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Official publication of the American College of Chest Physicians



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Chest 1998;114:398-403
DOI 10.1378/chest.114.2.398

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ISSN:0012-3692



Follow-up of Occupational Asthma After Removal From or Diminution of Exposure to the Responsible Agent*

Relevance of the Length of the Interval From Cessation of Exposure

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Study objective: We set the hypothesis that follow-up surveys of occupational asthma (OA) could now show better improvement in the asthmatic condition because of a more prolonged interval since removal from exposure than in previously reported studies.

Patients/methods: Ninety-nine subjects with OA were assessed and were separated into two groups according to the duration of cessation of exposure: (1) group removed for ≥ 5 years: 48 subjects studied 8.9 ± 2.2 years after cessation of exposure; (2) group removed for < 5 years: 51 subjects with OA, comparable in terms of history and functional results at time of diagnosis, with a time lapse from last exposure of 3.1 ± 1.2 years. On the follow-up visit, questionnaires including information on the current and previous use of inhaled steroids, spirometry, and methacholine tests were administered and results were compared with those obtained at the time of diagnosis.

Results: At the follow-up visit, no significant changes in spirometry were observed in the two groups. However, a significant improvement in provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) from a mean value of 1.5 to 3.7 mg/mL was documented ($p < 0.001$). The proportion of subjects having normal PC_{20} at the follow-up visit was significantly higher in the group removed from exposure for > 5 years than in the group removed for ≤ 5 years (16/33 vs 8/42; $p = 0.01$). Stepwise logistic regression showed that follow-up PC_{20} could be predicted from baseline PC_{20} ($p < 0.001$, odds ratio [OR] = 4.1, 95% confidence interval [CI] = 1.8 to 9.1), duration of exposure ($p = 0.04$, OR = 0.9, 95% CI = 0.8 to 1.0), the interval since removal from exposure ($p = 0.002$, OR = 1.7, 95% CI = 1.2 to 2.5), and the type of agent; subjects with OA due to high-molecular-weight agent showed a less favorable outcome ($p = 0.04$, OR = 0.2, 95% CI = 0.03 to 1.0). Current and past treatments with inhaled steroids were not significant predictors.

Conclusion: Results obtained in the group of this study removed for > 5 years show better prognostic figures than those reported in most previous studies. Comparison with the group removed for a shorter interval and the stepwise logistic regression analysis suggest that the longer duration of the interval from cessation of exposure appears to be a factor determining this difference.
(*CHEST* 1998; 114:398–403)

Key words: asthma; occupational asthma; occupational diseases

Abbreviations: CI = confidence interval; HMW = high molecular weight; LMW = low molecular weight; OA = occupational asthma; OR = odds ratio; PC_{20} = provocative concentration of methacholine causing a 20% fall in FEV_1

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This study was partly funded by the Centre québécois d'excellence en santé respiratoire.

Manuscript received April 15, 1997; revision accepted February 17, 1998.

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Most subjects with occupational asthma (OA) still report symptoms of asthma and show nonspecific bronchial hyperresponsiveness even years after cessation of exposure to the offending agent.^{1,2} Factors that can affect the prognosis have not been elucidated. It is known that the persistence of asthma after cessation of work is associated with a longer duration of exposure before and after the onset of

symptoms and with a more severe asthma as defined by the degree of airway obstruction and nonspecific bronchial hyperresponsiveness at the time of diagnosis.^{1,2} A plateau of improvement was reached 2½ years after removal from exposure in the specific case of OA due to a high-molecular-weight (HMW) agent, protein derived from snow crab.³ In a follow-up study of OA due to various agents, we found that after a mean follow-up of 5.8 years, no further improvement had generally been observed than with a shorter follow-up survey of 2 years carried out in the same subjects.⁴ Most follow-up surveys of subjects with OA after removal from exposure were carried out at a time when inhaled steroids were not widely recommended in the treatment of asthma. In a recently published 18-month duration crossover double-blind study carried out in 32 subjects with OA to HMW and low-molecular-weight (LMW) agents, we showed that inhaled steroids combined with removal from exposure led to a significant improvement of asthma.⁵

We therefore set the hypothesis that follow-up surveys of OA would now show improvement in the asthmatic condition because of a more prolonged duration of follow-up than that observed in previous surveys. The aim of the present study was to evaluate bronchial responsiveness to methacholine in a cohort of subjects with OA according to the duration of removal from exposure, separating those with an interval <5 years since removal from exposure (this representing the majority of cases reported in previous follow-up studies) from those

with an interval ≥5 years, taking into account the current and former use of inhaled steroids in these subjects.

MATERIALS AND METHODS

Study Design

Every subject was evaluated on two separate visits. The first visit took place at the time of diagnosis of OA. Patients were then referred by either the Quebec Workers' Compensation Board or by the treating physician. A questionnaire, assessment of spirometry and bronchial responsiveness to methacholine, and skin prick tests with ubiquitous inhalants were performed at the time the diagnosis was confirmed (see below). The same procedures were performed at the second visit. The follow-up questionnaire included additional questions on continuation or cessation of exposure as well as past and current need for medication.

Letters with an invitation to participate in the study were sent to 242 patients with a diagnosis of OA confirmed in 225 by specific inhalation challenges and in the remaining by suggestive pattern of peak expiratory flow monitoring. Subjects in the short-term follow-up group had previously been included in other follow-up studies.^{4,6} Fifty-three letters were returned because of address changes; 2 came back because the subjects had died; and 77 were simply not answered. Ten subjects declined to participate and one was found to be noneligible. The follow-up study took place between January and July 1996, at least 6 months after cessation of exposure in all subjects. Subjects included in the group removed from exposure for ≥5 years had been assessed first between 1979 and 1990 and those in the group removed from exposure for <5 years, between 1991 and 1995. There were no significant differences between the participants and nonparticipants in various relevant characteristics that were available at the time of the study except for smoking habits (more smokers in nonparticipants), duration of exposure that was longer

Table 1—Characteristics of Participants and Nonparticipants at the Time of Diagnosis*

	Participants			Nonparticipants (n=98)	Difference† p Value
	Short-term Follow-up (n=51)	Long-term Follow-up (n=48)	All (n=99)		
Sex, M/F	40/11	33/15	73/26	77/21	0.4
Age, yr	42 (12)	44 (12)	43 (12)	39 (13)	0.2
Atopy, yes/no	29/20	30/14	59/34	51/42	0.3
Smoking habits, S/ES/NS	7/22/22	8/17/23	15/39/45	28/40/30	0.03
Duration of exposure, yr	13.4 (12)	11.5 (10.5)	12.5 (11.5)	8.8 (8.3)	0.005
Duration of symptoms, yr	3.2 (3.3)	3.2 (3.4)	3.2 (3.4)	3.3 (3.6)	0.9
Agent, HMW/LMW/U	17/31/3	19/28/1	36/59/4	39/56/3	0.8
Time lapse from diagnosis, yr	3.1 (1.2)	8.9 (2.2)	6.0 (3.4)	9.8 (3.0)	<0.001
FEV ₁ , % predicted	88.3 (19)	93.3 (17)	90.7 (19)	92.4 (19.8)	0.6
PC ₂₀ , mg/mL					
>16	3	3	6	7	0.8
8 to 16	6	5	11	15	
1 to 8	22	23	45	38	
0.125 to 1	17	14	31	25	
<0.125	2	3	5	5	

*S=smokers; ES=ex-smokers; NS=nonsmokers; U=unknown; unpaired *t* test or χ^2 distribution used for statistical analysis of difference on comparisons between participants and nonparticipants. SD is given in parentheses.

†Comparing all participants with nonparticipants by unpaired *t* test or χ^2 analysis when appropriate.

in participants, and the time lapse from diagnosis that was longer in the nonparticipants (Table 1).

Two subjects reported occasional or reduced levels of exposure (wearing a mask or respirator) while all others had completely refrained from exposure. The duration of the follow-up was >10 years in 12 subjects. All participating subjects suspended treatment with their regular or as occasion requires-basis bronchodilators at least 24 h before the follow-up visit. Ninety-three subjects had a spirometry performed on the follow-up visit while 75 had a methacholine test. Eleven subjects had an FEV₁ smaller than 1.5 L and therefore did not have the test. Among participants, OA was due to HMW agents (protein-derived-allergen, *ie*, flour, psyllium, guar gum, etc) in 36 cases and to LMW (chemicals, *ie*, isocyanates, formaldehyde, etc) agents in 59 cases. In four cases, it was impossible to identify the sensitizing agent even though the asthma was clearly related to the workplace.

All subjects gave written consent to their participation. The protocol was accepted by the ethics committee of Sacré-Coeur Hospital.

Methods

Spirometry was performed according to the criteria of the American Thoracic Society.⁷ Bronchial responsiveness to methacholine was assessed with a standardized procedure at tidal-volume breathing for 2 min with a nebulizer (Wright; Baltimore, MD) (output=0.14 mL/min)⁸ using doubling concentrations from 0.03 mg/mL up to 128 mg/mL.

Analysis of Results

Predicted values for FEV₁ were those published by Knudson and coworkers.⁹ Abnormal results for FEV₁ were set at 80% of predicted as this percentage corresponds to the lower limit of the 95% confidence intervals (CI).⁹ Dose-response curves to methacholine were drawn on a semilogarithmic noncumulative scale, the provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) being interpolated from the curve. Bronchial hyperresponsiveness was considered to be significant at a PC₂₀ of

≤16 mg/mL.^{10,11} Logarithmic transformation of PC₂₀ was used. Changes in PC₂₀ were considered significant when there was a twofold or a 3.2-fold or greater difference from one visit to the next.¹²

As regards treatment between the two visits, subjects were defined as inhaled steroid treated if they had taken inhaled beclomethasone (≥1,000 µg/d or equivalent) for at least 6 months.

Statistical Analysis

The χ^2 test was used to compare categorical variables between participants and nonparticipants and between the subgroups removed from exposure for <5 years and ≥5 years, respectively. Student's *t* test for paired data was used to evaluate changes in FEV₁ and PC₂₀ between the two visits. Continuous variables in the different subgroups were compared by means of the Student's *t* test for unpaired data. A stepwise logistic regression was performed to evaluate the effects of potential factors (independent variables: baseline responsiveness [log PC₂₀], duration of exposure [years], length of follow-up [years], agent [HMW- vs LMW-agent], absence or presence of inhaled steroids) on the follow-up bronchial responsiveness normal PC₂₀ [>16 mg/mL vs abnormal PC₂₀-[≤16 mg/mL] (dependent variable). Length of follow-up was put in the model as a continuous or categorical (<5 years, ≥5 years) variable. Statistical analysis was performed by means of a statistical software package (SPSS for Windows, version 6.1; Chicago, IL). The level of statistical significance was set at a *p* value ≤0.05.

RESULTS

Forty-one of 99 subjects (41%) were receiving inhaled steroids at the follow-up visit (Table 2), while 49 subjects (50%) had been receiving inhaled steroids for >6 months between the two visits (not shown). One third of subjects had an abnormal FEV₁ value. There were no significant changes in mean

Table 2—Characteristics of the Groups Removed From Exposure for Short (<5 years) and Long (≥5 years) Intervals at the Follow-up Visit*

	Short Interval (n=51)	Long Interval (n=48)	All (n=99)	Difference† p Value
Treatment, none/bdt prn/is/os	11/17/21/2	9/19/20/0	20/36/41/2	0.5
FEV ₁ , % predicted	87.1 (19)	87.9 (21)	87.4 (20)	0.9
FEV ₁ (n<80% predicted)	16/50	16/43	32/93	0.6
PC ₂₀ , mg/mL				
Total performed	42	33	75	0.8
>16	8	16	24	0.01
8 to 16	5	1	6	
1 to 8	19	8	27	
0.125 to 1	10	4	14	
<0.125	0	4	4	
Changes in FEV ₁ , % predicted	-1 (14)	-3.8 (15)	-2.3 (15)	0.4
Changes in PC ₂₀ , mg/mL				
≥twofold (1.0 dilution)	21	20	41	0.4
≥3.2-fold (1.6 dilution)	17	15	32	0.7
≥twofold (1.0 dilution) and ≥16 at follow-up	5	13	18	0.003
≥3.2-fold (1.6 dilution) and ≥16 at follow-up	5	12	17	0.01
<16 baseline to ≥16 at follow-up	5	15	20	0.003

*bdt prn=bronchodilator on demand; is=inhaled steroids; os=oral steroids. SD is given in parentheses.

†Comparing short- and long-term follow-up groups by *t* test or χ^2 analysis when appropriate.

results for FEV₁ or in the number of subjects with abnormal FEV₁ values between the two visits (Table 2). One third of subjects had a normal level of PC₂₀ at the follow-up visit. There was a significant improvement in PC₂₀ from a mean value of 1.5 to 3.7 mg/mL ($p < 0.001$) (Fig 1). Forty-three percent of subjects had changes in PC₂₀ ≥ 3.2 -fold difference between the two visits (Table 2). Although 24 subjects had a normal PC₂₀ value, PC₂₀ was still measurable (*ie*, ≤ 128 mg/mL) in all subjects except two, which allowed for using PC₂₀ values on a continuous scale. Seventeen subjects (23%) had changes in PC₂₀ ≥ 3.2 -fold difference and normalized their PC₂₀ values between the two visits. This occurred in only 5 instances for the group removed for < 5 years but in 12 cases of the follow-up group removed for a longer interval ($p < 0.01$). A change in PC₂₀ from an abnormal (≤ 16 mg/mL) to a normal value (> 16 mg/mL) was found more often (15 cases) for the group removed for ≥ 5 years than for the group removed for < 5 years (five cases) ($p = 0.003$). Table 3 shows that those subjects with a normal PC₂₀ at the follow-up visit differed from those with persistent hyperresponsiveness by duration of exposure that was shorter and the time lapse from last exposure that was longer. FEV₁ was significantly lower at diagnosis and follow-up in those with persistent bronchial hyperresponsiveness. Both the initial FEV₁ and PC₂₀ were predictors of the PC₂₀ at the follow-up visit. The initial FEV₁ was significantly different in those subjects who had a PC₂₀ at the follow-up either ≤ 16 or > 16 mg/mL ($p = 0.006$, mean values of 87.8% and 99.6% predicted, respectively).

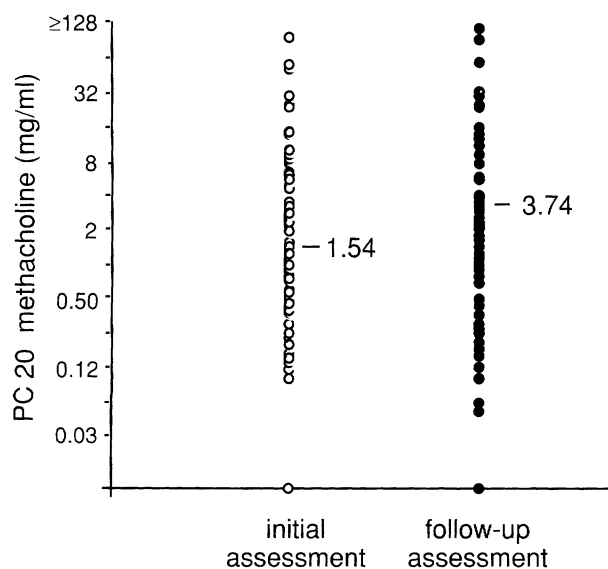


FIGURE 1. Individual results of PC₂₀ at the initial and follow-up assessments. The mean PC₂₀ values are shown and were significantly different.

Results of the stepwise multivariate logistic regression are shown in Table 4. In all models that are presented, baseline PC₂₀ and the duration of exposure are significant predictors of the persistence of hyperresponsiveness at the follow-up visit. The duration of follow-up since cessation of exposure, either as a continuous variable and, almost equally so, as a dichotomous variable (< 5 years vs ≥ 5 years) was also a predictor for the persistence of hyperresponsiveness at the follow-up visit (model 1, model 2, and model 3). The type of agent was a significant determinant of the outcome (model 3): being exposed to HMW agents vs LMW agents was associated with a lower PC₂₀ at follow-up. Introducing this variable in the analysis had the result of reducing the effect of the duration of exposure on the outcome. Model 3 that included variables listed in Table 4 was 91% accurate, 3% of values being falsely classified as negative and 6% being falsely classified as positive. Current and past treatment with inhaled steroids were not significant predictors of the persistence or absence of bronchial hyperresponsiveness.

The stepwise multivariate logistic regression "model 3" of Table 4 was repeated using FEV₁ $< 80\%$ predicted at the follow-up visit as the dependent variable and initial FEV₁ as well as all the other variables listed in Table 4 except for log initial PC₂₀. The initial FEV₁ only was found to be a significant determinant with a β -value of 3.40 (SE=0.76, odds ratio [OR]=29.9, 95% CI=14 to 64).

DISCUSSION

Our study examined the outcome of subjects with OA after removal from exposure with a specific focus on the importance of the duration since exposure stopped. Along with findings previously published,^{3,4,6} we showed that the level of bronchial responsiveness at the time of diagnosis, a factor that reflects the severity of asthma, and the duration of exposure are predictors of the persistence of bronchial hyperresponsiveness. Moreover, for the first time (to our knowledge), we showed that the length of removal from exposure was a significant predictor of improvement in bronchial responsiveness. Results of this study show better figures than those reported in previous follow-up studies. Most follow-ups of OA up to 5 years after cessation of exposure showed that the vast majority of subjects report the persistence of symptoms and still have nonspecific bronchial hyperresponsiveness.¹³⁻¹⁸ Results obtained in our group removed from exposure for > 5 years specifically differ as well from those of a preceding study from our center with a shorter duration of

Table 3—Association Between Presence or Absence of Hyperresponsiveness at the Follow-up and Selected Characteristics*

	PC ₂₀ ≤16 mg/mL (n=51)	PC ₂₀ >16 mg/mL (n=24)	Difference† p Value
Sex, M/F	40/11	17/7	0.5
Age, yr	44 (12)	41 (13)	0.3
Atopy, yes/no	30/17	16/6	0.5
Smoking habits, S/ES/NS	8/21/22	2/8/14	0.4
Duration of exposure, yr	16.0 (12.3)	5.9 (7.2)	<0.001
Duration of symptoms, yr	4.0 (3.7)	2.7 (3.3)	0.15
Agent, HMW/LMW/U	22/27/2	6/17/1	0.3
Time lapse from last exposure, yr	4.7 (3.1)	7.0 (3.6)	0.008
Current use of inhaled steroids	24	3	0.004
Use of inhaled steroids between the two visits	28	6	0.02
At diagnosis			
FEV ₁ , % predicted	88 (18)	100 (14)	0.007
FEV ₁ (n<80% predicted)	15	1	0.04
PC ₂₀ , mg/mL			
>16	0	3	0.01
8 to 16	2	8	
1 to 8	22	10	
0.125 to 1.0	24	3	
<0.125	3	0	
At follow-up			
FEV ₁ , % predicted	89 (17)	100 (15)	0.008
FEV ₁ (n<80% predicted)	18	3	0.02
Changes in FEV ₁ , % predicted	0.9 (11.7)	0.3 (9.6)	0.8

*SD is given in parentheses. See Table 1 footnote for explanation of abbreviations.

†Comparing the groups with PC₂₀ values respectively ≤16 and >16 mg/mL by *t* test or χ^2 analysis when appropriate.

the follow-up (mean=5.8; range, 4.3 to 10.9 years) where only one subject of the 23 had lost nonspecific bronchial hyperresponsiveness at the last follow-up visit.⁴ The fact that we dealt with a larger sample (n=99) with a broad spectrum of time lapse since exposure ended can explain why we were able to detect an effect of this factor in the current work which was not present in other reported follow-up studies.

Several factors should be considered for explaining differing outcomes in the group removed from exposure for >5 years and previous studies. The possibility of a selection bias should first be taken into account. The participation rate in the present study was lower than in previous studies. However, the severity of the disease at the time of diagnosis, as reflected by FEV₁ and PC₂₀, was not significantly different. It is known that the level of bronchial caliber and hyperresponsiveness at the time of diagnosis correlates with the likelihood of recovery.¹⁹ A lack of homogeneity between the present group removed from exposure for >5 years and the one included in a previous work⁴ in term of responsible agents could represent another factor affecting the outcome: OA to HMW and LMW agents accounted for 18% and 68%, respectively, in the previous study while it is 36% and 59%, respectively, in the present one. Concerning the treatment patients received

between the two visits, significant differences exist between data of the group removed for >5 years and our previous study.⁴ In the first study, only 17 to 28% of subjects received oral or inhaled steroids at one time or at another, while 49% had received inhaled steroids in the present study. However, the regression analysis showed that current or past treatment with inhaled steroids was not a significant predictor of the outcome in terms of bronchial hyperresponsiveness. We acknowledge that our study was retrospective and treatment was assigned to the different patients according to their needs rather than on a randomized basis. Such a design was used in a recent study that demonstrated the beneficial effect of inhaled steroids.⁵ This approach is feasible for short intervals (18 months in the quoted study) but not for long intervals such as in the current work.

We therefore think that the duration of the follow-up period, which was longer in the present study, represents a significant factor that determines the better outcome. The fact that a significantly higher proportion of subjects lost hyperresponsiveness in the group removed from exposure for >5 years than in the group removed for ≤5 years suggests that duration of the follow-up may be one of the factors responsible for the difference in prognosis. In addition, current or past use of inhaled steroids was not a significant predictor in the stepwise logistic regression analysis model.

Table 4—Summary of the Stepwise Logistic Regression Analysis for the Effects of Initial PC₂₀, Duration of Exposure, Duration of Follow-up, Nature of the Agent, and Treatment With Inhaled Steroids Among Subjects With PC₂₀ >16 and ≤16 mg/mL at Follow-up*

Variable	Unit	Model 0	Model 1	Model 2	Model 3
Log initial PC ₂₀	Log _e unit	1.0572 (0.3036) OR=2.88 (1.58-5.21) p<0.001	1.3269 (0.3759) OR=3.769 (1.80-7.87) p<0.001	1.0798 (0.3229) OR=2.94 (1.56-5.54) p<0.001	1.4113 (0.4093) OR=4.10 (1.83-9.14) p<0.001
Duration of exposure	Years	-0.1056 (0.0438) OR=0.90 (0.82-0.98) p=0.016	-0.1523 (0.0597) OR=0.86 (0.76-0.96) p=0.010	-0.1195 (0.0501) OR=0.89 (0.80-0.98) p=0.017	-0.1368 (0.0681) OR=0.87 (0.76-0.99) p=0.044
Interval since removal from exposure	Years	NI	0.4305 (0.1436) OR=1.54 (1.16-2.04) p=0.003	NI	0.5475 (0.1794) OR=1.73 (1.21-2.45) p=0.002
	<5 vs ≥5 yr	NI	NI	2.11 (0.7764) OR=8.248 (1.80-37.7) p=0.007	NI
Agent	HMW vs LMW agent	NI	NI	NI	-1.7577 (0.8921) OR=0.17 (0.03-0.99) p=0.04
Current inhaled steroids	Yes vs no	NI	NI	NI	p=0.67
Past inhaled steroids	Yes vs no	NI	NI	NI	p=0.76
Residual χ^2 % correct prediction		0.025, p=0.87 84.0	0.172, p=0.678 86.7	0.02, p=0.89 82.7	0.02, p=0.88 91.4

*Dependent variable: PC₂₀ >16 mg/mL. Independent variables (β , SE of β , OR with 95% CI, p of the β -coefficient). log_e unit=2.71-fold change in PC₂₀ methacholine; the variable "inhaled steroids" was not entered into the model due to lack of statistical significance; in model 3, for variable "agents," the three subjects with OA due an unidentified agent were excluded from this analysis; NI=variable not included in the model.

ACKNOWLEDGMENTS: The authors thank Lori Schubert for examining the manuscript and the reviewers for their very constructive and helpful criticisms.

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DOI 10.1378/chest.114.2.398

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