

Diagnosis of flour-induced occupational asthma in a cross-sectional study

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Abstract The diagnosis of occupational asthma is usually performed in epidemiology using a combination of symptoms and bronchial hyperresponsiveness, while in a clinical setting the 'gold standard' for the diagnosis of occupational asthma is the specific bronchial challenge test in the laboratory. The aim of this study was to detect new cases of flour-induced occupational asthma (OA) in a group of workers exposed to grain and/or flour dust, by means of a step-by-step approach, as used in a clinical setting. In an epidemiological study, 111 millers and 186 bakers were examined by means of questionnaire, pulmonary function tests and skin-prick tests (SPT) to common allergens and to wheat flour dust extracts. From the whole sample, 82 subjects who showed asthma-like symptoms in the questionnaire and/or low forced expiratory volume in 1 sec (FEV₁) were selected. Selected subjects underwent methacholine challenge test, and hyperreactive subjects underwent specific bronchial challenge with flour dust in the laboratory. Sixty-two of the selected subjects performed the methacholine challenge test, and 22 (33.8%) were hyperreactive (PD₂₀ FEV₁ <1 mg of methacholine). Fifteen of 22 hyperreactive subjects underwent specific bronchial challenge test (sBCT) with flour dust; a positive response was elicited in six subjects. These subjects can be diagnosed as having flour-induced occupational asthma. Atopy and skin sensitivity to flour was partially related to the response to flour bronchial challenge. Bronchial hyperreactivity can be observed in a small percentage of subjects with asthma-like symptoms and/or low FEV₁, and a positive response to sBCT was observed in a subgroup of hyperreactive subjects. Therefore, using these selection criteria, a diagnosis of flour-induced OA, as commonly performed in a clinical setting, can be performed in few previously undiagnosed subjects. This approach could be relevant for an early diagnosis of occupational asthma. © 2002 Elsevier Science Ltd
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INTRODUCTION

Occupational exposure to flour and grain dust can induce occupational asthma (OA) due to hypersensitivity to flour allergens and current registration data suggest that the number of cases with baker's asthma is increasing. The environmental agents responsible for asthma appear to be some components of the grain and flour itself or grain contaminants, such as mites, weevils, moulds and flour additives (1,2).

In epidemiological studies, prevalence of occupational asthma is usually evaluated by asthma-like symptoms, but the relationship between asthmatic symptoms and

bronchial hyperreactivity and/or bronchial sensitivity to flour allergen has been poorly proven (3–5). Questionnaire data provided excellent sensitivity but poor specificity (6,7), which is inherent to the definition of symptoms.

In the clinical setting the diagnosis of occupational asthma is usually performed by the presence of asthma-like symptoms associated with bronchial hyperresponsiveness and a positive specific bronchial challenge test (sBCT) in the laboratory (8), which is considered the "gold standard" for the diagnosis of occupational asthma.

The purpose of this study was to evaluate the prevalence of new cases of flour-induced occupational asthma, as evaluated by a step-by-step approach, in a group of workers currently exposed to grain or flour dust in mills and bakeries. In order to do this attempt subjects with asthma-like symptoms or low forced expiratory volume in the first sec (FEV₁) (<95% percentile limit of normal distribution) were selected from exposed

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workers; these subjects underwent methacholine challenge test and eventually sBCT with flour dust in laboratory.

SUBJECTS AND METHODS

Study design and population

Cross-sectional survey and workplace exposure measurements

A cross-sectional survey was conducted in three industrial mills and two bakeries. Of 311 eligible workers, 297 (95%) agreed to participate; there was no important difference in this proportion between sites.

The current exposure of examined subjects was characterized on the basis of job titles and working department at the time of the survey. Different working areas were considered in mills and bakeries and gravimetric air sampling for total dusts was carried out. The sampling rate was about 1.5 l min^{-1} , and the minimum sampling duration was 4 h. In the examined plants there were neither ventilation systems (systems built specially for a technological cycle or forced general ventilation) nor use of personal protective equipments.

Data on smoking habit, occupational risk factors, respiratory symptoms and diseases were collected by trained interviewers using a modified Italian version of the standard NHLI questionnaire (CNR-Questionnaire) (9). It contains questions concerning respiratory symptoms, diseases, and risk factors.

Non-smokers (NS) were defined as those who had never smoked regularly. Smokers (S) were those who were currently smoking at least one cigarette daily. Ex-smokers (ES) included those who had formerly smoked regularly, up to 6 months or more before the examination.

The following symptoms were considered for analysis: chronic cough (or phlegm), defined as cough (or phlegm) for as much as 3 months of the year for at least 2 yrs; wheeze, defined as wheeze apart from common colds; dyspnoea, defined as for shortness of breath (Grade ≥ 1); shortness of breath with wheeze (SOBWHZ), defined as any attack of shortness of breath with wheeze, apart from common cold; allergic rhinitis, defined as hay fever or any allergy making the nose runny or stuffy, apart from common colds; chronic bronchitis, defined with affirmative answer to the question "Have you brought up phlegm from your chest on most days for 3 consecutive months or more in the last 2 years?"; emphysema and asthma, defined with affirmative answer to the question "Have you ever had emphysema (or asthma)?" and were taken into account if the diagnosis was confirmed by a physician.

Spirometry was carried out using a computerized pneumotacograph (Vitalograph, Buckingham, UK).

Forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) were obtained in each subject after performing at least three reproducible forced expiratory manoeuvres as recommended (10). The data were expressed as percentage of the predicted values (11).

Skin-prick tests were performed with a panel of 11 common allergens, including mites, pollens, moulds, danders, and positive and negative control, and two wheat flour extracts (Lofarma Allergeni, Milano, Italy). All extracts were titred in RAST units. The results were evaluated after 20 min with measurement of a mean wheal diameter minus the negative control. Atopy was defined as the presence of a positive skin reaction (mean wheal diameter $\geq 3 \text{ mm}$) to one at least of common allergens (12).

Selection study

Subjects were selected by the presence of a positive response to one or more questions on asthma symptoms and/or diseases (wheezing, attacks of SOBWHZ, asthma diagnosed by a doctor), associated or not with low FEV_1 ($< 83\%$ of predicted, the lowest 95% percentile limit of normal distribution) (11). They were asked to participate to the selection study.

Bronchial challenge test with methacholine was performed in all subjects with a baseline $\text{FEV}_1 > 70\%$. Bronchial hyperresponsiveness to methacholine was defined in presence of a provocative dose ($\text{PD}_{20}\text{FEV}_1$) lower than 1 mg of methacholine.

Subjects with bronchial hyperresponsiveness to methacholine were submitted to a specific bronchial challenge test with flour dust in laboratory. In presence of a positive response, a control test with exposure to lactose dust was performed on a different day.

According to criteria usually employed in clinical setting, flour-induced occupational asthma was diagnosed in presence of asthma-like symptoms, bronchial hyperresponsiveness to methacholine and a positive response to sBCT with flour dust.

Methods

Methacholine challenge test

Methacholine (Sigma, St. Louis, MO, USA) was delivered by a Mefar nebulizer using the procedure described elsewhere (13). Briefly, phosphate-buffered saline was inhaled first, followed every 2 min by methacholine in different steps. Cumulative doses of methacholine were from 0.04 to 3.2 mg of methacholine. FEV_1 was measured 2 min after each step. The test was stopped when FEV_1 fell by 20% or more below the postdiluent value, and $\text{PD}_{20}\text{FEV}_1$ (the cumulative dose producing 20% fall in

FEV₁) was computed. A PD20FEV₁ value lower than 1 mg of methacholine was considered as a positive methacholine challenge.

Specific bronchial challenge test with flour

Subjects inhaled flour dust by a mouthpiece connected to a small box where a suspension of the dust was obtained by blowing air at 5 l min⁻¹ through a bottle containing the dust. A cumulative exposure of 30 min was obtained (1+2+3+4+5+7+8 min). After baseline evaluation, FEV₁ was monitored before and 2 min after each step of dust exposure, and the exposure was continued until a $\geq 20\%$ fall in FEV₁ or a total cumulative exposure of 30 min was obtained. Afterwards, FEV₁ was monitored each 10 min in the first hour, and hourly until 8 h after the end of the exposure. A positive response was defined as a fall in FEV₁ $\geq 20\%$ from the baseline value, both during the first hour (early airway response, EAR) or between the second and the eighth hour (late airway response, LAR).

Dust concentration in the box was measured by blowing air of the box through a cellulose nitrate filter of 0.8 μ g porosity by means of a vacuum pump (mod. ZB/2, Zambelli, Italia) with a flow of 2 l min⁻¹; the dust collected by the filter was measured by weighting the filter before and after the exposure. Geometric mean value of dust concentrations in the box during specific challenge tests with flour dusts was 19.5 mg m⁻³ (range: 0.9–35).

In subjects with a positive response to flour sBCT, a control challenge test with lactose dust was done on a different day and using the same technique, in order to confirm the specificity of the airway response to flour dust. Geometric mean value of lactose dust concentrations in the box was 18.2 mg m⁻³ (9.1–36.3).

Statistical analysis

Age, length of employment, and spirometric measurements are expressed as mean $\pm$ SD. Comparison between groups has been performed by means of chi squared test and ANOVA for categorical and continuous variables respectively. A *p* value lower than 0.05 was considered as statistically significant.

RESULTS

Environmental evaluation of dust exposure in the workplace showed mean values of total dusts lower than 4 mg m⁻³, with values frequently higher than 1 mg m⁻³ (Table I).

Figure 1 summarizes the participation rate in the different steps of the study design and the main results for each of the three parts of the survey.

The results of the cross-sectional study are reported in Table 2. In the whole sample there was a significantly higher prevalence of dyspnoea in non-smoking bakers with respect to non-smoking millers. In bakers, the prevalence of chronic cough was significantly higher in smokers than in non-smokers; in millers the prevalence of most symptoms and functional data were significantly different when non-smokers were compared with smokers and ex-smokers.

Asthma-like symptoms and/or low FEV₁ were observed in 82 subjects, who were selected for further examination (second step). Selected workers showed higher mean age (40.9 $\pm$ 10.2 yrs vs. 34.6 $\pm$ 10.2, *P* < 0.05) and length of employment (14.2 $\pm$ 9.7 yrs vs. 10.5 $\pm$ 7.8, *P* < 0.05) than the total population. Prevalence of atopy was similar in both groups, but skin sensitivity to flour allergens was higher in selected workers than in the total population (25.6% vs. 12.7%, *P* < 0.05).

Sixty-five out of 82 selected subjects (79%) agreed to underwent methacholine challenge test. No difference

TABLE I. Total dust measurements in the working areas obtained by area sampling

	<i>n</i>	Geom. mean (mg m ⁻³)	Range (mg m ⁻³)	Percent of samples with > 1 mg m ⁻³ (%)	> 4 mg m ⁻³ (%)
Mills					
Unloading area	11	1.1	0.1–6.9	54.5	27.3
Grain cleaning area	6	1.0	0.3–15.8	50	33.3
Flour mill	6	0.2	0.3–0.4	0	0
Packing area and transport	15	2.2	0.1–8.7	86.6	46.6
Bakeries					
Mixing and roll production	11	2.1	0.5–6.6	81.8	27.3
Ovens area	48	0.6	0.1–1.6	4	0
Bread wrapping	9	2.3	0.2–12.8	77.7	33.3

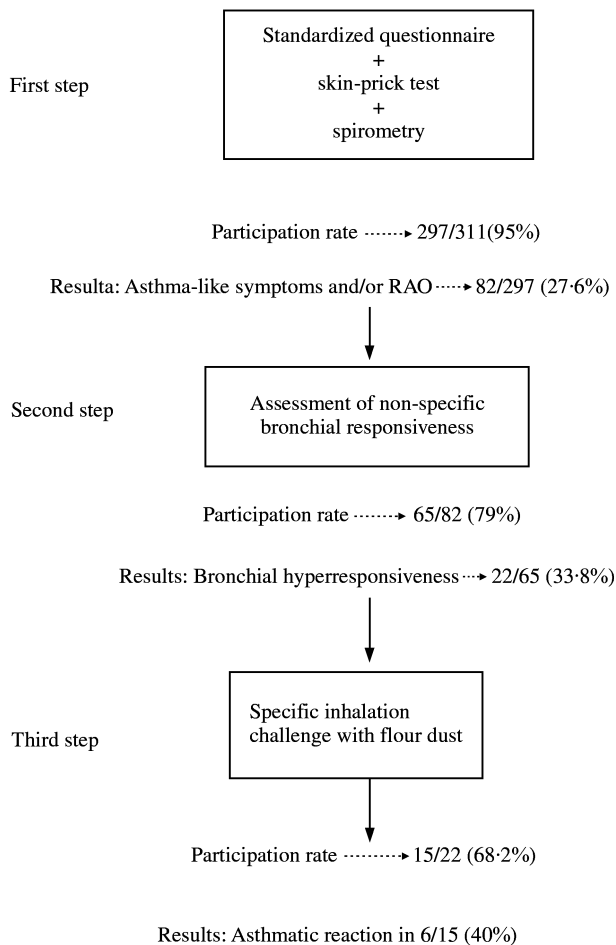


FIG. 1. Summary of participation rates for each of the three steps of the survey

was observed between this group of subjects and the group of subjects that did not agree to perform challenge test, as regards symptoms prevalence and other clinical findings. In three subjects, a diagnosis of occupational asthma to flour dust had been performed previously according to the usual standard criteria (8), and these subjects did not undergo the further selection steps; all of them had a FEV_1 lower than 70%. A positive response ($PD_{20}FEV_1 < 1$ mg of methacholine) was obtained in 22 subjects (nine millers and 13 bakers) out of the 65 who performed the methacholine challenge test. The clinical characteristics of subjects positive or negative for the methacholine challenge test are reported in Table 3. Hyperreactive subjects reported a significantly higher prevalence of SOBWHZ and diagnosis of asthma, but not of other respiratory symptoms or functional impairment.

The prevalence of bronchial hyperresponsiveness was higher in subjects selected by SOBWHZ and asthma (70·6% and 87·5%) than in subjects selected by wheeze, dyspnea or low FEV_1 (38·5%, 54·5% and 42·5%).

Fifteen of the 22 subjects (participation rate: 68·2%) with bronchial hyperresponsiveness to methacholine performed a specific bronchial challenge test with wheat flour dust. A positive response was elicited in six subjects (four millers and two bakers) with two dual, three late and one early airway responses (Table 4). In all six subjects with positive response to specific bronchial challenge with flour dust, control test with lactose dust did not elicit any positive airway response (Fig. 2). Skin sensitivity to flour was observed in only three out of six subjects with a positive response to sBCT to flour, and in three out of nine subjects with negative response. Of the three subjects with flour occupational asthma who did not undergo methacholine challenge test because of airway obstruction, all of them were atopic, and two showed also skin sensitivity to flour extract.

DISCUSSION

This study shows that a diagnosis of flour-induced occupational asthma can be performed in a small group of workers previously undiagnosed, by using a step-wise approach in subjects still exposed at work. According to clinical criteria for diagnosis of occupational asthma (8), a positive sBCT with flour dust was considered the "gold standard" for flour-induced occupational asthma. In fact, out of 297 workers we were able to select three subjects with already diagnosed occupational asthma and still at work, and six subjects with newly detected asthma due to flour dust, obtaining a prevalence of 3% at least of occupational asthma in subjects still at work. This prevalence is quite similar to the prevalence of occupational asthma obtained by the registers of occupational asthma available in some European countries (14), but probably it is underestimated because of the low rate of attendance at each step.

It is well known that the prevalence of asthma-like symptoms is higher than the diagnosis of occupational asthma obtained by an integrated evaluation of symptoms, non-specific and specific bronchial hyperreactivity (15). We obtained a diagnosis of occupational asthma in newly detected subjects by means of a positive sBCT with flour dust, which is the "gold standard" for the diagnosis of occupational asthma (8). The questionnaire has been found to be a sensitive but non-specific procedure for diagnosing occupational asthma (6); furthermore, the presence of non-specific bronchial hyperreactivity in a subject still at work is essential to raise suspicion of occupational asthma (8). Thus, in the present study the probability to have selected subjects without current asthma is quite low, because all subjects selected for sBCT were symptomatic and with bronchial hyperreactivity.

Instead, there is some possibility that diagnosis of occupational asthma could be underestimated. We have not

TABLE 2. Clinical and functional characteristics of bakers and millers who underwent to the first step of the selection, subdivided according to smoking habit

	Bakers		Millers	
	NS	S+ES	NS	S+ES
Number of subjects	30	84	50	119
Age (yrs, Mean $\pm$ SD)	36.3 $\pm$ 10.3	34.0 $\pm$ 10.9	39.3 $\pm$ 12.3	38.1 $\pm$ 11.2**
Sex (males, %)	24.5	75.5	26.7	75.3
Length of employment (yrs, mean $\pm$ SD)	9.5 $\pm$ 8.0	9.7 $\pm$ 8.3	14.3 $\pm$ 11.1	14.0 $\pm$ 9.5**
Chronic cough (%)	0	21°	4.1	16.0°
Chronic phlegm (%)	10.3	21.4	4.0	17.6°
Wheeze (%)	6.7	19.0	12.0	19.3
SOBWHZ (%)	6.9	4.8	6.4	10.5
Dyspnoea (%)	24.1	28.9	4.0**	19.3°
Asthma (%)	3.3	8.3	4.0	6.7
Rhinitis (%)	10.0	12.0	28.0	12.6°
Atopy (%)	36.7	28.6	34.0	26.0
Skin sensitivity to flour (%)	23.3	16.7	12.0	8.4
FEV ₁ <83% of pred. (%)	20.7	20.5	4.1*	27.1°°
FEV ₁ (% pred, mean $\pm$ SD)	102.6 $\pm$ 21.7	98.2 $\pm$ 18.2	104.5 $\pm$ 12.5	96.3 $\pm$ 17.7°

*: <0.05, **: <0.001, between bakers and millers, stratified by smoking habit.

°: <0.05, °°: <0.001 between smokers and non-smokers in bakers and millers. SD: standard deviation.

NS: non-smokers; S: smokers; ES: ex-smokers.

SOBWHZ: shortness of breath with wheezing.

TABLE 3. Clinical and functional characteristics of subjects who underwent to the second step of the selection, subdivided according to the response to methacholine challenge test

	Positive methacholine challenge	Negative methacholine challenge	Excluded from methacholine challenge (*)
n	22	40	3
Age (yrs, mean $\pm$ SD)	41.7 $\pm$ 8.4	40.5 $\pm$ 11.1	47.3 $\pm$ 2.9
Sex (male, %)	90.9	97.5	100
Length of employment (yrs, mean $\pm$ SD)	15.4 $\pm$ 8	13.7 $\pm$ 10.7	100
Chronic cough (%)	27.3	22.5	23.7 $\pm$ 9.3
Chronic phlegm (%)	9.1	20	100
Wheeze (%)	59	65	66.7
SOBWHZ (%)	45.5	17.5°	100
Dyspnoea (%)	45.5	30.0	100
Asthma (%)	31.8	2.5*	100
Rhinitis (%)	31.8	20.0	0
Atopy (%)	50	37.5	100
Skin sensitivity to flour (%)	22.7	12.5	66.7
FEV ₁ <83% of pred. (%)	36.4	37.5	100
FEV ₁ (% pred, mean $\pm$ SD)	87.1 $\pm$ 12.6	91.9 $\pm$ 16.0	57.2 $\pm$ 6.5

°: $P < 0.05$, *: $P < 0.001$ with respect to positive methacholine challenge.

SD=standard deviation.

SOBWHZ=shortness of breath with wheezing.

(*)=patients with a previous diagnosis of occupational asthma.

tested all subjects in the study population for bronchial hyperresponsiveness; only symptomatic subjects were selected. However, sensitization to occupational agents is strongly associated with work-related respiratory

symptoms and the probability that occupational asthma can occur in subjects without asthma-like symptoms identified by questionnaire is quite poor. Moreover, although flour dust allergens are the main sensitizers in

TABLE 4. Individual clinical and functional findings in selected subjects with bronchial hyperreactivity to methacholine, who performed a specific bronchial challenge test (sBCT) in laboratory with wheat flour dust

	Age (yrs)	Smoke	Symptoms	FEV ₁ (% pred)	Skin sensitivity		PD ₂₀ FEV ₁ (mg)	Response to sBCT with flour dust	Length of empl. (yrs)	Length of sympt. (yrs)
					com.all.	flour				
PL.	51	ex	W	96	pos	pos	0.987	neg	16	21
G.R.	54	yes	D	99	pos	pos	0.322	neg	11	3
A.G.	32	no	SOBWHZ,DW,A	84	pos	pos	0.029	dual	7	30
A.M.	21	no	A	105	pos	pos	0.149	neg	3	18
R.L.	50	no	W	96	neg	neg	0.830	late	23	23
F.L.	38	ex	W	73	neg	neg	0.292	late	13	0
B.C.	36	yes	SOBWHZ,W,A	70	neg	pos	0.040	early	9	8
P.P.	43	ex	SOBWHZ	80	pos	neg	0.324	neg	20	40
Q.N.	32	no	SOBWHZ,D	97	pos	neg	0.517	neg	11	8
L.E.	46	yes	SOBWHZ,DW	98	pos	neg	0.300	neg	27	26
D.M.A.	49	no	SOBWHZ,DW,A	86	neg	neg	0.209	neg	19	4
C.I.	34	no	SOBWHZ,W	93	pos	neg	0.085	neg	11	7
A.C.	44	yes	W	79	neg	neg	0.052	late	28	0
PL.	42	yes	—	79	neg	neg	0.800	neg	11	0
G.G.	46	no	W	98	pos	pos	0.111	dual	6	1

W=Wheeze; SOBWHZ= shortness of breath with wheeze; D=dyspnoea; A=asthma; empl.=employment; sympt.=symptoms; neg.=negative.

bakers and millers (16), we cannot exclude that other sensitizers (like mites, amylase etc.) could be responsible for occupational asthma in our subjects. In this case, we could have underestimated the real prevalence of the disease in these subjects with asthma-like symptoms and bronchial hyperresponsiveness at work. Furthermore, some investigators have pointed out that the exposure to endotoxins can be relevant in grain and other organic dust exposures, causing acute and chronic symptoms, but the present study did not measure bacterial endotoxins in the flour dust. An individual approach in the evaluation of possible sensitizers in each subject could have obtained different results and possibly a higher prevalence of occupational asthma.

Another possible explanation for the low rate of positive response to sBCT is that the duration of the exposure to flour dust in laboratory could be too short to elicit a positive response in all sensitized subjects. Some authors used exposure up to 2 h for specific bronchial challenge with flour dust (17). However, our subjects were exposed to a high level of dust during specific bronchial challenge, although the duration of exposure was 30 min. Thus, we believe that the possibility of a false negative response to sBCT in these subjects is quite low. Although there was a great variation in the amount of dust exposure during challenge test, there was no relationship between the level of dust exposure in the challenge box and the presence of a positive airway response to flour dust. A previous study (18) analyzed the level of dust exposure during a challenge chamber test in a large group of specific bronchial challenges with flour dust,

showing no relationship between the level of dust exposure and the presence of positive response. Dust levels during specific challenge test in the laboratory have been only seldom measured (19,20) and they were quite high. On the other hand, false positive responses due to these high levels of flour dust can be excluded by the low rate of positive response among subjects who performed specific bronchial challenge test (six out of 15 subjects) and by the negative response to challenge test with lactose.

There are several methods to verify the relationship between asthma-like symptoms and exposure to occupational sensitizers or irritants: changes in FEV₁ in the workplace, changes in methacholine reactivity or changes in PEF monitoring between out- and in-work periods (21). However, all these techniques only allow a diagnosis of "work-related asthma", and not of occupational asthma, which requires the identification of a specific compound as responsible for bronchoconstriction (22). Furthermore, PEF monitoring in the workplace has a low sensitivity in detecting subjects with occupational asthma diagnosed by a specific bronchial challenge tests in laboratory (23,24). Thus, specific bronchial challenge test in laboratory is essential for an aetiological diagnosis of occupational asthma (7,21). This approach is usually performed in clinical setting, and the results of the present study show that it can also be successfully performed in an epidemiological study.

The results of this study also show that bronchial hyperreactivity can be observed in a small percentage of subjects with asthma-like symptoms or pulmonary

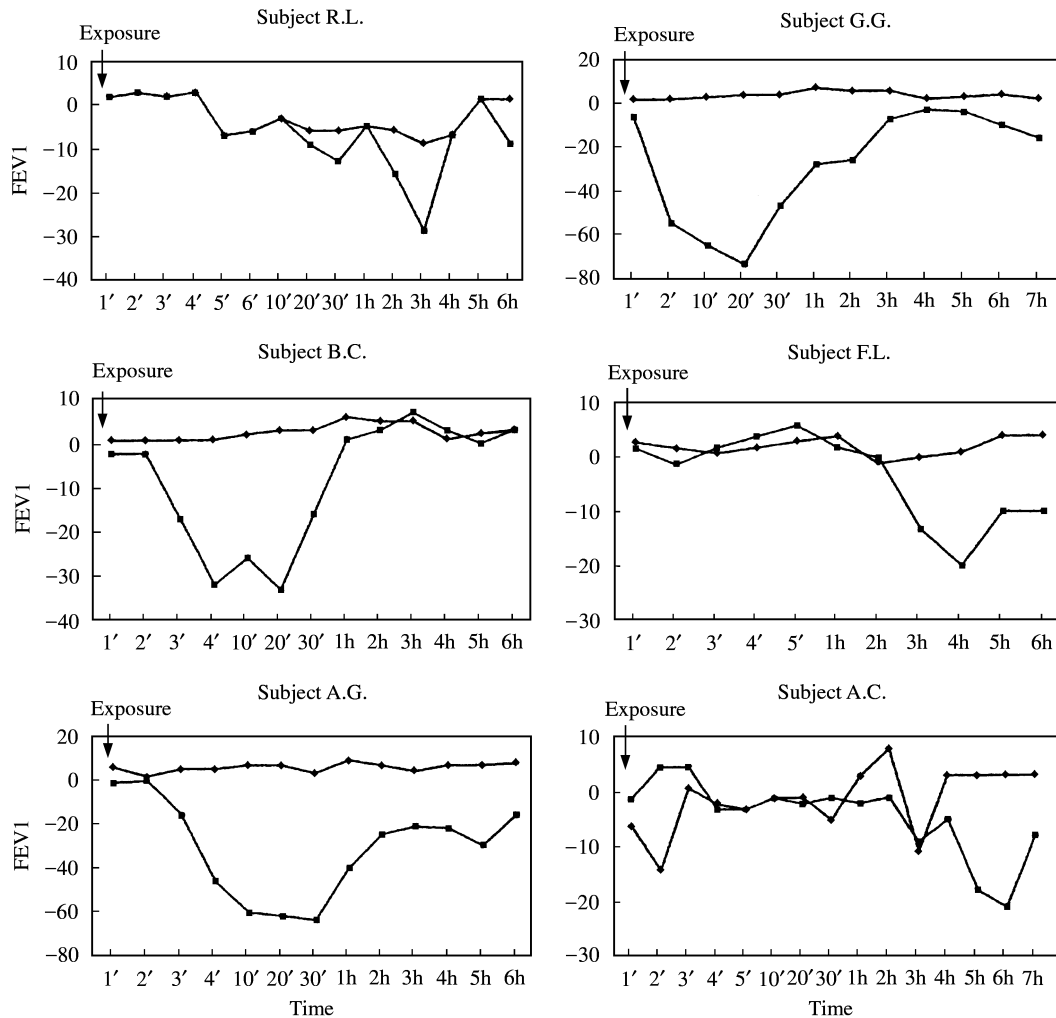


FIG. 2. Results of specific inhalation challenges with colour (—■—) and lactose (—◆—) dust in subjects with positive airway response to flour dust.

impairment at work; symptoms most suggestive of asthma such as attacks of chest tightness and wheeze and diagnosed asthma were, not surprisingly, most closely associated with bronchial hyperreactivity.

Skin sensitivity to the currently available extracts of flour seems to be a mild predictor of asthma symptoms and/or bronchial hyperreactivity, as reported by some authors (2). Different results on this point have been obtained with other types of sensitizers (i.e. latex) (25). As a consequence of flour exposure, workers who develop sensitivity to flour may selectively drop out of the workplace. If such self selection takes place in the baking industry, it is reasonable to expect workers who stay in the job to be less atopic and, consequently, relatively free of atopic-related symptoms and airway hyperresponsiveness; therefore, prevalence rates in cross-sectional studies may result in biased estimates of the actual risk. This finding is similar to that reported previously in bakers (26) and is compatible with self-selection due to the well known "healthy worker effect" (27). There is also

some discrepancy between the skin response to flour extracts and the airway response to flour dust during specific bronchial challenge, because three out of six subjects with positive sBCT were negative to the skin-prick test using flour extracts. This fact could be explained by a lower sensitivity of aqueous flour extract in comparison with flour dust in detecting a positive response. On the other hand, three out of 15 subjects who underwent sBCT were positive to SPT with flour extract but negative to sBCT with flour dust; this fact could be explained by a possible cross-reaction with grass pollen, since all three subjects were positive to mixed grass pollen extract.

We selected subjects for specific bronchial challenge test from exposed subjects with asthma-like symptoms and bronchial hyperresponsiveness. We did not consider other selection criteria (like skin-prick tests for commercially available flour extracts or work-related PEF changes) because the sensitivity of these tests in detecting subjects with occupational asthma is low. Also, sub-

jects not hyperreactive to methacholine were missed, but the probability of observing non-hyperreactive subjects with symptomatic occupational asthma at work is definitively low (8,17).

Finally, a moderately high drop-out rate was observed in our selection steps, which could underestimate the real prevalence of flour-induced asthma in our sample. However our drop-out rate was not particularly different from that reported by other authors (25).

In conclusion, our step-wise approach to a clinical diagnosis of occupational asthma allowed detection of a small number of cases of previously undiagnosed flour-induced asthma in an epidemiological sample of exposed workers. The definition of the aetiology of occupational asthma is important for prevention and compensation. It is well known that a long duration of symptoms before diagnosis is associated with a poor prognosis of occupational asthma, despite the cessation of work (28). Thus, an early diagnosis can allow an early removal from the offending agent and, possibly, a better prognosis of occupational asthma.

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