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Key terms: asthma; baker; bronchial responsiveness; flour; lung function; methacholine; occupational asthma; wheat; worker

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Methacholine bronchial responsiveness and variations in lung function among workers exposed to flour

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Objectives Methacholine bronchial responsiveness and variations in the pulmonary function of workers exposed to wheat flour and a reference group were compared.

Methods Each subject [140 men exposed to flour (bakers and pastry makers) and 77 controls] completed a standardized questionnaire. Bronchial responsiveness was quantified by measuring the slope between percentage decrements in forced expiratory volume in 1 second (FEV_1) and cumulative methacholine dose. FEV_1 and peak expiratory flow (PEF) were recorded four times a day for 15 days using a handheld electronic spirometer. The variability in the FEV_1 and PEF readings was expressed as variation coefficients (100 × standard deviation/mean).

Results The mean duration of exposure to flour was 14 (SD 9) years. Rhinitis was significantly more common in the exposed group than in the control group (30.7% versus 11.7%, P=0.001). The mean FEV_1 and PEF did not significantly differ between the two groups. The slope of the dose–response to methacholine and the variation coefficients were lower among the unexposed nonsmokers than among the exposed workers and smokers. The differences were significant for the exposed smokers. The two variation coefficients correlated with each other (r=0.82) but not with the slope of the methacholine challenge.

Conclusions Occupational exposure to flour and smoking increase bronchial responsiveness, as measured by the slope of the dose–response to methacholine and the variation coefficients of airflow. However, methacholine bronchial responsiveness and the variability of lung function do not measure exactly the same aspect of airway behavior.

Key terms asthma; baker; occupational asthma; wheat.

Bakers and mill workers are highly exposed to flour allergens. Workers occupationally exposed to flour have a higher than normal prevalence of respiratory symptoms, asthma, and chronic airway obstruction (1–8). They also have a higher degree of nonspecific bronchial responsiveness than control workers (1, 9, 10) and greater variability of lung function during the workweek (3, 11). No information is currently available about the relation between nonspecific bronchial responsiveness and the variability of lung function among workers exposed to flour.

Excessive lung function variability, as assessed by peak expiratory flow (PEF), has been suggested to be a useful indicator of bronchial hyperresponsiveness for clinical or epidemiologic purposes (12–16). However, several studies have failed to identify an index of PEF variability that could be used to distinguish asthmatic persons from others (16, 17), and PEF variability is not always significantly correlated with the slope of the dose–response curve of the methacholine challenge. Boezen et al (15) found a significant correlation, but concluded that nonspecific bronchial responsiveness and PEF variability could not be used interchangeably in epidemiologic settings. The variability of lung function has been determined using the PEF of the general population (15, 17–19), allergic persons (16, 20), and other workers (13, 14, 21). These studies did not include workers highly exposed to allergens and did not investigate the variability of forced expiratory volume in 1 second (FEV_1). Handheld spirometers that can automatically record the time of the test, PEF and FEV_1 (more reproducible than PEF) and construct flow-volume curves are now available (22, 23). These electronic devices may improve the quality of recorded data. However, their usefulness for epidemiologic studies with respect to occupational asthma remains to be evaluated. The importance of PEF and FEV_1 variability among exposed workers has not yet been established.

The aim of this study was to compare methacholine bronchial responsiveness and the variability of FEV_1 and

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PEF for workers exposed to wheat flour and reference workers over 15 workdays.

Study population and methods

Study population

The study population comprised 217 workers from nine plants in Paris or its suburbs. The plants were industrial bakeries, supermarkets with bakeries, or restaurants. The workers were examined in the plants.

The workers were divided into two groups according to their current occupational exposure to flour. Group E comprised all men who were highly exposed to flour, such as bakers and pastry makers (N=140). Group R comprised reference workers from the same plants who were never exposed to flour, other allergenic aerosols, or air pollutants (N=77). The reference group included sales staff, butchers, and persons with other job descriptions. Each worker was asked to participate in an interview and undergo methacholine challenge and lung function tests over a period of 15 days.

Questionnaire

The questionnaire was completed in 10 minutes by trained interviewers. It included personal questions on age, height, weight, medical history, and smoking habits. Nonsmokers were defined as those smoking less than one cigarette a day, and ex-smokers were those who had stopped smoking completely at least 6 months before the study. Questions about respiratory symptoms were adapted from the questionnaires of the British Medical Research Council and of the International Union Against Tuberculosis and Lung Disease. They included questions about usual and morning cough, phlegm, wheezing during the last 12 months, shortness of breath when hurrying on flat ground or when walking up a slight hill, asthma and rhinitis, and the use of medication (including inhalers, aerosols, or tablets) to help their breathing. Additional questions were included on the relationship between work and symptoms such as rhinitis, irritation of the eyes, and respiratory symptoms. Occupational history was recorded, both current and previous employment with special emphasis on type of exposure, nature of the job, duration of exposure per day, and duration of employment.

Pulmonary function tests

The pulmonary function of each person was tested at their place of work using a computerized pneumotachograph (Fleish no 3, Spiroanalyser, Fukuda, Tokyo, Japan) according to recommendations of the American Thoracic Society (ATS) (24). The spirometer was calibrated each day with a 3-liter syringe. Each person was seated, given a nose clip to wear, and asked to perform at least three satisfactory forced maximal expiratory maneuvers. The best values were selected in accordance with ATS criteria (24). The highest forced vital capacity (FVC), highest FEV_1, and highest PEF were not necessarily recorded from the same flow-volume curve. All the values were expressed as percentages of predicted values based on European Committee recommendations and were adjusted for age and height using regressions on the whole sample and then normalized (mean 0, SD 1).

Methacholine challenge

Nonspecific responsiveness was assessed by methacholine challenge for all the participants for whom there was no contraindication. Three cumulative doses were used for nonasthmatic subjects (100, 500, 1500 µg). Four cumulative doses were used for asthmatic subjects (50, 200, 500, 1500 µg). The solution of methacholine (2.5 mg/ml) was delivered in aerosol form in puffs of 50 or 100 µg at the beginning of the inhalation (FDC88, Médiprom, Paris, France). The increasing cumulative doses were obtained by increasing the dose of each puff (50 or 100 µg) and the number of puffs.

One minute after each cumulative dose, lung function was assessed. The challenge was stopped if the change in FEV_1 was greater than 15% or if the cumulative dose of 1500 µg was reached. Those for whom the FEV_1 fell by ≥15% were considered responders. For the responders, the result of the bronchial challenge was expressed as the provocative dose of methacholine causing a 15% decrease (PD_{15}). The provocative dose was determined from the logarithm of the cumulative dose from the beginning of the challenge (25). The slope of the dose–response curve was calculated for each person as the ratio between the percentage of variation in FEV_1 and the cumulative dose (26).

Variations in lung function

The participants were asked to use a handheld electronic spirometer four times a day for 15 days (One-Flow, STI Plastics, Saint Romans, France). The device automatically recorded the highest FEV_1 and highest PEF with date and time for each of these four tests (22).

The variation coefficients (100 × standard deviation/mean) of the FEV_1 (Vc FEV_1) and PEF (VcPEF) were calculated for each participant because of their statistical performance and simplicity (14).

Ethics

Each participant was informed that all personal data were confidential. They all gave their written consent

Table 1. Demographic data of the exposed and unexposed groups.

Group	Age (years)		Height (cm)		Weight (kg)		Duration of exposure (years)		Smoking					
									Nonsmokers		Exsmokers		Current smokers	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	N	%	N	%	N	%
Exposed (N=140)	37	9	173	6	71	11	14	9	52	37.1	76	54.3	12	8.6
Unexposed (N=77)	37	11	174	7	76	13	0	·	22	28.6	43	55.8	12	15.6
P-value	NS		NS		0.03		–				NS			

for participation. The ethics committee for human research at the Cochin – Port-Royal Hospital, Paris, approved the study. The ethics committee requested that the maximum dose be 1500 µg of methacholine and that the trial be stopped if the FEV_1 decreased by over 15%.

Data analysis

The statistical package for the social sciences (SPSS) was used. Contingency tables (2 × 2) with chi-square tests were used to determine whether the relationships between the qualitative variables were statistically significant. Arithmetic means and standard deviations were calculated for all the quantitative variables. They were compared using Student's t-test. An analysis of variance (ANOVA) was used to examine the relationships between respiratory symptoms, work exposure, smoking, and pulmonary function. When needed, log-normal transformation was applied (variation coefficients).

A stepwise multiple regression analysis of the lung function values was used to calculate adjusted values: (observed – predicted values)/residual SD.

Results

The smoking habits and general characteristics, except for weight, did not differ significantly between the two groups (table 1). The exposed group included 140 bakers and pastry makers. They cooked bread and pastry 8 hours a day. The workhours depended on the plant and the shift. Airborne exposure was not measured, but the work process was similar to that used in small bakeries. Their mean duration of exposure was 14 (SD 9) years. The control group included 77 workers from the same plants with the same workhours, but not occupationally exposed to air pollutants.

The prevalence of respiratory symptoms was slightly higher in the exposed group, but the difference was significant only for rhinitis (table 2). The history of allergies, including asthma and hay fever, did not differ significantly between the two groups. In the whole population, the association between a history of asthma and rhinitis was significant (P=0.02).

Table 2. Prevalence of symptoms according to the exposure.

Symptom	Exposed group (N=140)		Unexposed group (N=77)		P-value
	N	%	N	%	
Morning cough	14	10.0	5	6.5	NS
Morning phlegm	16	11.4	4	5.2	NS
Light dyspnea	39	27.8	16	20.8	NS
Wheezing	24	17.1	13	16.9	NS
Use of drugs for breath	9	6.4	2	2.6	NS
Rhinitis	43	30.7	9	11.7	0.001
History of asthma	13	9.3	6	7.8	NS
History of hay fever	27	19.3	10	13.0	NS

Table 3. Mean adjusted values, not significantly different according to the exposure and the smoking habits. (FEV_1 = forced expiratory volume in 1 second, PEF = peak expiratory flow, FVC = forced vital capacity)

Group	FEV_1	PEF	FVC
Exposed			
Nonsmokers (N=52)	–0.25	–0.05	–0.29
Current smokers (N=76)	0.09	–0.12	0.19
Exsmokers (N=12)	0.12	0.05	–0.05
Total (N=140)	–0.03	–0.08	–0.01
Unexposed			
Nonsmokers (N=22)	0.1	0.11	0.001
Current smokers (N=43)	0.05	0.16	0.04
Exsmokers (N=12)	0.02	0.15	–0.02
Total (N=77)	0.06	0.15	0.02

Before the methacholine challenge, the lung function values were normal in both groups according to the predicted European values (table 3). The means of the adjusted lung function values for the smokers were slightly, but not significantly, higher than those of the nonsmokers. There was no significant difference in lung function according to exposure.

Methacholine challenge was performed for 210 persons. Seven were excluded (3 in the exposed group, 4 in the unexposed group) due to a recent asthma attack (in the last 6 months) or lung function impairment (FEV_1/FVC <75%). The protocol for asthmatic persons was used for seven exposed persons (5%) and three unexposed persons (4%). The prevalence of a response greater than 15% was similar in the exposed and unexposed

Table 4. Bronchial responsiveness according to the exposure. (FEV_1 = forced expiratory volume in 1 second, PEF = peak expiratory flow)

Group	Responder with variation in FEV_1 of >15%		Slope of dose–response curve		Variation coefficient			
					FEV_1 %		PEF %	
	N	%	Mean (%/mg)	SD	Mean	SD	Mean	SD
Exposed (N=137)	23	16.8	–7.9	25.9	10.2	8.6	12.7	8.4
Unexposed (N=73)	12	16.4	–4.5	13.8	8.7	6.9	11.1	7.1
P-value	NS		NS		NS		NS	

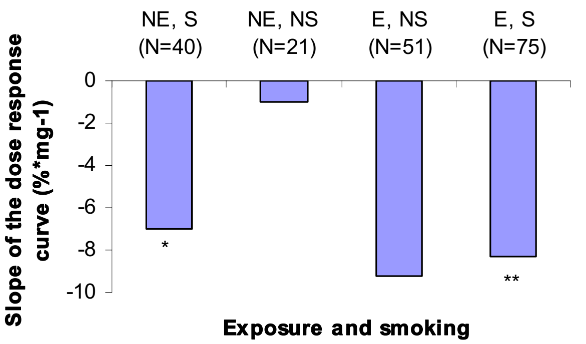

Figure 1. Mean slope of the methacholine dose–response curve according to exposure and smoking habits. The nonspecific responsiveness of the reference group [unexposed nonsmokers (NE, NS)] was lower than that of the exposed workers (E) regardless of whether they were smokers (S) or not. (*P<0.05; **P<0.01)

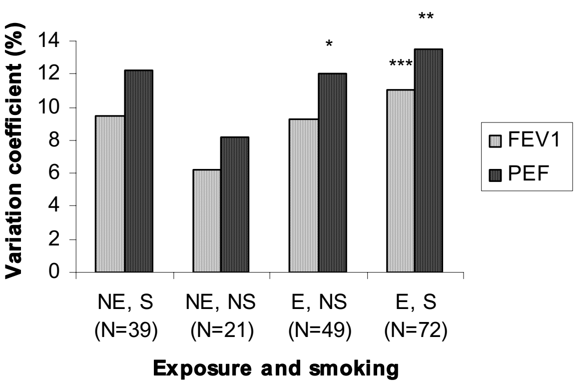

Figure 2. Mean of the variation coefficients for FEV_1 and PEF according to the exposure and smoking habits. The means of the variation coefficients for the reference group [unexposed nonsmokers (NE, NS)] were lower than those for the exposed workers (E) regardless of whether they were smokers (S) or not. (* P<0.05; ** P<0.01; *** P<0.001)

groups (table 4). The mean slopes of the dose–response curves did not differ significantly according to the exposure (table 4). However, when both smoking habits and exposure were considered, the mean of the slope was significantly lower for the unexposed nonsmokers than for the unexposed smokers and exposed smokers (figure 1). Therefore, occupational exposure and smoking increased the methacholine bronchial responsiveness, but no synergistic effect was observed.

Daily curves were recorded every day for 15 days for 211 of the 217 persons. The coefficient of variation for FEV_1 was slightly lower than that for PEF (table 4, figure 2). The two coefficients were significantly correlated (r=0.82), but were not significantly correlated with the slope of the methacholine challenge (Vc FEV_1 versus slope r=0.27; VcPEF versus slope r=0.16). The mean coefficients of variation of the FEV_1 and PEF were higher for the exposed workers and smokers than for the unexposed nonsmokers (table 4, figure 2). The effect was significant for the exposed smokers without interaction between the two exposure groups.

Discussion

The main finding of this study was that the variation in pulmonary function and methacholine bronchial responsiveness differed significantly between the persons occupationally exposed to flour and unexposed persons when smoking habits were taken into account. We found no correlation between the slope of the methacholine challenge and the coefficients of variation of FEV_1 (r=0.27) or PEF (r=0.16).

Our study confirms that rhinitis and nonspecific respiratory symptoms are more prevalent among workers exposed to flour than among unexposed workers. These findings resemble the results described in the literature for bakers and mill workers (1–6, 11). Most epidemiologic studies have found no significant difference in the mean lung function values between people with extended exposure to flour dust and unexposed workers, a finding consistent with our results (table 3) (1, 6, 11). However, the cross-sectional studies were limited to the current workforce, and workers who had left the plant due to occupational asthma or other health conditions were not included. In our study, rhinitis but not asthma was more common among the exposed workers than among the unexposed workers. A healthy worker effect could have led us to underestimate the prevalence of allergic symptoms, bronchial hyperresponsiveness, and lung function variability.

Nonspecific bronchial hyperresponsiveness is common in cases of baker's asthma, and a relationship has been demonstrated between exposure to flour and bronchial responsiveness in industrial bakeries and in flour mill workers (1, 9, 10). Leuenberger et al (21) found that occupational exposure to inhaled irritants is associated with hyperresponsiveness. The methacholine slopes were lower for persons exposed to dust, fumes, vapors, gases, or aerosols who had never smoked than for unexposed persons (21). Smoking is also associated with bronchial hyperresponsiveness, and a dose–response relationship has been suggested, as methacholine responsiveness increases with the number of cigarettes smoked per day (18). Therefore, we had taken into account occupational exposure and smoking habits when analyzing nonspecific bronchial responsiveness. We found that both increased nonspecific bronchial responsiveness.

The variations in the lung function values over 24 hours or a few weeks are small among normal unexposed persons (19, 27, 28). The lowest values usually occur during the night and on waking, and the highest values usually occur at noon or in the afternoon (27, 28). Various indices can be used to express variations in lung function over 24 hours or a few weeks (14, 16, 29). We used the variation coefficient because PEF variability assessed using this index is less sensitive to decreases in the number of daily measurements than the other indices are (14). In our study, the variations in PEF and FEV_1 differed significantly between the exposed and unexposed persons when smoking habits were taken into account. The higher variability in the PEF among the unexposed smokers was consistent with previous findings (19, 28). Holcroft et al (19) studied variations in PEF over a week in a relatively unexposed population of healthy adults. They observed that PEF varied significantly more among current smokers than among nonsmokers.

The new handheld spirometers satisfy ATS criteria and automatically store date, time, PEF, FEV_1, and even the whole flow-volume curve (22, 23). They improve the accuracy of self-reported data and probably the quality of the maximal expiratory maneuver. These electronic devices record PEF and other lung function values. The reproducibility is better for FEV_1 than for PEF. This good reproducibility of FEV_1 explains why FEV_1 is recommended for the expression of bronchial challenge (methacholine, specific provocation tests) and for epidemiologic purposes (25). Our results confirm this finding. The variation coefficient was slightly lower for FEV_1 than for PEF. Therefore, we were very interested in comparing FEV_1 to PEF variability according to the exposure groups. However, no significant difference was observed between the groups studied.

We also compared bronchial responsiveness and the variation in lung function for each person. We found no correlation between the slope of the methacholine challenge and the coefficients of variation of FEV_1 (r=0.27) or PEF (r=0.16). Lung function variability and nonspecific bronchial responsiveness are new tools in epidemiology, and each has different advantages and disadvantages. Only a few studies have analyzed the link between these two factors. In a community-based population sample, Higgins et al (30) found that the PD_{20} was weakly but significantly correlated with PEF variability (r = –0.44, P<0.001) (30). The variability and bronchial responsiveness increased with current smoking (31). Neukirch et al (13, 14) demonstrated that the variability of PEF correlated significantly with the slope of bronchial responsiveness in a study including 117 workers in a detergent plant. The correlation coefficients were low, between 0.37 and 0.41, according the number of daily measurements (N=2–4). Boezen et al (15) found a significant correlation between the slope of the dose–response curve for the methacholine challenge and PEF variability (r = –0.39) in a random population of 399 persons. However, they concluded that slope and PEF variability could not be used interchangeably in epidemiologic settings. Goldstein et al (16) did not find a significant correlation between methacholine challenge and 28 different indices of PEF variability in a group of 121 patients with suspected asthma. Prieto et al (20) did not find a significant correlation between methacholine challenge and PEF variability among 43 nonasthmatic patients with allergic rhinitis. They concluded that PEF variability and airway responsiveness are not interchangeable terms. Indeed, several studies failed to identify an index of PEF variability that can be used to identify asthmatic persons (16, 17). Lewis et al (17) suggested that the provocative dose of methacholine causing a 20% decrease in FEV_1 provides the best diagnostic measurement of asthma except for questionnaires.

In spite of the limitations imposed by the ethics committee for the methacholine challenge (maximal dose 1500 µg; stoppage of the challenge if FEV_1 decreased by >15%), we found significant differences between the two groups using the slope of the dose–response curve. PD_{20} is used to quantify the degree of nonspecific reactivity in an asthmatic person (25). The slopes and variability of lung function could be calculated for each person. These indices are more appropriate for epidemiologic purposes than the measurement of provocative dose, which can only be calculated if FEV_1 drops by >20% (26). The study was also limited by the lack of exposure measurements. However, we know that exposure to flour is high even in industrial bakeries (5, 7, 8).

The methacholine bronchial responsiveness and variability in PEF and FEV_1 were higher among the workers exposed to flour than among the unexposed workers. However, variability in lung function and nonspecific bronchial responsiveness do not measure exactly the same aspect of airway behavior. They are different tools, both of which may be useful in analyses of the effects of occupational exposure to allergens when smoking habits are taken into account.

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