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THE SHAPE OF THE MAXIMUM EXPIRATORY FLOW-VOLUME CURVE REFLECTS EXPOSURE IN FARMING

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Abstract: The objective of the study was to examine the effect of farming exposure, respiratory symptoms and smoking on the shape of the MEFV-curve in 1,691 male farming students and 407 male controls and to relate the slope ratio with FEV_1 and FEV_1/FVC. Each subject underwent a medical interview and the slope ratios from the MEFV-curve at 75 (SR75), 50 (SR50) and 25 (SR25) %FVC together with FEV_1 and FVC were recorded. Histamine bronchial reactivity (Yan method) was measured and skin prick test with inhalant allergens was performed. In smokers, SR75 increased with increasing exposure to: general farming, swine and dairy cattle ($p \leq 0.020$). SR50 increased with increasing exposure to farming ($p = 0.015$). In non-smokers, SR25 increased with increasing exposure to swine and dairy cattle ($p = 0.021$) and increased SR25 was associated with sensitisation to house dust mite ($p = 0.017$). Data revealed an interaction between smoking and exposure to farming. FEV_1 and FEV_1/FVC was not associated with farming exposure or production animals. FEV_1 and FEV_1/FVC ($p \leq 0.003$) were lower among subjects with bronchial hyperresponsiveness and asthma (FEV_1 and asthma only in smokers). SR75 ($p = 0.037$) and SR50 ($p = 0.024$) were increased in subjects with asthma and SR75 was increased in subjects with bronchial hyperresponsiveness, but only in smokers ($p = 0.002$). In conclusion, exposure to farming seems to influence the shape of the MEFV-curve and there are indications of interaction between exposure to organic dust and smoking. These changes are seen only in the slope ratios and not in FEV_1 and FEV_1/FVC. However, FEV_1 and FEV_1/FVC are superior to slope ratios in differentiating healthy subjects from those with respiratory symptoms.

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INTRODUCTION

The forced expiratory spirogram is one of the most frequently used and one of the most validated tests of ventilatory lung function. Changes in the FEV_1 or in the ratio of FEV_1 and FVC are generally accepted as an early sign of airflow obstruction. Less frequently, the maximum expiratory flow-volume (MEFV) curve has been used as a tool in large scale lung function studies, probably because the interpretation of the results is not as straightforward as that of the FEV_1. If properly performed, the reproducibility of the MEFV-curve within subjects is good, both concerning the initial effort dependent part of the maximal expiratory flow [27] and the remainder effort independent part [24]. However, the between-subject variability is wide [10], partly due to procedural variation [5], gender [11], age [3] and smoking habits [4]. Other important factors related to the between-subject variability are physiological parameters

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such as the nature of flow limitation involving negative effort dependence [12], the non-linear behaviour of the flow-limiting process [17], the non-homogeneous emptying of the lungs [16] and the size of the peripheral airways and the lung elastic recoil [22].

The slope ratio (the slope of the tangent of the curve divided by the slope of the chord through the point and RV) is an index of curve shape. It is a dimensionless expression insensitive to flow magnitude but sensitive to concavities and convexities of the curve [5, 16]. Increase in concavity will be reflected in a larger slope ratio.

The shape of the MEFV-curve has been used in population based epidemiological studies [23] and in occupational settings as a measure of lung function [21, 25, 28]. In these studies the exposure to organic dust did show an effect on the MEFV-curve. In a recent study of young farmers entering the trade [20] we found no association between occupational farming exposure and lung function measured as FEV_1, FVC and FEV_1/FVC. We therefore wanted to examine the effect of farming exposure, respiratory symptoms and smoking on the shape of the MEFV-curve in the same group of young adults and to relate the shape of the MEFV-curve expressed as slope ratio with FEV_1 and FEV_1/FVC.

MATERIALS AND METHODS

Study subjects. All the 2,478 students in their second term at farming schools in Denmark in the period February 1992–February 1994 were invited to participate. Of these, 2,004 (81%) accepted, but 40 (2%) failed to attend the initial examination. Only those subjects under 26 years of age were selected for further study so that a satisfactory match for rural controls could be made. The final population of farming students was 1,901 (77%) of whom 1,691 were men and 210 women. The age and gender distribution did not differ between the 474 who failed to attend and the participants. Among the nonattendants the most frequent reason for not participating was no interest for the study or no reason at all, while the second commonest reason was fear of blood sampling.

Control subjects were obtained by inviting 967 young army conscripts from three counties. Inclusion criteria were living in rural areas and no intention of a farming career. There were 592 (61%) who agreed to participate and a random sample of 407 were included. The study was approved by the Ethics Committee and all participants gave a written consent. The present study involved only males due to gender differences in MEFV-curves and a too low number of females for meaningful analysis for associations between changes in slope ratios and increasing exposure. Altogether, 2,098 males were enrolled in the study.

Methods. A modified BMRC questionnaire on respiratory symptoms [2] was used for the medical interview extended with questions on allergy, asthma, family history of allergy, smoking and occupational history. Every period of employment was registered with duration of work, type of job and type of farm involved. The data was transformed to normal years of work (45 weeks of work with 40 hours work weekly) for all employments. The diagnosis of asthma was based on a questionnaire [20]. The subjects were categorised as having asthma if they answered positively to at least one of the group A questions (Have you been told by a doctor that you have asthma?, Do you have asthma?, Have you ever had asthma?, Do you ever wheeze?) and two group B questions (Do you ever have chest tightness?, Do you wake in the morning with chest tightness?, Do you wake up in the night wheezing?, Do you cough when you wake up in the morning?, Do you wake in the morning with cough?, Do you wheeze on exposure to cold air?, Do you wheeze when you exercise?, Do you wheeze on exposure to pollen?, Do you wheeze on exposure to animals?, Do you use asthma drugs?).

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were recorded in accordance with American Thoracic Society guidelines [1] using a dry wedge spirometer (Vitalograph Buckingham, UK). Predicted values for FEV_1 and FVC with residual standard deviation (RSD) were computed by means of multiple regression based on data on height (H) in metres and age (A) from healthy non-smokers in the study cohort. The computed equation with residual standard deviation were:

$FEV_1 = 4.874*H - 0.00936*A - 4.0214$ (RSD 0.50)

$FVC = 6.187*H + 0.01990*A - 6.2004$ (RSD 0.58)

The standardized residuals (SR) were calculated from the equation:

$$variable_{measured} - variable_{predicted}/RSD \text{ [20].}$$

MEFV-curves were obtained by a trained team of two operators 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 (Vitalograph, Buckingham, UK) with a differential capacitance transducer (FC040, Furness Controls, Bexley, UK). The pneumotachograph assembly showed acceptable approximation to linearity when testing between measured flow and calibrated flow in the range from two to 14 l/s (residual standard deviation 0.108 l/s). The amplitude response increased considerably for rise time below 10 ms, whereas at 30 ms the error was about 10% overestimation. The temperature and humidity of the pneumotachograph was stabilized by use of a fan [18]. The subjects were instructed to hold their head in a neutral position. The manoeuvre was initiated by a partial inspiration followed by a forcible expiration for as long as possible and on command immediately followed by a maximum inspiration that without hesitation was followed by a forcible expiration for as long as possible. A time display of the whole manoeuvre was available to help both the operator and the subject obtain technically acceptable exhalations. The manoeuvre was considered finished when the flow signal ceased. The exhalations were repeated until

acceptable with intervals of at least 30 seconds. Only slopes from the maximum MEFV-curves are reported in the present study. Maximal expiratory flow were measured at 87.5, 75, 62.5, 50, 37.5, 25 and 12.5 %FVC remaining to be expired. In the calculations below we assume that the slope of the tangents can be approximated by slope of the chords connecting the curves in the 25 %FVC interval spanning the actual points. In case of pronounced curvature there may be a slight difference between the "true slope ratio" and the estimated slope ratio. The cord will be the straight line connecting 0% FVC and that point on the curve where maximal expiratory flow was measured. On the other hand, the estimate is much less sensitive to noise-related oscillations on the curve than the true slope ratio. Using the approximation, the slope ratios (SR) were calculated by the following simple equation: A% FVC (yet to be expired):

$$SRA = k * (MEF_{A+12.5\%} - MEF_{A-12.5\%})/MEF_A),$$

and a SR > 1 indicates a flow-volume curve concave to the axis. The constant k will be 3, 2 and 1 when calculating SR75, SR50 and SR25 respectively. A detailed decription of the calculations is given in the Appendix and Figure 1.

Bronchial responsiveness was measured using the Yan method [30] with calibrated DeVilbiss No. 40 nebulizers (Pennsylvania, USA) delivering a cumulative dose of up to 1.44 mg histamine. Subjects whose FEV_1 fell by 20% or more of the largest FEV_1 recorded at baseline or after inhalation of 0.9% saline (PD_{20}), were considered as having bronchial hyperresponsiveness (BHR).

A skin prick test (SPT) was performed to evaluate immediate allergic reaction to a panel of 10 common inhalant allergens (Soluprick ALK; ALK-Abello, Copenhagen, Denmark) extended with allergens from storage mites (*Tyrophagus putrescentiae, Acarus siro* and *Lepidoglypus destructor*), moulds (*Alternaria alternata* and *Cladosporium herbarum*), cow hair, pig bristle and horse dander.

Analysis. Analysis was applied to the data for all subjects, both farming students and controls stratified for smoking to avoid a low a number of subjects in the strata for analysis. The few ex-smokers were included in the non-smoking group. For analysis of variance ANOVA test was performed. Multivariate analysis was undertaken with linear regression for continuous variables. The model contained independent explanatory variables to control for confounding factors. A probability of 5% or less was taken as significant, unless otherwise stated.

RESULTS

Demographic characteristics. The farming students were slightly but significantly taller and younger than their control counterparts (181.9 cm (6.9) vs. 180.6 cm (7.0), and 18.3 yr. (1.3) vs. 18.5 yr. (0.9)). As expected, the farming students had significantly more previous experience in general farming, working with swine and cattle (3.9 yr. (2.6), 2.4 yr. (2.7), and 2.1 yr. (2.9), respectively) compared to the controls (0.8 yr. (1.8), 0.4 yr. (1.2), and 0.3 yr. (1.3), respectively). Smoking habits were generally the same, although there were significantly more ex-smokers among the farming students, 33 subjects (2%) than in the control group of one subject (0.2%) [20].

Slope ratios, FEV_1 (standardised residual) and FEV_1/FVC and farming exposure. The mean and SD for the slope ratios and FEV_1 (standardised residual) and FEV_1/FVC are presented in Table 1, stratified for smoking and years of farming exposure. In smokers SR75 ($p = 0.013$) and SR50 ($p = 0.015$) increased significantly with increasing exposure time for farming while no similar significant trend was observed for any of the other indices. In non-smokers there was no significant change in any of the indices. In Table 2 the mean and SD for the slope ratios and FEV_1 (standardised residual) and FEV_1/FVC are shown stratified for smoking and years of work in swine confinement buildings. SR75 ($p = 0.020$) was the only index that significantly changed with increasing exposure and only in smokers.

With increasing exposure in dairy barns there was a non-significant increase in SR75, SR50 and SR25 for smokers, while in non-smokers no changes were observed in the slope ratios. In smokers SR75 ($p = 0.019$) and in non-smokers SR25 ($p = 0.021$) increased significantly with increasing exposure in both swine confinement buildings and dairy barns. With increasing exposure to production animals other than pigs and cattle (horses, hens and ducks) there was a non-significant increase in SR75 in non-smokers while no change in the slope ratios was observed among the smokers. No significant reduction in FEV_1 (standardised residual) or FEV_1/FVC with increasing exposure was observed when analysing for years of exposure in dairy barns, years of exposure in both swine confinement buildings and dairy barns, or years of exposure to production animals other than pigs and cattle, neither in smokers nor in non-smokers. No interaction (ANOVA) was found between any of the exposure variables and smoking for SR75, while there was significant interaction between years of farming and smoking for SR50 ($p = 0.008$) and between exposure to other production animals and smoking for SR25 ($p = 0.023$). To be raised on a farm was associated with an increased SR50 ($p = 0.039$) compared to subjects raised outside a farm in smokers. No other indices were affected by the place of upbringing. In smoking farming students SR75 ($p = 0.001$) and SR50 ($p = 0.015$) were significantly increased and FEV_1/FVC ($p = 0.008$) was significantly reduced compared to smoking controls. FEV_1 (standardised residual) was significantly ($p < 0.0001$) reduced in farming students compared to controls irrespectively of smoking habits.

Slope ratios, FEV_1 (standardised residual) and FEV_1/FVC and skin prick test. In non-smokers sensitisation to house dust mite (HDM) was associated with increased SR25 ($p = 0.017$) and sensitisation to storage mites (STM) was associated with reduced FEV_1/FVC ($p = 0.001$). In smokers, positive reaction to any of the skin prick tests (SPT) was

Table 1. SR75, SR50, SR25, FEV_1 (standardised residual) and FEV_1/FVC *vs* years of exposure in farming. Mean (SD).

	Smokers			Non-smokers		
Years of exposure	0	0.1 < 5	5–10	0	0.1 < 5	5–10
SR75	0.59 (0.65)	0.73 (0.65)	0.84 (0.55)	0.71 (0.79)	0.76 (0.59)	0.81 (0.62)
SR50	0.86 (0.32)	0.93 (0.33)	0.99 (0.32)	0.95 (0.33)	0.88 (0.32)	0.91 (0.36)
SR25	0.94 (0.27)	0.94 (0.25)	0.96 (0.24)	0.93 (0.26)	0.91 (0.26)	0.95 (0.25)
FEV_1	0.17 (0.96)	-0.08 (0.96)	-0.01 (1.06)	0.12 (1.02)	-0.04 (0.98)	-0.02 (1.02)
FEV_1/FVC	85.6 (6.3)	84.4 (6.8)	83.6 (6.7)	86.4 (6.5)	86.1 (6.4)	86.0 (6.5)
N	88	456	128	161	851	414

Smokers: SR75, p = 0.013 (ANOVA); SR50, p = 0.015 (ANOVA).

Table 2. SR75, SR50, SR25, FEV_1 (standardised residual) and FEV_1/FVC *vs* years in swine confinement bulidings. Mean (SD).

	Smokers			Non-smokers		
Years of exposure	0	0.1 < 5	5–10	0	0.1 < 5	5–10
SR75	0.71 (0.64)	0.77 (0.60)	1.11 (0.49)	0.77 (0.63)	0.71 (0.57)	0.90 (0.66)
SR50	0.92 (0.34)	0.96 (0.28)	1.02 (0.21)	0.90 (0.34)	0.92 (0.30)	0.92 (0.36)
SR25	0.94 (0.26)	0.97 (0.22)	0.95 (0.26)	0.93 (0.26)	0.93 (0.24)	0.92 (0.24)
FEV_1	-0.02 (1.01)	-0.04 (0.87)	-0.37 (0.77)	-0.01 (1.00)	-0.02 (0.96)	-0.04 (1.14)
FEV_1/FVC	84.5 (6.7)	84.1 (7.2)	84.6 (5.5)	86.1 (6.6)	86.2 (6.0)	86.5 (5.7)
N	545	109	19	1185	184	56

Smokers: SR75, p = 0.020 (ANOVA).

associated with a significantly reduced FEV_1/FVC (p = 0.007). No other indices were associated with positive reaction to HDM, STM or SPT neither in smokers nor in non-smokers.

Slope ratios, FEV_1 (standardised residual) and FEV_1/FVC and respiratory symptoms. In Table 3, the mean and SD for the slope ratios and FEV_1 (standardised residual) and FEV_1/FVC ratio are listed stratified for smoking and asthma. In smokers, SR75 (p = 0.037) and SR50 (p = 0.024) were significantly larger and FEV_1 (standardised residual) (p < 0.0001) and FEV_1/FVC (p = 0.0001) were significantly reduced among subjects with asthma compared to subjects with no symptoms of asthma. In non-smokers FEV_1/FVC (p = 0.003) was significantly reduced among subjects with asthma while no increase in the slope ratio was observed among the non-smoking subjects with asthma. The mean and SD for the slope ratios and FEV_1 (standardised residual) and FEV_1/FVC stratified for smoking and BHR are illustrated in Table 4. In smokers, SR75 (p = 0.002) was significantly increased among subjects with BHR compared to subjects without bronchial hyperresponsiveness. Both for smokers and non-smokers FEV_1 (standardised residual) (p < 0.0001) and FEV_1/FVC (p < 0.0001) were significantly reduced in subjects with BHR compared to subjects without bronchial hyperresponsiveness.

Multiple linear regression for all subjects. The initial model contained variables of occupational exposure, including years of farming experience in all, years of tending swine, cattle, both swine and cattle, other animals, and years of field work. Also included in the model were whether the subject had been raised on a farm, was a farming student or control, family history of allergy and asthma, asthma, BHR, number of positive SPT, positive SPT to house dust mite and positive SPT to storage mites. Tables 5 (smokers) and 6 (non-smokers) present those variables that contributed significantly to the model. In smokers the shape of the initial part of the MEFV-curve (SR75) was related to exposure to animals in the farming production (p ≤ 0.041) and BHR (p = 0.003), whilst the shape of the mid part of the curve (SR50) was related to years of farming exposure (p = 0.003) and asthma (p = 0.013). No factors significantly influenced the tail of the MEFV-curve (SR25). In non-smokers, only occupational exposure to animals (p = 0.019) had any significant influence on the shape of the initial part of the MEFV curve whilst no variable was associated to the mid part. Sensitisation to house dust mite (p = 0.010) appeared to influence the shape of the last part of the MEFV-curve as did working with both pigs and cattle (p = 0.010).

Being a farming student (p ≤ 0.0004), BHR (p ≤ 0.001) with asthma (p = 0.004) (only in smokers) were associated

Table 3. SR75, SR50, SR25, FEV_1 (standardised residual) and FEV_1/FVC *vs* asthma. Mean (SD).

	Smokers		Non-smokers	
	No asthma	Asthma	No asthma	Asthma
SR75	0.71 (0.64)	0.87 (0.60)	0.77 (0.62)	0.77 (0.64)
SR50	0.92 (0.33)	1.01 (0.27)	0.90 (0.33)	0.92 (0.37)
SR25	0.94 (0.25)	0.92 (0.24)	0.93 (0.25)	0.87 (0.29)
FEV_1	0.02 (0.94)	-0.39 (1.02)	0.00 (1.00)	-0.17 (0.99)
FEV_1/FVC	84.9 (6.5)	81.2 (7.6)	86.2 (6.4)	84.4 (6.6)
N	587	86	1329	96

Smokers: SR75, p=0.037 (ANOVA); SR50, p=0.024 (ANOVA); FEV_1, p<0.0001 (ANOVA); FEV_1/FVC, p<0.0001 (ANOVA).
Non-smokers: FEV_1/FVC, p=0.003 (ANOVA).

Table 4. SR75, SR50, SR25, FEV_1 (standardised residual) and FEV_1/FVC *vs* BHR. Mean (SD).

	Smokers		Non-smokers	
	No BHR	BHR	No BHR	BHR
SR75	0.71 (0.62)	0.94 (0.71)	0.76 (0.62)	0.84 (0.57)
SR50	0.93 (0.33)	0.96 (0.34)	0.90 (0.33)	0.94 (0.36)
SR25	0.94 (0.26)	0.95 (0.22)	0.93 (0.25)	0.93 (0.27)
FEV_1	0.04 (0.94)	-0.46 (1.06)	0.03 (0.99)	-0.33 (1.03)
FEV_1/FVC	85.5 (6.2)	79.9 (8.4)	86.3 (6.4)	84.0 (7.1)
N	593	74	1298	125

Smokers: SR75, p=0.002 (ANOVA); FEV_1, p<0.0001 (ANOVA); FEV_1/FVC, p<0.0001 (ANOVA).
Non-smokers: FEV_1, p<0.0001 (ANOVA); FEV_1/FVC, p<0.0001 (ANOVA).

to the FEV_1 (standardised residual). Asthma ($p \leq 0.018$) and BHR ($p \leq 0.0003$) were the factors significantly associated with reduced FEV_1/FVC both in smokers and non-smokers.

DISCUSSION

We have found that changes in the shape of the MEFV-curve are related to farming exposure, asthma-like symptoms, BHR and sensitisation to house dust mite. We have also found evidence of an interaction between occupational exposure to production animals and smoking habits which influences the shape of the MEFV-curve. Changes in peripheral part of the lungs seem to be reflected by changes in slope ratio at all lung volumes. In our opinion, this indicates that our findings reflect early changes in the peripheral airways even before changes in FEV_1 and FVC can be detected. Changes in slope ratio might, therefore, be an early indicator of discreet changes in the lungs in subjects exposed to organic dust with inflammatory potential.

Tielemans *et al.* [28] studied the effect of organic dust on the configuration of the MEFV-curve and found that increase in the mean organic dust exposure was associated with decreased flow at high lung volumes, whereas an increasing number of years of dust exposure was associated with decreased flow at all lung volumes. In the present study the exposure to farming and production animals was associated with changes on the shape of whole the MEFV-curve (increased SR75, SR50 and SR25). We have no data on mean organic dust exposure so that a comparison with the Dutch data [28] is not possible, but our data indicate changes of flow at both high and low lung volumes without a parallel change in FEV_1 (standardised residual) or FEV_1/FVC. The configuration of the MEFV-curve has also been used to measure lung function in cotton textile workers [25] and in grain handlers [21]. Although in neither of the studies was there a significant difference in the shape of the MEFV-curve between exposed and controls, both papers suggest that the curve shape might be an indicator of the effect of dust exposure. Recent studies of workers in swine or dairy production have shown an impact of smoking on FEV_1 [7, 13], FEV_1/VC and FEV_{25-75} [29], and VC [6]. However, Mauny *et al.* [15] found no significant effect of smoking in their multiple linear regression analysis of annual decline in lung function among dairy farmers. Tielemans *et al.* [28] found an interaction between smoking and organic dust which have an impact on indices of the shape of the MEFV-curve, results similar to the results of the present study.

We found that SR25 in non-smokers was significantly associated with a positive SPT to house dust mite. To our knowledge, no studies have been published where the shape of the MEFV-curve has been analysed in association with

Table 5. Factors significantly associated with increased slope ratio and reduced FEV_1 (standardised residual) and FEV_1/FVC (dependent variables) for smokers in the cohort. Multiple linear regression analysis. Regression coefficients with their standard error (SE). All factors in the final model are shown.

	SR75	SR50	SR25	FEV_1	FEV_1/FVC
Asthma	-	0.10 (0.04)	-	0.12 (0.13)	0.14 (0.81)
BHR	0.12 (0.08)	-	-	0.14 (0.13)	0.22 (0.82)
Farming student	-	-	-	0.16 (0.10)	-
Farming	-	0.12 (0.02)	-	-	-
Working with pigs	0.14 (0.06)	-	-	-	-
Working with cattle	0.10 (0.05)	-	-	-	-
Working with pigs and cattle	0.10 (0.05)	-	-	-	-

SR75: $R^2 = 0.180$, p (BHR) = 0.003, p (pigs) = 0.003, p (cattle) = 0.041, p (pigs & cattle) = 0.028.
SR50: $R^2 = 0.150$, p (asthma) = 0.013, p (farming) = 0.003.
FEV_1: $R^2 = 0.307$, p (asthma) = 0.004, p (BHR) = 0.001, p (farming student) = 0.0004.
FEV_1/FVC: $R^2 = 0.286$, p (asthma) = 0.0004, p (BHR) <0.0001.

Table 6. Factors significantly associated with increased slope ratio and reduced FEV_1 (standardised residual) and FEV_1/FVC (dependent variables) for non-smokers in the cohort. Multiple linear regression analysis. Regression coefficients with their standard error (SE). All factors in the final model are shown.

	SR75	SR50	SR25	FEV_1	FEV_1/FVC
Asthma	-	-	-	-	0.06 (0.73)
BHR	-	-	-	0.11 (0.10)	0.10 (0.64)
Farming student	-	-	-	0.11 (0.07)	-
Pos. SPT to house dust mite	-	-	0.07 (0.01)	-	-
Working with pigs and cattle	-	-	0.08 (0.01)	-	-
Working with other animals	0.07 (0.05)	-	-	-	-

SR75: $R^2 = 0.065$, p (other animals) = 0.019.
SR25: $R^2 = 0.104$, p (HDM) = 0.010, p (pigs & cattle) = 0.010.
FEV_1: $R^2 = 0.161$, p (BHR) < 0.0001, p (farming student) <0.0001.
FEV_1/FVC: $R^2 = 0.127$, p (asthma) = 0.018, p (BHR) = 0.0003.

atopy or sensitisation, but a dose-response relationship between specific IgE antibody to house dust mite and impaired standardised FEV_1 has been found [19]. In the present population we have shown [26] that the size of the house dust mite wheal and the number of positive skin prick reactions were significantly associated with bronchial hyperresponsiveness. These findings might support the present association between sensitisation to house dust mite and the shape of the MEFV-curve. As in the previous analysis in the cohort [20] being a farming student was significantly associated with reduced FEV_1 (standardised residual) in contrast to FEV_1/FVC and the slope ratios. For the latter two indices there was an association in the univariate analysis but not in the multivariate, and for smokers only. The heterogeneity of the associations between the indices and the variable might be a reflection of a greater between-subject variability in the slope ratios than in traditional lung function parameters [10] and of the fact that minor changes in FEV_1 precede changes in FEV_1/FVC.

FEV_1 (standardised residual) and FEV_1/FVC were better than slope ratios for differenting between subjects with asthma and BHR *vs* subjects with no respiratory symptoms, and for FEV_1/FVC this was independent of smoking habits. This might be due to greater between-subject variability in the slope ratios than in traditional lung function parameters [10]. Another explanation for our results could be that the irritant effect of smoking on the lungs is necessary to induce changes in the airways, mirrored by changes in the shape of the MEFV-curve. SR75 and SR50 were significantly larger in subjects with asthma and BHR compared to subjects with no respiratory symptoms, but only in smokers. Likewise, data from the regression analysis indicate an interaction between respiratory symptoms and smoking that influences the shape of the MEFV-curve. Only in smokers are asthma and BHR significantly related to the initial (SR75) and mid (SR50) part of the MEFV-curve. The present findings are in accordance with the data from the Dutch population based on a study of 4,397 subjects [23]. When analysing for associations between respiratory symptoms and the shape of the MEFV-curve, it was found that the types of MEFV-curves related to symptoms of bronchitis and asthma were more prevalent among smokers than non-smokers in males.

The associations presented might be false positive associations, explained by multiple comparisons, although

in our opinion the risk for such a misinterpretation is not greater in this study than in other studies using a cross-sectional design. The strength of the majority of the associations presented exceeds substantially the 0.05 level of significance, and the trend in data that the slope ratios reflect exposure as opposed to conventional lung function parameters can hardly be explained as a result of multiple comparisons. The pathophysiology behind these exposure induced changes in the shape of the MEFV-curve can be related to local effects in the airways, different for the various exposure types. Model and animal studies [17, 22] and clinical observations [9] indicate that uneven distribution of ventilation caused by inhomogeneity of the lungs and airways, increased resistance in the peripheral airways, decreased elastic recoil of the lungs, and increased compliance of the airways are mechanisms to be reflected in increased slope ratios. All these changes lead to a more peripheral location of the flow determining sites (i.e. the choke points). Initially, these changes lead to curvilinearity in the tail of the flow-volume curve, but with increasing effect the concavity which will be evident at increasingly higher lung volumes. An inflammatory effect in the peripheral airways is therefore likely to manifest itself first in the curvilinearity at low lung volumes, as seen in non-smokers in Table 6, where positive SPT to house dust mite and working with pigs and cattle influence SR25 even without influencing FEV_1 (standardised residual) and FEV_1/FVC. Should these findings be confirmed, they indicate that sensitisation to house dust mite and exposure to production animals may cause inflammation in the peripheral airways influencing the MEFV-curve shape even before changes in conventional lung function parameters become manifest. The association between asthma, BHR, and increased slope ratio could be explained if asthma independently leads to both. But upstream motion of the flow determining segments in asthma could be a common denominator for the following reason: the peripheral airways are more compliant than the central airways [14], and the relative thickness of smooth muscles in peripheral airways is greater than in central airways [8]. It can therefore be expected that a given stimulus has a larger effect on the peripheral than on the central airways [8], leading to both increased slope ratios and BHR.

In conclusion, we have found changes in slope ratios indicating an effect of exposure and an interaction between exposure to organic dust and smoking. These associations were not found with conventional lung function parameters. Longitudinal studies in this cohort of young rurals will hopefully elucidate how exposure to organic dust, smoking, respiratory symptoms and allergy affect the shape of the MEFV-curve and lung function.

APPENDIX

Calculation of slope ratios for maximum expiratory flow-volume curves when 75, 50 and 25 %FVC remains to be expired. The slope ratio was originally defined by Mead [16] to describe the shape of the flow-volume curve by a non-parametric index. It was defined as the slope of a tangent to the curve in a given point divided by the slope of the line drawn through that point and the curve at the residual volume. The slope of the tangent is very dependent on “noise”, i.e. small irregularities on the curve. Therefore we decided to modify the calculation. Instead of the slope of the true tangent we chose the slope of a chord connecting

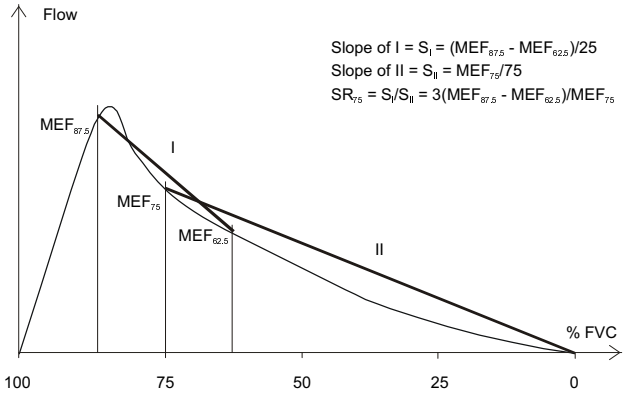

Figure 1. Calculation of slope ratio at 75% FVC (SR75) remaining to be expired (see Appendix).

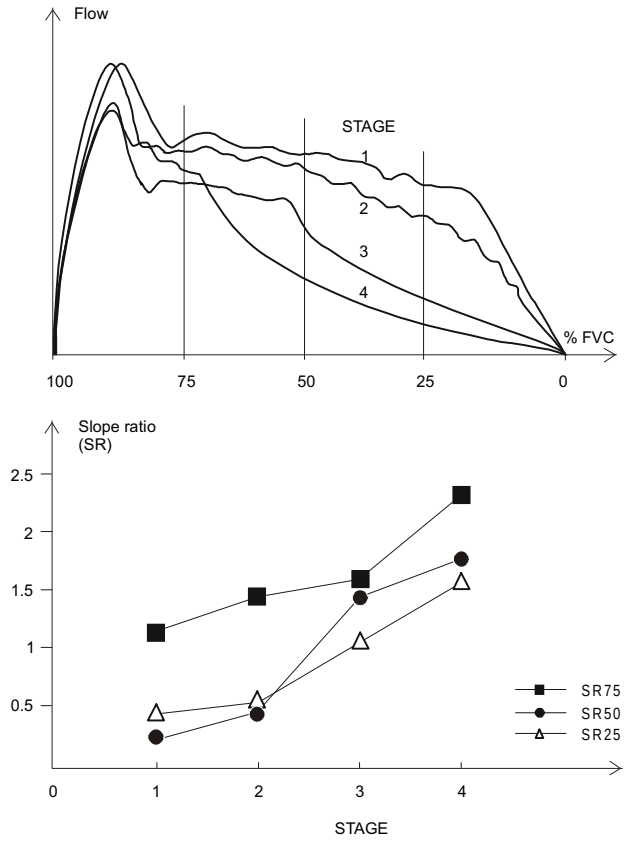

Figure 2. Upper panel: Superimposed flow-volume curves from a patient with 4 stages of bronchiolitis following lung transplant (see Appendix) (modified from [9]). Lower panel: SR75, SR50 and SR25 shown as a function of the stages of the disease.

points at 12.5% of FVC on each side of the given point. Figure 1 shows the calculation of SR75, at the point where 75% FVC remains to be expired. SR50 and SR25 were similary calculated to be $2(MEF_{62.5} - MEF_{37.5})/MEF_{50}$ and $(MEF_{37.5} - MEF_{12.5})/MEF_{25}$, respectively.

The influence of peripheral lung disease on slope ratio illustrated by a clinical example. Peripheral airway disease changes the flow-volume curve in a characteristic manner. Figure 2, upper panel, (modified from [9]) shows 4 superimposed flow-volume curves from a patient who received a double lung transplantation, and who developed brochiolitis after the transplantation. The curve passes through different stages with increasing convexity towards the volume axis. The lower panel shows that SR75, SR50 and SR25 all increase with the severity of the disease, indicating that peripheral lung lesion influences the shape of the flow-volume curve also at high lung volumes.

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