

## Occupational asthma: validity of monitoring of peak expiratory flow rates and non-allergic bronchial responsiveness as compared to specific inhalation challenge

B. Perrin\*, F. Lagier\*, J. L'Archevêque\*, A. Cartier\*, L-P. Boulet\*\*, J. Côté\*\*, J-L. Malo\*

*Occupational asthma: monitoring of peak expiratory flow rates and non-allergic bronchial responsiveness as compared to specific inhalation challenges. B. Perrin, F. Lagier, J. L'Archevêque, A. Cartier, L-P. Boulet, J. Côté, J-L. Malo.*

**ABSTRACT:** The sensitivity and specificity of monitoring peak expiratory flow rates (PEFR) and bronchial responsiveness to the provocative concentration of histamine or methacholine ( $PC_{20}$ ) has been determined as compared to specific inhalation challenges in the diagnosis of occupational asthma.

A prospective study of 61 subjects referred for occupational asthma to various agents was performed. PEFR was assessed every 2 h during a period away from work for at least 2 weeks. The period at work was 2 weeks, or less if there was increased symptomatology or marked changes in PEFR. At least one  $PC_{20}$  assessment was obtained at work and away from work. Graphs of PEFR and  $PC_{20}$  values were interpreted in blind fashion by three experienced readers.

There was complete agreement among the three in 54 out of 61 instances (78%). Twenty five out of 61 subjects (41%) had positive specific inhalation challenges. The best index for comparing results of PEFR with specific inhalation challenges was the visual analysis of PEFR with sensitivity and specificity of 81% and 74%. All of the numerical indices were significantly less satisfactory.

We conclude that visual analysis of PEFR is an interesting tool for investigating occupational asthma, although sensitivity and specificity values do not seem satisfactory enough to warrant using it alone.

*Eur Respir J, 1992, 5, 40-48.*

\* Dept of Chest Medicine,  
Hôpital du Sacré-Coeur,  
Montreal, Canada.

\*\* Centre de Pneumologie,  
Hôpital Laval, Quebec City,  
Canada.

Correspondence: J-L. Malo,  
Dept of Chest Medicine,  
Hôpital du Sacré-Coeur,  
5400 W. Gouin,  
Montreal, Canada H4J 1C5.

Keywords: Bronchial provocation tests; histamine; methacholine; obstructive lung diseases.

Received: February 5, 1991; accepted after revision July 1, 1991.

A diagnosis of occupational asthma can be suspected when there is a history of asthmatic symptoms that are worse at work or immediately after work. Nevertheless, the history could be misleading and the occupational asthma literature [1, 2] as well as statements by experts [3, 4] generally recommend documenting the diagnosis with an objective assessment. Specific inhalation challenges in a laboratory or at work have been suggested since 1970 by PEPYS and co-workers, as summarized previously [5]. These tests consist of exposing the subject to the offending agent in a hospital laboratory under the close supervision of a technician and a physician. They are considered to be the gold standard in diagnosing occupational asthma. However, they can only be carried out in specialized centres. This represents an experimental environment which can differ from the workplace. Furthermore, a subject may be exposed at work to several agents recognized as causing occupational asthma. This could result in unduly prolonged testing as subjects can only be exposed to one product at a time in the laboratory. Finally, the sensitizing product at work has sometimes not been

identified, making exposure in the laboratory impossible.

The effect of the exposure at work can also be studied by examining the changes in peak expiratory flow rates (PEFR) and non-allergic bronchial hyperresponsiveness. BURGE and co-workers [6, 7] were the first to propose serial assessment of peak expiratory flow rates at work and away from work. However, collecting data requires satisfactory collaboration and honesty on the part of the subject. There can be significant changes even when the subject has only been exposed to irritant, non-sensitizing agents at work. In order to overcome these problems, it has been suggested that this monitoring be coupled with assessment of non-allergic bronchial responsiveness in a hospital laboratory [8, 9], which cannot be malingered. Indeed, non-allergic bronchial responsiveness is altered in the presence of a sensitizing bronchospastic reaction, particularly of the late type [10, 11]. This kind of reaction is often seen with occupational asthma [1, 2]. Furthermore, changes in bronchial responsiveness can also occur after isolated immediate reactions [11, 12].

If this methodology of assessing occupational asthma is found to be sensitive and specific, it could possibly replace specific inhalation challenges, making the assessment of a larger number of subjects possible. The tests can be carried out in less specialized centres and might be useful as a screening tool in high-risk industries where a known sensitizing agent is used.

To the best of our knowledge, there has been only one prospective study [13] to compare the two tests (assessment of peak expiratory flow rates and non-allergic bronchial responsiveness) with specific inhalation challenges in a hospital laboratory in 23 subjects continuously exposed to Western red cedar. The authors found that the sensitivity and specificity of serial monitoring of peak expiratory flow rates were 86% and 89%, respectively. They also found that including changes in non-allergic bronchial responsiveness did not improve the validity of the comparison.

The aim of our study is to assess the validity of the combined monitoring of peak expiratory flow rates and bronchial responsiveness at work and away from work among 61 subjects exposed to various sensitizing agents.

## Methods

### Subjects

Sixty one subjects were referred for investigation of occupational asthma to the Department of Chest Medicine at Hôpital du Sacré-Coeur in Montreal (n=51) or Hôpital Laval in Quebec City (n=10). All had a history which was suggestive of occupational asthma, *i.e.* asthma symptoms (dyspnoea, cough, wheezing, tightness in the chest) which worsened at work and improved at the time of a period off-work. The subjects had been exposed to a wide variety of agents:

- isocyanates including toluene diisocyanate (TDI) among foam industry workers, hexamethylene diisocyanate (HDI) and isophorone diisocyanate (IPDI) among spray painters, diphenylmethane diisocyanate (MDI) among workers in various plastic industries and foundries (n=18);
- Western red cedar among workers in various plants manufacturing windows and doors (n=9);
- flour among bakers (n=5);
- tertiary amines (n=3), formaldehyde (n=3), colophony (n=2), guar gum (n=1), grain dust (n=1), barium (n=1), phthalic anhydride (n=1), cotton (n=1), ethanolamine (n=1), polystyrene resin (n=1), phosphoric and nitric acid (n=1), various poultry antigens (n=1).

Eleven subjects were employed in sawmills for which the offending agent is still unknown [14] and one was exposed to various sensitizing agents (azobisformamide, tertiary amines, isocyanates). Safety data sheets of all the products present in the workplace were obtained for all subjects.

Comparisons of PEFR monitoring were made for periods at work and away from work during which the anti-asthmatic medication remained constant. Twenty one subjects took inhaled and two oral steroids during the monitoring. Twenty were on regular sustained released theophylline preparations and twenty on regular inhaled beta<sub>2</sub>-agonists.

### Study design

**Clinical history.** A clinical history and information on work were recorded by trained physicians including sex, age, height, smoking habits, duration of exposure and onset of symptoms at work, types of sensitizing agents handled at work, *etc.*

**Immunological testing.** Skin prick tests were carried out using a battery of 15 common inhalant allergens, a control solution and histamine phosphate (1 mg·ml<sup>-1</sup>). Atopy was defined by the presence of at least one skin reaction (wheal  $\geq 3$  mm) 15 min after introducing the antigen when there had been a negative control test and a positive histamine test. For subjects with occupational asthma mediated by an immunoglobulin E (IgE)-dependent mechanism, we also performed skin prick tests with the relevant allergens, *i.e.* cereals: wheat, oat, barley, corn, rye (Hollister-Stier Lab., Rexdale, Ontario, USA) for flour, guar gum (1 mg·ml<sup>-1</sup>), and hen feathers.

**Peak expiratory flow rate monitoring.** PEFR were obtained using a Wright mini peak-flow meter [15] every 2 h (or at least four times a day for the 10 subjects in Quebec City) after at least 2 weeks away from work, the subject having been instructed in its use. Three assessments were performed and recorded every 2 h and the best reproducible values ( $\pm 20$  ml·min<sup>-1</sup>) were kept for analysis [16].

The mean duration of the monitoring period at work was 12.2 $\pm$ 4.1 (sd) days and 13.9 $\pm$ 2.0 days for the period away from work. Thirty two subjects were monitored for  $\geq 15$  days, 20 subjects for 8–15 days and 9 for  $\leq 7$  days at work. Among the last nine, monitoring was stopped because the subjects had significant falls in PEFR (n=8) or severe cough (n=1). For those subjects in whom monitoring took place over  $\geq 15$  days, only the final 15 days or the period during which most intense exposure occurred were kept for analysis. Weekends were not considered in the analysis as the length of time for recovery was not judged to be sufficient. Subjects could begin recording PEFR during a period at work or away from work first, depending on which was most convenient. Medication was kept constant throughout the study period, except for inhaled beta<sub>2</sub>-adrenergic agents which were used if required.

**Assessment of non-allergic bronchial responsiveness.** At least one assessment of non-allergic bronchial hyperresponsiveness was carried out at work and away

from work in 54 out of 61 cases; in 16 subjects, two assessments were obtained for each period (at work and away from work). The tests were performed with a Wright's nebulizer (output =  $0.14 \text{ ml}\cdot\text{min}^{-1}$ ) at tidal volume breathing for 2 min using a standardized procedure [17] with histamine or methacholine, the pharmacological agent being constant in any one individual. Measurement of forced expiratory volume in one second ( $\text{FEV}_1$ ) was performed on a Collins 9-L water spirometer (W.E. Collins, Braintree, Mass, USA) according to the standards of the American Thoracic Society [18].

*Specific inhalation challenges.* Specific inhalation tests were performed in a challenge room as proposed by PEPYS and HUTCHCROFT (5) in a hospital laboratory or at the workplace in the case of sawmills. For sensitizing agents in powder form (*i.e.* Western red cedar, flour, guar gum), a special apparatus was used [19]. This recently described apparatus guarantees that subjects are exposed to low ( $<10 \text{ mg}\cdot\text{m}^{-3}$ ) and steady concentrations of the dust. The method proposed by PEPYS and HUTCHCROFT [5] of asking subjects to tip dust from one tray to another was used for grain dust and hen antigens. Methods of exposure to isocyanates are detailed elsewhere [20]. For the other agents, attempts were made to reproduce exposure at work. Anti-asthma medication was stopped before the test, *i.e.* 8 h before for short-acting inhaled  $\beta_2$ -adrenergic agents and 24h before for theophylline. In nine subjects, specific challenges were performed during steroid treatment (inhaled in seven subjects, oral in two) because otherwise stability of spirometry could not be obtained on the control day. However, the dose of inhaled or oral steroids was given the night before initiating the challenge (8–12 h before the challenge) and the dose was kept constant during the challenge period.

The following sequence of tests was performed on each subject. On the first day of non-exposure,  $\text{FEV}_1$  was monitored every 10 min for 1 h, every 30 min for 2 h and hourly for the next 5 h. Maximum daily fluctuations in  $\text{FEV}_1$  had to be  $<10\%$  for a subject to continue with the tests. On the second day, subjects were exposed to the control product (diluent, lactose) for 15–30 min. For isocyanates, the control product was the paint diluent containing aromatic hydrocarbons, ketones, aliphatic and ether ester for HDI, various aromatic hydrocarbons and fluorocarbons for MDI, a commercial preparation made of polyol (99%) and aliphatic amine (1%) for TDI. Western red cedar subjects were exposed to wood dust of local species (spruce, fir, pine) not containing any white or red cedar on the control day. For subjects exposed to flour, guar gum and barium, lactose powder was used. For the agents where the mechanism is IgE-dependent (flour, guar gum, grain), the challenge was performed on one day only in the following way: one breath, 10, 15, 30s, 1, 2, 5 min, up to a maximum of 2 h divided into intervals of 30 min. For the other agents, subjects were exposed on the third day and

subsequent days if required in the following way: they were asked to remain in the challenge room for progressively longer periods of time: one breath, 15 and 45 s for a total of 1 min on the third day; 1 min, 2 min and 2 min for a total of 5 min the next day; and total periods between 15 and 120 min on subsequent days. Every evening, the subjects continued to measure PEFR every 2 h until bedtime, and during the night if they awakened with asthmatic symptoms.

#### Analysis of results

Dose-response curves to histamine or methacholine were drawn on a semilogarithmic non-cumulative scale, the concentration on the abscissa and the percentage change in  $\text{FEV}_1$  on the ordinate. Reference values for  $\text{FEV}_1$  were obtained from KNUDSON *et al.* [21].

PEFR data were recorded according to the method of BURGE and co-workers [6], which produced graphs of maximum, minimum and mean daily values. We also drew graphs of individual data. If there was evidence from the history that the subject had been exposed to the sensitizing agent it was considered a working day. This information was important as subjects could be exposed to the sensitizing agent on a non-continuous basis. The graphs were interpreted using direct visual analysis by three observers (B.P., J-L.M. and A.C.) in a double-blind and randomized way. Graphs identified as indicating occupational asthma required complete agreement among the three observers as to whether they showed a real pattern of deterioration during days at work and with recovery during the period away from work, or instability in maximum, minimum and mean values, when the days at work and days away from work were compared.

PEFR were also analysed using individual data. The following indices were assessed:

Index 1: number of days with daily changes  $>20\%$  between periods at work and off work;

Index 2: mean of maximum, minimum and mean PEFR at work and off work;

Index 3: number of days at work with highest, lowest and mean values  $>2$  sd of values away from work.

Furthermore, we used recently proposed indices [22]:

Index 4: amplitude percent mean (highest reading - lowest/mean  $\times 100$ );

Index 5: amplitude percent highest (highest - lowest/highest  $\times 100$ );

Index 6: sd percent of PEFR readings: (sd of PEFR/mean)  $\times 100$ .

For each of these indices, we derived the sensitivity and specificity as compared to specific inhalation tests. If the PEFR analysis suggested occupational asthma, the following positive criteria were required:

Index 1: an excess of at least three or more days at work as compared with the period away from work with daily changes  $>20\%$ ;

Index 2: mean of maximum, minimum, and mean

PEFR at work <off work (difference of more than 50  $l \cdot \text{min}^{-1}$ );

Index 3: an excess of at least three or more days at work as compared with the period away from work with maximum, minimum, and mean PEFR >2 sd of off-work values;

Index 4: at least three more days at work than away from work with values >12%, 20% and 26.3% [22];

Index 5: at least three more days at work than away from work with values >12%, 20% and 23.4% [22].

Mean percentage sd at work and away from work (Index 6) as well as Indices 4 and 5 (above) were analysed statistically with Student's paired t-test.

Significant non-allergic bronchial hyperresponsiveness was set at a provocative concentration producing a 20% fall in  $FEV_1$  ( $PC_{20}$ ) value  $\leq 16 \text{ mg} \cdot \text{ml}^{-1}$  [23]. Changes in non-allergic bronchial responsiveness were considered to be definite when changes in  $PC_{20}$  were 3.2 fold or more comparing values obtained at work and away from work. This represents the upper limit of the 95% confidence interval for the between-day reproducibility of the test in one of the two laboratories [24]. A change in  $PC_{20}$  between 2 and 3.2 fold was considered borderline as this corresponds to the upper limit of the 95% confidence interval for the reproducibility of the test by others [25].

Graphs of specific inhalation challenge reactions were drawn showing time on the abscissa and percentage of changes in  $FEV_1$  on the ordinate. An inhalation challenge was considered to be positive when there was a sustained fall in  $FEV_1$  after exposure (minimum of 20%) on the test day as compared to changes on the control day (<10% of changes).

Several types of temporal reactions were defined before they were interpreted in blind fashion. The readers classified them as either a classical temporal pattern (immediate or isolated early, late, early late and dual) [5] or an atypical pattern according to our experience (progressive, square-waved and prolonged immediate) [26].

Statistical analysis was done using Student's paired t-test and Chi-square. The level of statistical significance was set at a p value  $\leq 0.05$ .

## Results

Baseline anthropometric, clinical and functional results are listed in Table 1. The majority of subjects were male, non-atopic and former smokers. Significant airway obstruction during a period away from work was documented in 12 subjects who had a  $FEV_1$  <80% predicted and in 19 who had a fraction of forced vital capacity expired in one second ( $FEV_1/FVC$ ) <85% predicted. Significant bronchial hyperresponsiveness was present in 56 out of 58 subjects tested (97%).

PEFR measurements were taken at least four times a day in 97% of subjects. However, compliance with the recording was not perfect as 31% did not record

their PEFR on one to three days and 28% failed to record it for more than three days.

Specific inhalation challenges induced significant bronchoconstriction in 25 subjects (41%). Seventeen subjects had typical bronchospastic reactions (seven immediate, two early late, seven late and one dual). Atypical reactions were encountered in eight subjects (two progressive, five square-waved and one prolonged immediate).

Table 1. - Baseline anthropometric, clinical and functional results

Characteristic	
Sex (M/F)	55/6
Age (mean $\pm$ sd) yrs	41 $\pm$ 10.8
Atopy (present/absent)	23/36
Smoking habits (smokers, ex-smokers, nonsmokers)	13/31/17
Length of exposure at work (mean $\pm$ sd) (yrs)	10.4 $\pm$ 8.3
Duration of symptoms (mean $\pm$ sd) (yrs)	3.2 $\pm$ 3.2
$FEV_1$ (mean $\pm$ sd) % pred*	93 $\pm$ 18
number <80% pred	12
$FEV_1/FVC$ (mean $\pm$ sd) % pred*	89 $\pm$ 12.7
number <85% pred	19
$PC_{20}$ $\text{mg} \cdot \text{ml}^{-1}$ †	
<2	19 (29)
2-16	23 (20)
>16	12 (5)

\*: values obtained during a period off-work; †: values obtained for periods off-work and at work (in brackets).  $PC_{20}$  was recorded in four other subjects during one or the other of the periods;  $PC_{20} \leq 16 \text{ mg} \cdot \text{ml}^{-1}$  was found in two of these four subjects;  $PC_{20}$  was not measured in three subjects.  $FEV_1$ : forced expiratory volume in one second;  $FEV_1/FVC$ :  $FEV_1$  as a fraction of forced vital capacity;  $PC_{20}$ : provocative concentration producing a 20% fall in  $FEV_1$ .

Table 2 shows the sensitivity and specificity of the various indices. This table distinguishes the 54 subjects for whom the interpretation was the same among the three readers (89% agreement). For the seven other subjects, the reading was dubious but a decision was made. In these seven cases, five were monitored for 15 days at work and off-work. The other two subjects were monitored for shorter periods. One had a very troublesome cough and had to leave work, and the other was exposed only intermittently at work. Among the seven dubious cases, there were four false positive and two false negative assessments, the last subject being correctly judged as negative for both tests. The best index derived from the PEFR analysis was three or more days with daily changes >20% for the period at work as compared with away from work. Visual analysis proved the best index in terms of sensitivity and specificity. Values >80% were reached by considering the 54 subjects in whom the analysis was uniform among the three readers. Combining visual analysis of PEFR and changes in  $PC_{20}$  increased the sensitivity and specificity values as compared with  $PC_{20}$  results alone.

Table 2. — Specificity and sensitivity of different indices derived from the analysis of PEFR and PC<sub>20</sub> for periods at work and away from work as compared with specific inhalation challenges

PEFR Index no.	Description	Sensitivity %			Specificity %		
		max	min	mean	max	min	mean
1.	Difference >3 between the number of days with daily changes >20%	64 (65)			72 (71)		
2.	Mean of... PEFR lower at work	44 (48)	76 (83)	56 (57)	81 (84)	58 (68)	75 (81)
3.	Three or more days at work with values >2 SD of values away from work	highest 56 (52)	lowest 52 (48)	mean 48 (43)	highest 14 (13)	lowest 22 (19)	mean 19 (19)
4.	Amplitude percent mean (highest reading - lowest/mean × 100)	≥26.3%	≥20%	≥12%	≥23.4%	≥20%	≥12%
		52 (57)	60 (65)	40 (39)	78 (81)	78 (77)	67 (71)
5.	Amplitude percent highest (highest - lowest/highest × 100)	≥23.4%	≥20%	≥12%	≥23.4%	≥20%	≥12%
		52 (57)	64 (65)	40 (39)	75 (75)	72 (71)	69 (77)
<b>Visual analysis</b>		81 (87)			74 (84)		
<b>PC<sub>20</sub></b>	Changes ≥2 fold difference	61 (67)			52 (54)		
	Changes ≥ 3.2 fold difference	43 (48)			65 (64)		
<b>Combined PEFR (visual analysis) and changes in PC<sub>20</sub> ≥2 fold difference</b>		84 (91)			61 (46)		

Figures in brackets are the values when the seven subjects for whom the interpretation was dubious are excluded. PEFR: peak expiratory flow rate; PC<sub>20</sub>: provocative concentration producing a 20% fall in forced expiratory volume in one second.

Amplitude percent mean (Index 4) and amplitude percent highest (Index 5) PEFR were significantly different ( $t=11.5$  and  $11.6$ ,  $p<0.001$ ) in those with negative from those with positive challenges. Standard deviation percent of PEFR readings ( $(SD \text{ of PEFR} / \text{mean}) \times 100$ ) (Index 6) was also significantly different in those with negative from those with positive challenges ( $t=2.26$ ,  $p=0.01$ ).

Of 32 subjects with what was considered as a negative PEFR monitoring, 16 also had a clinical history of occupational asthma which was unlikely. Fifteen of these 16 subjects had negative specific inhalation challenges.

Of the 26 subjects who showed maximum changes <20% in PEFR at work or away from work, 15 had positive challenges. Of the 22 subjects who had mean maximum changes in PEFR <20%, 10 had positive

challenges. Only one of the five subjects with a PC<sub>20</sub> >16 mg·ml<sup>-1</sup> at work had a positive challenge. Of the 54 subjects for whom complete agreement was reached in the interpretation of PEFR, 10 with positive and 10 with negative specific inhalation challenges changed their PC<sub>20</sub> by ≥3.2 fold difference during a period away from work. Four subjects had a PEFR pattern suggestive of occupational asthma and changes in PC<sub>20</sub> ≥3.2 fold difference during a period away from work but had negative specific inhalation challenges.

Figure 1 shows typical positive patterns of changes in PEFR at work and away from work, whereas figures 2 and 3 show graphs for the seven dubious cases. The latter subjects were nevertheless classified as positive or negative (two of three identical assessments).

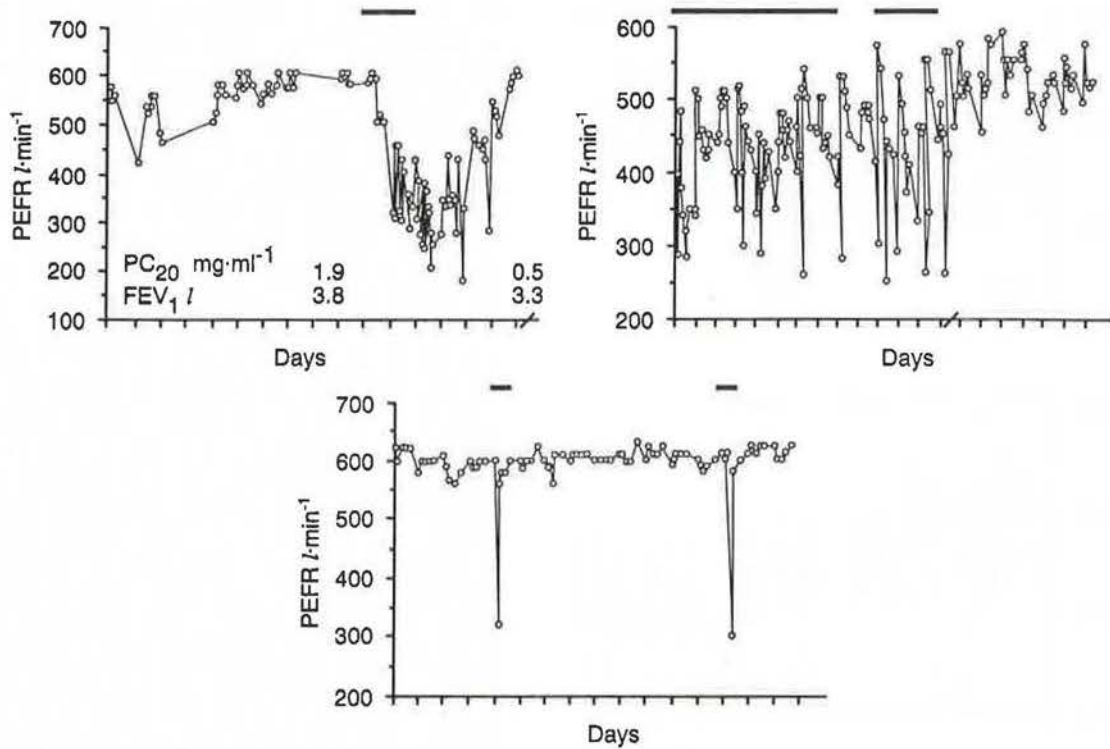


Fig. 1. - Typical positive patterns of peak expiratory flow rate (PEFR) in three subjects who had positive specific inhalation challenges. Values of  $PC_{20}$  and  $FEV_1$  are shown. Periods at work are indicated by the thick line. PEFR values include some results taken after bronchodilator (*i.e.* when subjects experienced asthma symptoms).  $FEV_1$ : forced expiratory volume in one second;  $PC_{20}$ : provocative concentration producing a 20% fall in  $FEV_1$ .

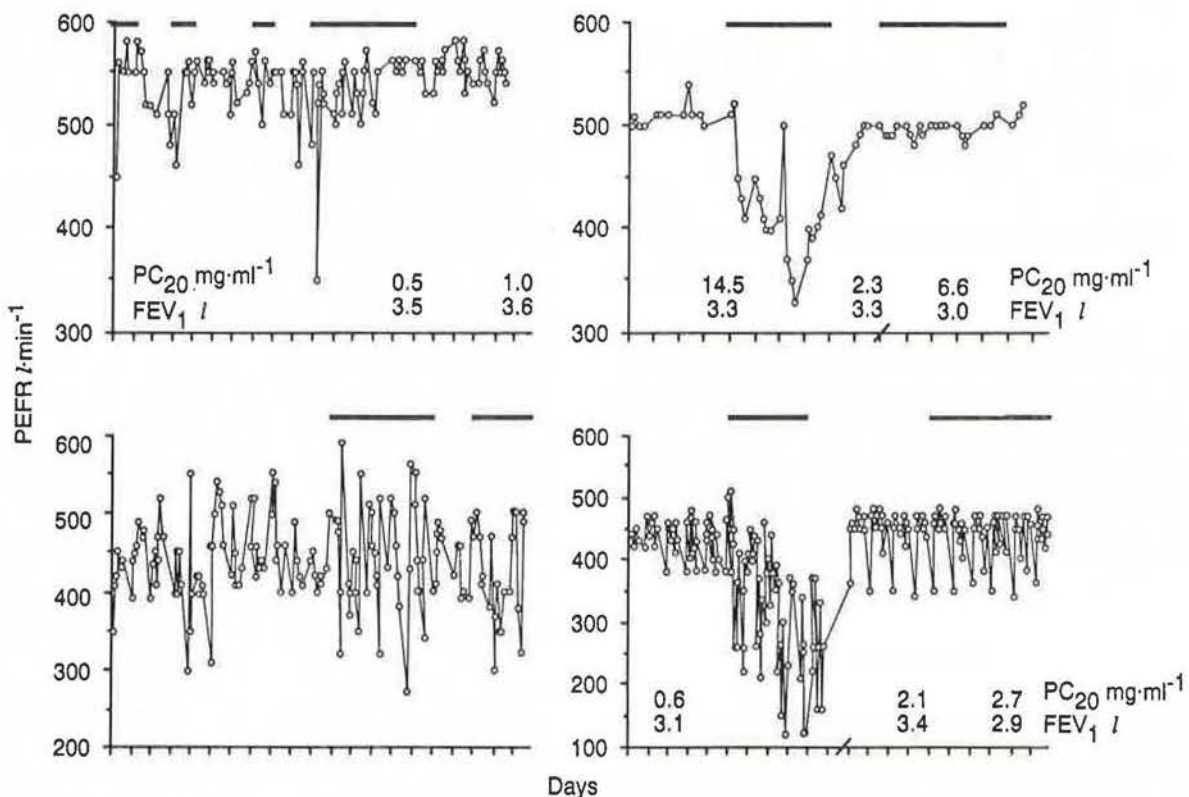


Fig. 2. - Patterns of PEFR in the four false positive dubious cases are illustrated. Although there was no consensus among the three readers in interpreting these graphs, the decision was nevertheless made that these graphs suggested occupational asthma. Specific inhalation challenges were negative. Values of  $PC_{20}$  and  $FEV_1$  are shown. Periods at work are indicated by the thick line. PEFR values include some results taken after bronchodilator (*i.e.* when subjects experienced asthma symptoms). For definitions see legend to figure 1.

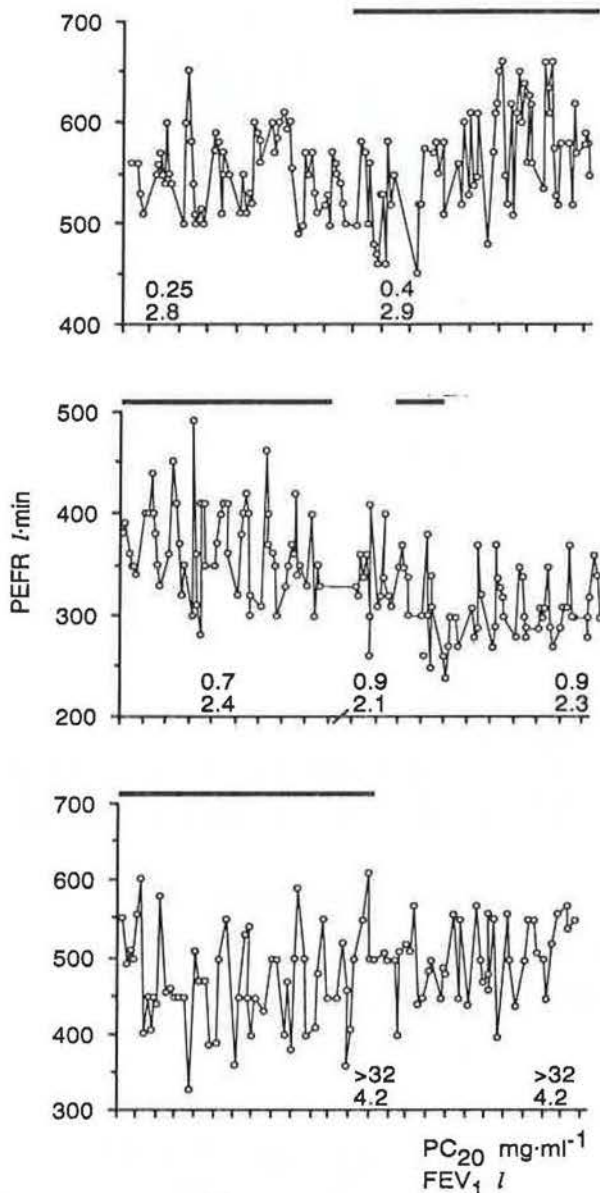


Fig. 3. — Patterns of PEFR in the three remaining dubious cases are illustrated. Although there was no consensus among the three readers in interpreting these graphs, the decision was nevertheless made that these graphs did not suggest occupational asthma. The two false negative interpretations are shown on the top and bottom panels whereas the third subject (middle panel) had a negative specific inhalation challenge. Values of  $PC_{20}$  and  $FEV_1$  are shown. Periods at work are indicated by the thick line. PEFR values include some results taken after bronchodilator (*i.e.* when subjects experienced asthma symptoms). For definitions see legend to figure 1.

### Discussion

Although serial monitoring of PEFR had been advocated in the assessment of asthma before [27, 28], BURGE and co-workers [6, 7] were the first to propose the use of PEFR in the investigation of occupational asthma. They studied the sensitivity and specificity of PEFR and specific inhalation challenges as compared with the final assessments based on the history

and the effects of subsequent exposure at work after provocation testing. They found a 100% sensitivity and specificity for PEFR analysis in workers exposed to isocyanates [7] and an 83% sensitivity and a 100% specificity in workers exposed to colophony [6]. For subjects not taking anti-inflammatory preparations during the monitoring, PEFR sensitivity was 77%, whereas specificity was 100% in the case of colophony [6]. They therefore concluded that regular recording of PEFR at home and at work was a very specific and reasonably sensitive method of diagnosing occupational asthma due to solder-flux fumes and a suitable alternative to bronchial provocation testing among workers with mild to moderate work-related symptoms.

CÔTÉ *et al.* [13] compared serial monitoring of PEFR (for 3 weeks at work and 2 weeks away from work) and assessment of non-allergic bronchial responsiveness with specific inhalation challenges to plicatic acid among 23 workers continuously exposed to Western red cedar. They found a sensitivity and a specificity of 86%, and 89%, respectively, for the visual analysis of PEFR. The sensitivity was 100% if the analysis was combined with a positive clinical history. Using changes in  $PC_{20}$  or combining changes in PEFR and in  $PC_{20}$  did not prove to be more satisfactory. We also found that this combination of tools is not more useful than PEFR alone. CÔTÉ *et al.* [13] concluded that the specific inhalation challenges with plicatic acid were not necessary when both clinical history and PEFR were negative. If one of those two assessments is positive, the plicatic acid test should be done. Results of this study would suggest a similar approach. Indeed, only one subject with a history of occupational asthma which was unlikely and who had a negative PEFR monitoring was found to have positive specific inhalation challenges.

The results of this study extend those of CÔTÉ *et al.* [13], including more subjects (61 as compared to 23) and more sensitizing agents. The figures for sensitivity and specificity of PEFR which we obtained are comparable to those of CÔTÉ *et al.* [13] if we exclude subjects for whom there was not complete agreement between the three readers. However, by including the seven subjects for whom the reading was dubious, our sensitivity and specificity dropped to 81 and 74%, respectively. There are possible explanations for the lower sensitivity and specificity found in our study. Firstly, our subjects were exposed to a wide variety of agents and, in some, the exposure was not necessarily continuous. Secondly, the criterion used by CÔTÉ *et al.* [13] for a positive interpretation was that two of the three readers should agree. We requested complete consensus among the three readers in our study. Furthermore, we analysed our subjects' compliance in recording their PEFR. Twenty eight percent of subjects omitted more than three days of assessment. Compliance is thus far from perfect.

It is unlikely that the use of steroids during monitoring had a significant impact on our results. Among the seven dubious cases, three were on inhaled steroids and two were also on oral steroids. However, among

the 54 remaining subjects, 18 were on inhaled and/or oral steroids and were correctly classified. BURGE and co-workers [6, 7] found that the interpretation of PEFR is more satisfactory when subjects are not on regular anti-inflammatory medication.

No numerical index proved as satisfactory as visual interpretation of PEFR. This can be explained by the fact that the interpretation takes into account several factors instead of one as do the numerical indices. Monitoring of  $PC_{20}$  did not prove to have a good sensitivity or specificity. One explanation for this may be that bronchial hyperresponsiveness can take a long time to improve after the cessation of the exposure.

The results of this study have practical implications for the investigation of occupational asthma in both the usual medical practice and the medicolegal expertise. We favour the following scheme for the investigation of occupational asthma. If one recognized sensitizer is present at work and a subject has significant bronchial hyperresponsiveness at work, efforts should be made to use specific inhalation challenges in the laboratory first if access to a specialized centre is possible. If the test is negative, this can indicate several possibilities: 1) desensitization can have occurred if the subject had been away from work for a prolonged interval; 2) an insufficient duration of exposure to the agent for the specific inhalation challenge; 3) the wrong agent could have been used; 4) this represents a true negative. Provisions should be made to record PEFR and bronchial responsiveness during a period at work. If several recognized sensitizers are present at work, monitoring of PEFR and  $PC_{20}$  might be carried out first as specific inhalation challenges with each agent could take too long. The same procedure should prevail if no known sensitizer is present in the workplace. Monitoring of  $FEV_1$  at work under supervision by a technician can then be considered. The rationale behind these recommendations is as follows: we showed that the interpretation of the tests can be dubious in a significant proportion of subjects (14%), even after being analysed by experienced physicians. Sensitivity and specificity figures of around 80% are not high enough for us to give proper advice to the worker, the employer or the Workers' Compensation Boards for medicolegal purposes. Although PEFR monitoring can be done on a larger number of workers than specific inhalation challenges, it is our experience that it is time consuming. It requires close supervision by the technician to verify the honesty and collaboration of the subject. Development of improved means for specific inhalation challenges could make them less risky; direct information about the concentration and diameter of inhaled particles is now available [19]. Dose-response curves can be drawn. These tests using commercially available machinery can become more easily available. PEFR monitoring can be even more risky in highly sensitized individuals as they may show brisk and pronounced reduction in airway calibre unless they are directly supervised by a technician

in a hospital (fig. 1). Furthermore, the monitoring has to be performed at a time when the subject is symptomatic. Finally, even if monitoring of PEFR can be accurate in identifying work-related asthma, it cannot refer the asthmatic condition to a specific agent and it does not permit proper advice to be given to the worker on his future possibilities of employment. In this context, efforts should be made to identify the causal agent.

**Acknowledgements:** The authors would like to thank the Workers' Compensation Board of Quebec and those physicians who referred cases. They would also like to thank K. Tallman for reviewing the manuscript.

#### References

1. Chan-Yeung M, Lam S. - State of the art: occupational asthma. *Am Rev Respir Dis*, 1986, 133, 686-703.
2. Pauli G, Bessot JC, Dietemann-Molard A. - Occupational asthma: investigations and aetiological factors. *Clin Respir Physiol*, 1986, 22, 399-425.
3. Cartier A, Bernstein IL, Burge PS *et al.* - Guidelines for bronchoprovocation investigation of occupational asthma. Report of the subcommittee on the bronchoprovocation for occupational asthma. *J Allergy Clin Immunol*, 1989, 84, 794-805.
4. Ad Hoc Committee on Occupational Asthma of the Standards Committee, Canadian Thoracic Society. - Occupational asthma: recommendations for diagnosis, management and assessment of impairment. *Can Med Assoc J*, 1989, 140, 1029-1032.
5. Pepys J, Hutchcroft BJ. - Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am Rev Respir Dis*, 1975, 112, 829-859.
6. Burge PS, O'Brien IM, Harries MG. - Peak flow rate records in the diagnosis of occupational asthma due to colophony. *Thorax*, 1979, 34, 308-316.
7. Burge PS, O'Brien IM, Harries MG. - Peak flow rate records in the diagnosis of occupational asthma due to isocyanates. *Thorax*, 1979, 34, 317-322.
8. Cockcroft DW, Cartier A, Jones G, Tarlo SM, Dolovich M, Hargreave FE. - Asthma caused by occupational exposure to a furan-based binder system. *J Allergy Clin Immunol*, 1980, 66, 458-463.
9. Cartier A, Pineau L, Malo JL. - Monitoring of maximum expiratory flow rates and histamine inhalation tests in the investigation of occupational asthma. *Clin Allergy*, 1984, 14, 193-196.
10. Cartier A, Thompson NC, Frith PA, Roberts R, Hargreave FE. - Allergen-induced increase in bronchial responsiveness to histamine: relationship to the late asthmatic response and change in airway caliber. *J Allergy Clin Immunol*, 1982, 70, 170-177.
11. Malo JL, Ghezzi H, L'Archevêque J, Cartier A. - Late asthmatic reactions to occupational sensitizing agents: frequency of changes in non-specific bronchial responsiveness and of response to inhaled beta<sub>2</sub>-adrenergic agent. *J Allergy Clin Immunol*, 1990, 85, 834-842.
12. Malo JL, L'Archevêque J, Cartier A. - Significant changes in non-specific bronchial responsiveness after isolated immediate bronchospastic reactions but not after a late reaction to occupational agents. *J Allergy Clin Immunol*, 1989, 83, 159-165.



13. Côté J, Kennedy SM, Chan-Yeung M. - Sensitivity and specificity of  $PC_{20}$  and PEF in cedar asthma. *J Allergy Clin Immunol*, 1990, 85, 592-598.
14. Malo JL, Cartier A, Boulet LP. - Occupational asthma in sawmills of Eastern Canada and United States. *J Allergy Clin Immunol*, 1986, 78, 392-398.
15. Wright BM. - A miniature Wright peak-flow meter. *Br Med J*, 1978, 2, 1627-1628.
16. Venables K, Burge PS, Davidson A, Taylor AN. - Peak flow rate records in surveys: reproducibility of observers' reports. *Thorax*, 1984, 39, 828-832.
17. Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. - Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy*, 1977, 7, 235-243.
18. American Thoracic Society. - Standardization of spirometry - 1987 update. *Am Rev Respir Dis*, 1987, 136, 1285-1307.
19. Cloutier Y, Lagier F, Lemieux R, Blais MC, St-Arnaud C, Cartier A, Malo JL. - New methodology for specific inhalation challenges with occupational agents in powder form. *Eur Respir J*, 1989, 2, 769-777.
20. Cartier A, Grammer L, Malo JL, Lagier F, Ghezzi H, Harris K, Patterson R. - Specific serum antibodies against isocyanates: association with occupational asthma. *J Allergy Clin Immunol*, 1989, 84, 507-514.
21. Knudson RJ, Slatin RC, Lebowitz MD, Burrows B. - Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis*, 1983, 127, 725-734.
22. Higgins BG, Britton JR, Chinn S, Jones TD, Jenkinson D, Burney PGJ, Tattersfield AE. - The distribution of peak expiratory flow variability in a population sample. *Am Rev Respir Dis*, 1989, 140, 1368-1372.
23. Malo JL, Pineau L, Cartier A, Martin RR. - Reference values of the provocative concentrations of methacholine that cause 6% and 20% changes in forced expiratory volume in one second in a normal population. *Am Rev Respir Dis*, 1983, 128, 8-11.
24. Dehaut P, Rachiele A, Martin RR, Malo JL. - Histamine dose-response curve in asthma: reproducibility and sensitivity of different indices to assess response. *Thorax*, 1983, 38, 516-522.
25. Ryan G, Dolovich MB, Roberts RS, Frith PA, Juniper EF, Hargreave FE, Newhouse MT. - Standardization of inhalation provocation tests: two techniques of aerosol generation and inhalation compared. *Am Rev Respir Dis*, 1981, 123, 195-199.
26. Perrin B, Cartier A, Ghezzi H, Grammer L, Harris K, Chan H, Chan-Yeung M, Malo JL. - Reassessment of the temporal patterns of bronchial obstruction after exposure to occupational sensitizing agents. *J Allergy Clin Immunol*, 1991, 87, 630-639.
27. Turner-Warwick M. - On observing patterns of airflow obstruction in chronic asthma. *Br J Dis Chest*, 1977, 71, 73-86.
28. Hetzel MR, Clark TJH, Houston K. - Physiological patterns in early morning asthma. *Thorax*, 1977, 32, 418-423.