for repeated measures of LDS for indices were also assessed. Intra-class correlation coefficients (ICC) were derived to express the equivalent of a signal : noise ratio. The ICC is the ratio of between person variance to the sum of within- and between-person variances, such that an ICC of 1·0 is best when the within-subject variance is zero. A level of 5% was taken as significant.

Results

From the 29 subjects, mean age 19 (SD 3·44) years, there were seven subjects with a recordable PD_{20} for FEV_1 on the first testing and six on the second, with five having a PD_{20} on both occasions.

The results for the lung function indices are shown in Table 1. There were significant changes in all the indices between the two tests except for MEF_{30} and $\alpha_1$90%, with the second test being larger for $\alpha_1$75% and smaller for all other indices. Table 2 shows the mean (SD) of the LDS for FEV_1, $FEF_{25–75\%}$, MEF_{30}, MEF_{40}, $\alpha_1$75%, $\alpha_1$90%, and LDS calculated for the absolute change in FEV_1 and $\alpha_1$75%. There were no significant changes in any of the LDS. Intra-class correlation coefficients (ICC) showed that the LDS for FEV_1 (0·87) was the best test, with the LDS for MEF_{30} (0·65) and MEF_{40} (0·67) being the next best. The ICC for $\alpha_1$75% was 0·49 and for $\alpha_1$90% was 0·48. Figures 1 and 2 show the differences against the means for repeated measures of the LDS for FEV_1 and MEF_{40}, respectively.

When considering the indices from the PEFV curve the number of subjects with an admissible start of their PEFV curve was 18 and 12 for MEF_{40} and MEF_{30}, respectively,

TABLE 1. Mean and standard deviation (SD) of the lung function indices for the 29 subjects on the first test, together with the mean differences between the two tests. The *P*-value is from a Wilcoxon sign-rank test on the difference

	Mean first	SD first	Mean differences	SD difference	*P* (difference)
FEV_1 (l)	4·38	0·70	0·16	0·23	<0·01
FVC (l)	5·25	0·79	0·10	0·26	0·02
PEF ($l\,sec^{-1}$)	9·01	1·85	0·41	0·80	0·02
$FEF_{25-75\%}$ ($l\,sec^{-1}$)	4·51	1·07	0·25	0·61	0·02
MEF_{30} ($l\,sec^{-1}$)	2·90	0·95	0·16	0·62	0·12
MEF_{40} ($l\,sec^{-1}$)	3·94	1·08	0·26	0·70	0·03
$\alpha_1$75%	0·30	0·06	−0·02	0·04	0·04
$\alpha_1$90%	0·43	0·09	−0·02	0·06	0·08

TABLE 2. Mean and SD of the LDS from indices from the MEFV curve for the first reading, the differences between the two readings, their intra-class correlation coefficient (ICC), the mean within-subject variance (w_var) and the number of subjects with valid data on both occasions (N). The *P*-value is from a Wilcoxon sign-rank test on the differences

	Mean first	SD first	Mean difference	SD difference	*P* difference	ICC	w_var	N
FEV_1 (l)	0·93	0·47	−0·04	0·19	0·24	0·87	0·02	23
$FEF_{25-75\%}$ ($l\,sec^{-1}$)	1·09	0·70	−0·24	0·64	0·10	0·28	0·22	26
MEF_{30} ($l\,sec^{-1}$)	1·32	0·52	−0·04	0·33	0·32	0·65	0·05	23
MEF_{40} ($l\,sec^{-1}$)	1·33	0·45	−0·02	0·30	0·32	0·67	0·04	23
$\alpha_1$75%	1·20	0·33	−0·002	0·32	0·98	0·49	0·07	24
$\alpha_1$90%	1·18	0·41	−0·09	0·38	0·35	0·48	0·08	25

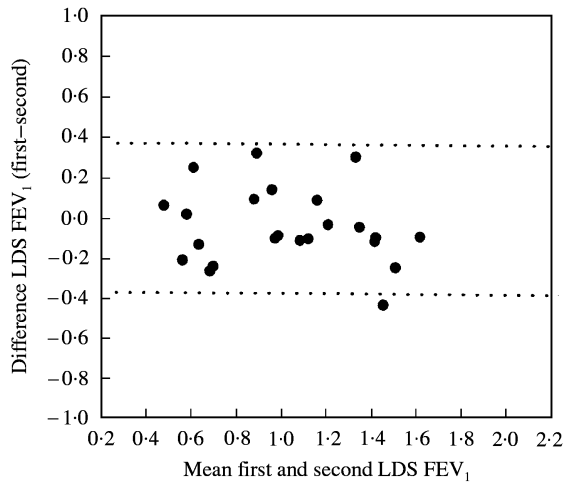

FIG. 1. Difference against mean for repeated measures for the LDS of FEV_1.

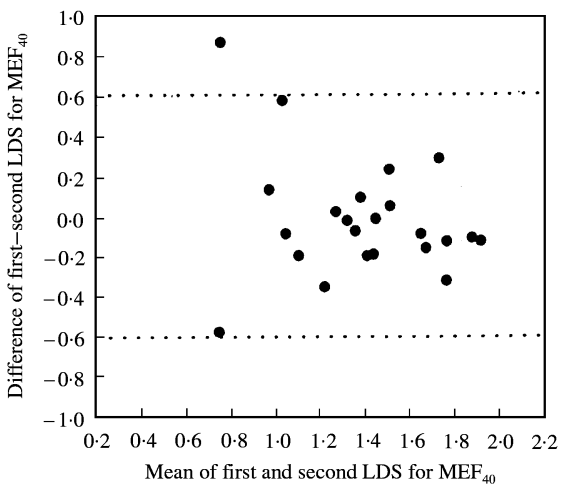

FIG. 2. Difference against mean for repeated measures for the LDS of MEF_{40}.

and for the moment indices the number was 10 and 11, respectively. The results for the LDS for these indices are shown in Table 3. None of these showed a significant change in value between the two tests, but the ICC for all were much smaller than for the other indices (0·35–0·05).

The within-subject variance in LDS of the indices was neither significantly different for the eight atopic subjects compared with the non-atopic, nor for the 11 current smokers compared with the non-smokers, nor for the five PD_{20} FEV_1-positive compared to the PD_{20} FEV_1-negative.

TABLE 3. Mean and SD of the LDS from the indices from the PEFV curve for the first reading, the differences between the two readings, their intra-class correlation coefficient (ICC), the mean within-subject variance (w_var) and the number of subjects with valid data on both occasions (N). The *P*-value is from a Wilcoxon sign-rank test on the differences

	Mean first	SD first	Mean difference	SD difference	*P* difference	ICC	w_var	N
$MEF_{30}P$	1·50	0·21	−0·05	0·29	0·37	0·27	0·04	18
$MEF_{40}P$	1·41	0·33	−0·06	0·49	0·64	0·05	0·11	12
$\alpha_1$75%P	1·20	0·43	−0·21	0·43	0·18	0·26	0·21	10
$\alpha_1$90%P	1·18	0·40	−0·18	0·42	0·45	0·35	0·11	11

Discussion

We have found that the LDS for FEV_1 remains the most repeatable test of BHR and yet retains sufficient between-subject variation to reflect true subject differences. The LDS from indices of the PEFV curve do not seem to offer any advantage. Repeatability for the dose–response slope of FEV_1 was found to be good in Australian children (10) and in adults with a $PD_{20}FEV_1$ and but was less repeatable in subjects with no recordable $PD_{20}FEV_1$ (11). Chinn *et al.* (12) found an ICC of 0·66 to $PD_{20}FEV_1$ using a least-squares slope of FEV_1. Whilst indices from PEFV curves yield information about the resting bronchial tone and whether this can be relieved by a deep inspiration, we have not found any merit from LDS derived from indices from the partial curve. Others have found a high sensitivity and repeatability of indices derived from the partial curve in respiratory healthy subjects (4) and in subjects with asthma (5) with an ICC of (0·69) close to the value for $PD_{20}FEV_1$ (0·79) (5). The difference in our findings might be due to different methods and techniques, study populations and outcome variables. Both Sterk *et al.* (4) and Knox *et al.* (5) derived the provocation dose that caused a 40% drop in flow at 40% (4) and 30% (5) of vital capacity measured from the partial curve, whereas we derived LDS.

Second to the LDS for FEV_1 were the LDS for MEF_{30} and MEF_{40} that were the next most promising. The response slope of MEF_{50} and MEF_{25} has been found with a higher sensitivity than FEV_1 but their suitability might be limited due to larger baseline variations (13,14). Although the moment indices have been found to be highly repeatable in normal spirometry (3), we found them to be less good as indices of BHR, with a reasonable between-subject variance but less repeatable within-subject variance. It was a surprise that the $FEF_{25–75\%}$ was not very good. This is usually a repeatable test within subjects (15) but the LDS for this varied widely; some subjects had a negative slope (i.e. a rise in $FEF_{25–75\%}$ after histamine) on one test and positive slope (i.e. a fall in $FEF_{25–75\%}$ after histamine) on the next.

Our results for ICC depend on both the within-subject variation and the between-subject variation in the group. Between-subject variance is predetermined by group composition and if this variance was unduly small it would minimize the importance of a particular test. Our subjects were chosen at random from a larger population and selection was independent of any lung function or other characteristic. Among our subjects were five who had a recordable PD_{20} for FEV_1 on both occasions. We therefore believed that there were sufficient subjects in our group with a change in FEV_1 and their airway function to histamine to give a reasonable between-subject variance.

We found that our subjects did less well in their conventional lung function tests on the second testing. This might have been due to changes in calibration of the pneumotachograph. However, the moment indices are not susceptible to changes in calibration as they are volume-standardized and both these indices were also less good on the second test. This suggests that the subjects did less well in their manoeuvres on the second test due to a change in motivation or other factor between the two series. Any effect from the histamine should have worn off as the shortest interval between tests was 5 h and full recovery from histamine effect has been found to be about 40 min (16). The LDS derived from percentage change would not be influenced by any change in calibration factor and would only be changed by within-subject motivation altering within the test. We did not find any evidence for this, and there was no significant change in any LDS between tests.

In conclusion, we have found that the short-term repeatability of BR to histamine was highest for LDS FEV_1, followed by LDS MEF_{40} and MEF_{30}. These tests appear satisfactory for use in population studies. The LDS for the moment indices were much less repeatable, as were those from the PEFV curves, and these tests are less likely to offer any useful signal when testing BHR.

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