Recovery of Methacholine Responsiveness after End of Exposure in Occupational Asthma

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Recent data suggest that responsiveness to methacholine continues to improve 2 and more years after cessation of exposure to agents causing occupational asthma (OA). The goal of this study was to characterize further the curve of improvement to methacholine responsiveness in subjects with OA. Eighty subjects with confirmed OA who had at least two assessments of a provocative concentration of histamine causing a 20% drop in FEV_1 (PC_{20}) and were seen for at least 2 years after cessation of exposure. The shape of recovery of PC_{20} was assessed by CARMA (James K. Lindsey, Liège, Belgium) analysis. Slopes of recovery were compared in the first 2.5 years in 55 subjects and from 2.5 years until the end of observation in 56 subjects. Recovery curves showed progressive improvements in PC_{20} significantly influenced by time lapse since end of exposure, sex, baseline PC_{20}, and FEV_1. The slopes of recovery were significantly different from zero both for the first 2.5 years after cessation of exposure (0.27 ± 0.05 SEM natural logarithm of PC_{20} per year) and later (0.09 ± 0.008 SEM natural logarithm of PC_{20} per year), with the slope significantly steeper for the first 2.5 years. This study shows that improvement in responsiveness to methacholine continues for years after cessation of exposure but that the improvement is more rapid in the first 2.5 years.

Keywords: occupational diseases; occupational asthma; bronchial diseases; asthma; bronchial hyperresponsiveness

It has been shown that workers with occupational asthma (OA) are often left with permanent asthma after cessation of exposure; asthma improves, but generally not to the extent of cure (1).

We have described the slope of recovery of spirometry and responsiveness to methacholine assessed by the provocative concentration of histamine causing a 20% drop in FEV_1 (PC_{20}) in snow-crab processing workers removed from exposure for 5 years and have shown that the improvement occurs in the first 2 years with a plateau afterward (2). However, in more recent work performed in subjects with OA caused by various agents, we have found that there is improvement in PC_{20} after the landmark of 5 years (3, 4).

We therefore planned to describe better the recovery fit of responsiveness to methacholine in subjects with OA after removal from exposure, testing the specific hypothesis that the slope of recovery is steeper in the first 2 years after cessation of exposure with a slower rate of improvement thereafter. For this, we examined PC_{20} results in subjects who were seen at least twice, 6 months and more after cessation of exposure to an agent causing OA.

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METHODS

Eighty subjects with OA satisfied the criteria of having at least three PC_{20} values, one at the time of diagnosis and two after 6 months or more of follow-up, at which time subjects were no longer exposed to the causal agent. OA had been confirmed by specific inhalation challenges in all instances with changes in FEV_1 that reached 20% or more of pre-exposure value. At the time of follow-up visits, subjects were judged to be in a stable clinical state and had stopped using medications according to guidelines for specific inhalation challenges (5). Spirometry (6) was performed, as were methacholine inhalation challenges according to a standardized method with a Wright's nebulizer (output = 0.14 ml/minute) at tidal volume breathing (7). PC_{20} values were generally interpolated from dose–response curves drawn on a noncumulative logarithmic scale but had to be extrapolated to either 32 or 128 mg/ml, depending on the last dose of methacholine used, in 20 of 271 instances. Reference values for spirometry were those derived from Knudson and coworkers (8).

Curves relating time lapse since the end of exposure on the abscissa and changes in PC_{20} per year on the ordinate were analyzed using the program CARMA (James K. Lindsey, Liège, Belgium) from the "Growth" software package (9). Briefly, "Carma" is designed to handle a polynomial within-subject design matrix with unequally spaced observations that can be at different intervals for different subjects. The origin of interval is taken as the mean interval of follow-up of all subjects, the shift of the curve being performed by the software and the results reported on a normal scale. The within-subject errors are assumed to be independent Gaussian or have a continuous time autoregressive moving average (ARMA) (p parameters for the auto-regressive, q parameters for the moving average) Gaussian structure. ARMA of first order only was used in the analysis. The between-subject random coefficients are assumed to have an arbitrary covariance matrix. The fixed-effect design matrix is a polynomial of an order equal to or higher than the within-subject design matrix. The method is based on exact maximum likelihood using the Kalman filter that is part of the dynamic ARMA modeling performed by the software. The covariates included in the initial model were sex, age, and smoking habits at diagnosis, molecular weight of the agent causing OA, use of inhaled steroids at the time of diagnosis, the natural logarithm of PC_{20} ($\ln PC_{20}$) at the time of diagnosis, FEV_1 at the time of diagnosis, duration of exposure, and duration of exposure with symptoms. A generalized estimated equation was used to compare slopes for the first 2.5 years after cessation of exposure by comparison with the later period.

RESULTS

Table 1 shows the baseline characteristics of subjects. The majority were men, and a slightly greater number of causal agents were of the low molecular weight type. Isocyanates were the causal agent in 32 instances, flour in 14, drugs in 10, and wood dusts in 7. A minority of the subjects were smokers, and slightly more than half were atopic. Subjects remained exposed with symptoms for more than 3 years on average. FEV_1 was lower than 80% predicted in 22 subjects at the time of diagnosis. The majority had mildly increased bronchial responsiveness to methacholine (PC_{20} from ≥ 0.25 to < 2 mg/ml).

The majority of subjects had three or more follow-up visits. The mean ± SD maximum duration of follow-up was 8.3 ± 3.4 years. The mean (± 95% confidence interval) curve relating the $\ln PC_{20}$ value at several visits after cessation of exposure to duration of the follow-up (in years) is shown in Figure 1. Table

TABLE 1. BASELINE AND FOLLOW-UP CHARACTERISTICS

Baseline						
Sex, male/female		64/16				
Age, mean ± SD		42.8 ± 12.4				
Causal agent, HMW/LMW/unknown*		32/46/2				
Smoking, smokers/ex-smokers/nonsmokers		16/30/34				
Atopy†		43/32				
Duration of exposure, mean ± SD yr		11.5 ± 10.7	(Q1 = 3; median = 9; Q3 = 15.5)			
Duration of exposure with symptoms, mean ± SD, yr		3.3 ± 4.2	(Q1 = 1; median = 1.5; Q3 = 5)			
FEV_1, % predicted, mean ±SD		90.2 ± 16.5				
Use of inhaled steroids at the time of diagnosis		38				
PC_{20} methacholine (mg/ml) at the time of diagnosis						
< 0.25		21				
⩾ 0.25 to <2		38				
2–16		21				
Number of follow-up visits						
Two and more		80				
Three and more		47				
Four and more		27				
Five and more		16				
Six and more		13				
Seven and more		8				
Intervisit time intervals, yr						
Visits	0–1	1–2	2–3	3–4	4–5	5–12
Q1	0.25	1.98	1.5	1.5	1.88	2.0
Median	1.68	4.05	4	5.2	2.75	4.9
Q3	3	7.7	8.52	7.13	9.1	9.2

Definition of abbreviations: HMW = high molecular weight; LMW = low molecular-weight; PC_{20} = provocative concentration of histamine causing a 20% drop in FEV_1; Q = quartile.

* Test carried out by monitoring spirometry at the workplace.

† Atopy in the presence of at least one immediate skin reaction to 15 common aeroallergens.

2 shows the final equation that depicts this curve. This model includes only the covariates significantly associated with recovery of PC_{20}, which are sex, duration of follow-up, baseline PC_{20}, and FEV_1, but not total duration of exposure, duration of symptoms while being exposed, molecular weight of the agent causing OA, smoking habits at the time of diagnosis, as well as treatment with inhaled steroids at the time of diagnosis. The estimated curve presents some interesting characteristics. The overall fit is a fifth-degree polynomial in time (years), with all coefficients statistically significant, implying a nonlinear response. Sex has no significant effect shortly after cessation of exposure (intercept of 0.31 $\ln PC_{20}$, p = NS). However, its interaction with time (linear of 0.12, quadratic of 0.02, and cubic of −0.003, p = all significant) implies a difference in the speed of recovery process according

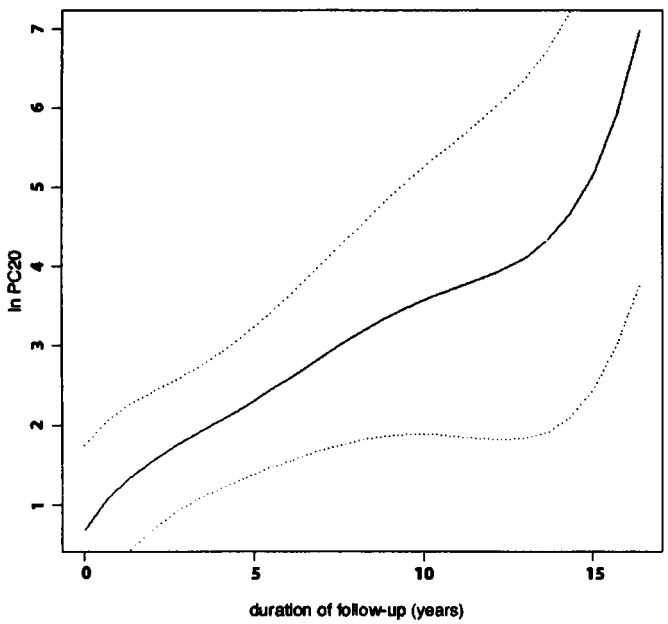

Figure 1. Mean ± SD curve relating duration of follow-up after cessation of exposure (in years) and $\ln PC_{20}$ value at various time intervals.

TABLE 2. EQUATION OF THE FIT OF THE NATURAL LOG OF PROVOCATIVE CONCENTRATION OF HISTAMINE CAUSING A 20% DROP IN FEV_1 WITH SIGNIFICANT COVARIATES DURING THE RECOVERY PERIOD*

	Estimate	SEM	z Value
Duration of follow-up, yr			
Intercept	0.0773	0.272	0.28
Trend			
Linear	−0.2178	0.0757	2.89
Quadratic	−0.0334	0.0155	2.16
Cubic	0.0103	0.0031	3.24
Quartic	−0.0012	0.0001	2.16
Quintic	0.0001	0.0001	2.39
Sex			
Intercept	0.2137	0.1409	1.51
Trend			
Linear	0.1156	0.0340	3.38
Quadratic	0.0228	0.0114	2.00
Cubic	−0.0035	0.0012	2.96
$\ln PC_{20}$ at the time of diagnosis			
Intercept	0.5353	0.0533	10
Trend			
Linear	−0.0485	0.0139	3.48
FEV_1 at the time of diagnosis			
Intercept	0.158	0.0477	3.31
Trend			
Linear	0.0242	0.0126	1.93

* Detailed description provided in the results section.

to sex, the process being more rapid in females. The PC_{20} measured at the time of diagnosis has a strong effect shortly after diagnosis (intercept of 0.53 $lnPC_{20}$), but the linear interaction with time (−0.05) shows that this effect decreases by approximately 10% per year. The FEV_1 value at the time of diagnosis also has a significant impact on the curve at the beginning (intercept of 0.16 $lnPC_{20}$) with a borderline positive influence in the recovery rate with time (0.02, $z = 1.93$).

Figure 2 details the curve that estimates the changes in the recovery rate of $lnPC_{20}$ for the first 5 years after cessation of exposure. This instantaneous rate of recovery is derived from the estimated recovery curve shown in Figure 1. It shows a significant diminution of the rate of recovery approximately 2.5 years after cessation of exposure. Slopes of recovery obtained for each subject from a generalized estimated equation were significantly different from zero ($p < 0.001$) and significantly steeper for the first 2.5 years after cessation of exposure (0.2729 ± 0.0477 $lnPC_{20}$ per year) by comparison with slopes assessed after this time interval (0.0932 ± 0.0083 $lnPC_{20}$ per year) ($p < 0.001$).

DISCUSSION

Original contributions by Chan-Yeung and colleagues initially indicated that subjects with OA often remain with permanent symptoms of asthma and bronchial hyperresponsiveness (10, 11). These findings were later confirmed by follow-up studies in workers whose OA was caused by various agents as reviewed (1). The design of these studies was similar, with observations made at the time of diagnosis and at one follow-up visit. To our knowledge, only one study has examined workers on two occasions after leaving work and concluded that subjects with OA caused by snow-crab showed improvement in the first 2.5 years after leaving work, with a plateau of improvement thereafter (2). More recently, there has been a suggestion of improvement even after this time interval (3, 4).

This study confirms that the rate of recovery of bronchial responsiveness to methacholine, although faster in the first 2.5 years after exposure, continues thereafter, but at a rate three times slower on average. It is relevant to comment on factors that contributed to the general equation of the curve of recovery. Recovery was faster in women, but these results cannot be generalized as there were a minority of women in our sample. Factors such as duration of follow-up and severity of asthma at the time of diagnosis assessed by FEV_1 and PC_{20} values are known predictors of improvement (1). Duration of exposure and, moreover, duration of exposure with symptoms were also often found to be associated with recovery (1). The finding that the latter factors were not significantly associated with the recovery in this study can be related to the different designs used: previous studies had one assessment at the time of diagnosis and only one assessment after, whereas this study had one assessment at the time of diagnosis and more than one after diagnosis. The former design can be more likely to detect acute and short-lived effects, whereas the latter might be more sensitive to effects of long duration. If this hypothesis is true, the duration of exposure and the duration of exposure with symptoms can have a more pronounced effect shortly after cessation of exposure, but this effect can be "diluted" with time of observation after diagnosis. One study has suggested that the prognosis was less satisfactory, although only marginally, in subjects with OA because of high molecular weight agents (3). We could not confirm these results in this study, although the numbers of subjects with OA caused by high and low molecular weight agents were approximately equal. Taking inhaled steroids at the time of diagnosis did not seem to play a role in the rate of recovery. Because the design of this study was not prospective or controlled, we could not assess the effect of taking inhaled steroids after the diagnosis was made. It has been found that the recovery is faster in the first year after cessation of exposure if subjects not only cease exposure to the causal agent but also take inhaled steroids (12). Only a prospective and controlled design will answer the question as to whether maintaining inhaled steroids for a longer interval than 1 year can result in further improvement.

The subjects included in our study were sampled from all patients who had attended our OA clinics for a follow-up visit 6 months or more after the diagnosis was made. The only criterion for inclusion of subjects was that of having two or more assessments of PC_{20} on follow-up. It was therefore a sort of "intention to treat" situation. This being said, the sample is highly comparable to a recent follow-up study performed in our center in terms of sex, atopic status, age, duration of exposure, duration of exposure with symptoms, FEV_1, etc. (3).

This study has socioeconomic implications. The suggestion of assessing permanent disability approximately 2 years after cessation of exposure (13) is further justified by our findings because the slope of recovery is maximal in this time interval. However, the fact that further improvement can occur, although at a slower rate, should also be taken into account when assessing disability. Workers with OA should be advised that their improvement is not over.

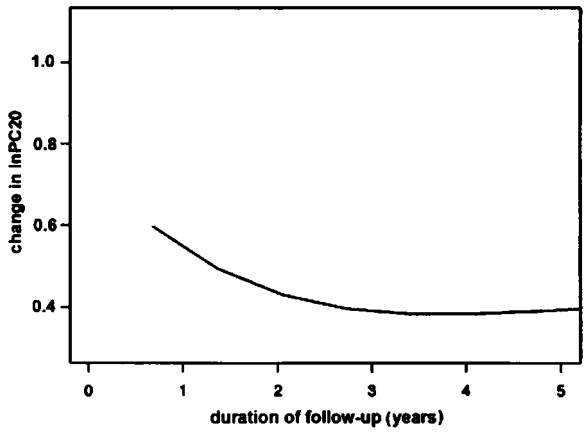

Figure 2. Curve showing the changes in the recovery rate of $lnPC_{20}$ for the first 5 years after cessation of exposure. This instantaneous rate of recovery is derived from the estimated recovery curve shown in Figure 1.

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