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Thorax published online 2 May 2006;
doi:10.1136/thx.2005.054080

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Key words: Occupational asthma, FEV₁ decline, removal from exposure, continued exposure, prognosis.

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ABSTRACT

Background: In occupational asthma continued workplace exposure to the causative agent is associated with a poor prognosis. However, there is little information available on how rapidly lung function declines in those who continue to be exposed, nor how removal from exposure affects lung function.

Methods: We studied FEV₁ in 156 consecutive subjects with occupational asthma (87% due to low molecular weight agents) using simple regression analyses to provide estimates of FEV₁ decline before and after removal from exposure.

Results: In 90 subjects who had FEV₁ measurements made over at least a year prior to removal (median 2.9 years), mean rate of FEV₁ decline was 100.9 ml per year (standard error 17.7). One year after removal from exposure, FEV₁ had improved by 12.3 ml (standard error 31.6). FEV₁ declined at an average of 26.6 ml per year (standard error 18ml) in 86 subjects who had measurements over at least one year (median 2.6 years) following removal from exposure. FEV₁ decline was not significantly worse in current versus never smokers, nor was it affected by use of inhaled corticosteroids.

Conclusion: FEV₁ declines rapidly in exposed workers with occupational asthma. Following removal from exposure FEV₁ continued to decline but at a slower rate, similar to the rate of decline in healthy adults.

INTRODUCTION

The FEV₁ is an important measure of disease severity in obstructive lung disease and is a strong predictor of long term outcome. The rate at which FEV₁ declines is also a prognostic marker and has been shown to be a predictor of survival independent of the FEV₁. [1] FEV₁ has been found to decline at about 25 ml per year in healthy adults, about 40 ml per year in asthmatic subjects [2] and about 60 ml per year in smokers with COPD. [3] In occupational asthma, continued exposure to the causative agent is recognized as being associated with a poorer outcome. [4] It is frequently assumed that removal from exposure leads to an improvement in asthma but it is unclear how removal from exposure influences FEV₁. Pirilla reported an average rate of decline of 40 ml per year in 91 selected subjects with isocyanate induced occupational asthma, though only 12 of these continued to be exposed to the causative agent in the workplace during the period of follow up. [5] The aim of this study was to determine how removal from exposure to the causative agent in workers with occupational asthma influenced the rate of change in lung function.

METHODS

Subjects

Subjects previously diagnosed as having occupational asthma were retrospectively identified from the SHIELD database (occupational asthma reporting scheme for the West Midlands region of the U.K.). All the following inclusion criteria had to be satisfied:

1. Seen at the Birmingham Chest Clinic with a clinical history suggestive of occupational asthma and reported to SHIELD with a date of diagnosis between 1/1/1993 and 15/7/1999.
2. Serial peak expiratory flow (PEF) record diagnostic of occupational asthma (Oasys-2 score >2.5). [6]

158 subjects were identified, 2 were excluded as there was evidence of co-existing interstitial lung disease.

Protocol

Subjects with a diagnosis of occupational asthma are routinely followed up at the Birmingham Chest clinic even after they are removed from exposure. Spirometry was performed at all visits. Results of pre-bronchodilator FEV₁ from the time of first diagnosis were retrospectively sought from clinic notes in all study subjects and entered into a database along with the date of measurement. Spirometric recordings were checked for acceptability and reproducibility. If there was documented evidence of a respiratory tract infection in the clinic notes on the date of spirometry, the reading was ignored. All study subjects were interviewed between July 1999 and November 2001 and the date of removal from significant exposure to the causative agent was identified. Evidence taken into consideration for deciding the date of removal from exposure included:

1. The subject's own recollection of events, with particular emphasis on when work-related respiratory symptoms by and large ceased and dates of relocation.
2. The place of work, level of exposure and presence of work-related respiratory symptoms as recorded in clinic notes by the attending physician at follow-up clinic appointments.
3. PEF records performed subsequent to the one used for diagnosis; an ongoing work-related deterioration was seen as evidence of ongoing exposure.
4. Correspondence pertaining to removal from exposure from an occupational physician and/or human resources for the place of work.

Results of spirometry or non-specific bronchial hyperresponsiveness were not used as evidence for identifying the date of substantial removal from exposure. FEV₁ measurements made (either at the chest clinic or at the place of employment where hard copies were available) were defined as being made whilst exposed or post-removal from exposure on the basis of the date of removal from exposure. Smoking status was categorized as current if they were smoking at the time of final follow-up, ex-smoker if they had stopped smoking for at least one month at final follow-up, and never smoked if they had smoked less than 100 cigarettes in total.

Statistics

The model used for analysis of FEV₁ decline is shown diagrammatically in figure 1. Average annual rate of FEV₁ decline was calculated separately for the exposed period and post-removal from exposure period using simple linear regression for each subject. FEV₁ measurements made before the age of 25 years were not included in regression estimates for any individual. FEV₁ decline values were only determined in subjects who had readings over at least one year for the relevant pre- or post-removal period. In addition, for the post-removal period readings at less than six months post-removal were excluded. The model also includes an uplift effect on FEV₁ occurring over one year following cessation of exposure. This uplift effect is the difference in FEV₁ estimated at the time of removal and the estimated FEV₁ one year after removal from exposure. The estimated FEV₁ at the time of removal was calculated by extrapolating the exposed regression line to the time of removal. The estimated FEV₁ one year after removal was calculated using a regression line fitted to readings more than one year post-removal. However, as there were generally fewer readings taken more than one year after cessation of exposure, data at least six months after removal were also included in this regression line. This was to minimise variability of the magnitude of the step-up and slope of the post-removal regression line, at the expense of slightly underestimating the step-up and post-removal slope. Where there were insufficient data to calculate a slope for the pre and post-removal regression lines (e.g. readings not spread over at least one year), a step-up was still calculated using the average of readings for pre- and /or post-removal periods as necessary. However, in these cases pre- and / or post-removal FEV₁ slope could not be calculated.

Paired t-tests were used to compare the step-up against the rate of decline prior to removal in subjects in whom both values were available. The null hypothesis was that the step-up over the one year period post-removal was no different to the average rate of decline whilst exposed, i.e. removal from exposure had no effect. Similarly the rate of decline post-removal from exposure was compared to rate of decline whilst exposed in subjects whom both values could be calculated.

RESULTS

156 subjects were identified with occupational asthma confirmed by PEF records, the main causative agents are listed in table 1. 90 workers had FEV₁ measurements made over at least one year prior to removal from exposure. The step-up in FEV₁ after one year of removal from exposure could be calculated in 114 subjects, FEV₁ decline following removal from exposure could be determined in 86 subjects. 44 subjects had measurements in all three phases. The number of subjects with sufficient data for FEV₁ regression estimates to be determined for exposed, step-up and follow-up periods is shown in figure 2. Demographic data of the whole group and the subgroups were similar and are shown in table 2.

Annual average change in FEV₁ whilst exposed to causative agent

143 subjects had 952 FEV₁ measurements prior to removal from exposure to the causative agent, although only 90 subjects had FEV₁ measurements made over a period of at least one year (median 2.9 years, IQR 1.8 to 4.8 years) prior to removal. In these 90 subjects, mean rate of decline in FEV₁ was 100.9 ml per year (standard error 17.7 ml per year). Individual regression estimates for class of agent is shown in figure 3.

Rate of decline did not correlate with age at baseline ($r = -0.17$, $p = 0.13$) nor was it related to gender (98 ml/yr in males, 107 ml/yr in females, $p = 0.81$). Rate of change in FEV₁ did not correlate significantly with initial FEV₁ percent predicted, $r = -0.12$, $p = 0.28$. Atopic subjects declined at a mean of 128 ml per year, non-atopic subjects at 72 ml per year ($p = 0.16$). Rate of decline in current smokers was 129.2 ml per year, 132.8 ml per year in never smokers. FEV₁ decline was 43.7 ml per year in ex-smokers, 95% CI of difference between current and ex-smokers is 2 to 159 ml/year, $p = 0.023$). Rate of decline was not statistically different between those treated and not treated with inhaled corticosteroids; those on inhaled corticosteroids declined at 104.9 ml per year (standard error 17.9), those not on inhaled steroids declined at 83.7 ml per year (s.e. 51.7), ($p = 0.63$). Rate of decline was not related to latent interval between first exposure and first symptoms (Spearman's $\rho = -0.07$, $p = 0.52$).

Step-up in FEV₁ on removal from exposure

A value for the step-up in FEV₁ one year after removal was calculated in 114 of the 156 subjects. The mean step-up for the group as a whole was +12.3 ml (standard error 31.6).

Step-up was not related to age ($r = 0.06$, $p = 0.54$), atopic status, or smoking status (one way ANOVA, $p = 0.42$). Step-up was not related to latent interval between first exposure and first symptoms ($r = -0.13$, $p = 0.16$), duration of symptomatic exposure ($r = 0.05$, $p = 0.6$), nor the initial FEV₁ per cent predicted ($r = 0.03$, $p = 0.79$). Treatment with inhaled corticosteroids prior to removal from exposure did not influence the step-up in FEV₁, nor was there any evidence that the addition of inhaled corticosteroids after removal from exposure had a major beneficial effect on step-up in FEV₁:

- 8 subjects on inhaled steroids prior to removal had stopped treatment prior to final follow up, their median step-up was +67.5 ml.
- 19 subjects had a significant increase in inhaled steroids, their median step-up was -9 ml.
- 56 subjects had no major change in treatment, their median step-up was +45 ml.
- In 31 subjects, it was unclear whether significant changes in treatment occurred; 22 were known to be on inhaled corticosteroids prior to removal, median step-up was +13.5 ml. 9 were known not to be on inhaled corticosteroids prior to removal, median step-up = +10 ml.

Average annual change in FEV₁ after removal from exposure

137 subjects had 684 FEV₁ measurements after removal from exposure, although only 86 subjects had FEV₁ measurements made over a period of at least one year (median 2.6 years, IQR 1.7 to 4.6 years), ignoring measurements made within the first six months of removal from exposure.

Mean rate of FEV₁ decline after removal from exposure was 26.6 ml per year (standard error 18 ml per year).

Rate of decline post-removal from exposure was not related to duration of symptomatic exposure or the latent interval between first exposure and first symptoms ($p = 0.52$ and 0.49 respectively), nor was it related to smoking status (current smokers 27.1 ml/year, ex-smokers 19.7 ml/year, never smokers 22.7 ml/year).

Comparison of FEV₁ decline prior to removal and subsequent up-step in FEV₁

63 subjects had FEV₁ measurements over at least one year prior to removal and in whom an FEV₁ up-step could be calculated, subjects demographics are shown in table 2. The mean rate of change in FEV₁ prior to removal was -111.6 ml per year (standard error 23.5). The up-step in FEV₁ one year after removal was +57.7 ml (standard error 45.2). Paired t-tests showed a mean difference 169.2 ml per year, 95% C.I. 52 to 286, p=0.005. This shows that there was a significant up-step in FEV₁ following removal from exposure.

Comparison of FEV₁ decline prior to removal and FEV₁ decline after removal

44 subjects had FEV₁ measurements made over at least one year prior to removal and one year after removal (excluding first six months after removal), subjects demographics are shown in table 2. The mean rate of change in FEV₁ pre-removal was -119.8 ml per year (standard error 26.3). The mean rate of change in FEV₁ after removal = +9.8 ml per year (standard error 31). Paired t-tests showed a mean difference of -129.6, 95% C.I. of difference -217 to -42,, p=0.005. The rate of decline following removal from exposure was significantly less than whilst exposed.

DISCUSSION

We have shown that in occupational asthma, FEV₁ declines rapidly at a rate of about 100 ml per year whilst the worker is exposed to the causative agent in the workplace. According to the model of FEV₁ used in this study, removal from exposure to the agent results in an uplift in FEV₁ of about 12 ml in the first year, followed by a subsequent decline at 26 ml per year. The nature of the causative agent, current smoking, or treatment with inhaled corticosteroids did not appear to influence the rate of FEV₁ decline.

The study population included all workers seen at the Birmingham Chest clinic that were reported as having occupational asthma to SHIELD (the West Midlands reporting scheme) with a date of diagnosis between 1/1/93 and 15/7/99 and who had a positive PEF record. It is unclear how representative this group of workers is of all workers with occupational asthma. All respiratory physicians and most occupational physicians within the region regularly notify cases to SHIELD and this would tend to reduce bias. Cases that are often missed include young people in whom occupational asthma develops quickly on starting a job, e.g. hairdressers, and who often leave soon after respiratory symptoms first occur without even consulting a doctor. Those who are staying at work and exposed are likely to be least affected. There may be a tendency for more severe cases to be referred and those from known high-risk industries. The reported incidence of occupational asthma in the West Midlands region is the highest in the UK. This suggests that selection bias due to under-reporting is likely to be less in the West Midlands region than anywhere else in the U.K.

The model of FEV₁ decline used assumes three components: a decline in FEV₁ whilst exposed, followed by an up-step in FEV₁ over a year, after which there is a decline in FEV₁, the rate of which may change. The rationale for choosing a one-year period during which the step-up occurs is that data from snow-crab workers suggests that FEV₁ showed maximal improvement by about one year after removal from exposure.[7] As the first follow-up visit in this study was at 12 months after removal, it possible that the plateau in FEV₁ could have occurred much earlier than at 12 months. Our model assumes a definite time point at which significant exposure ceased. In practice, determining this point in time is subject to significant error. After the diagnosis and recommendations regarding removal from exposure have been made, there is often a period where there is reduced or intermittent exposure that can last for many years. There was a large degree of subjective input by the worker in determining the time point of significant removal from exposure apart from those who lost their jobs, and faulty recollection of events is likely to increase error further. The exact time point chosen is likely to have a significant influence on all three components of the FEV₁ decline model. Use of spirometric measures to support the choice of the time point that exposure ceased would bias the model hence this was avoided.

Simple regression analyses were used to provide individual estimates of FEV₁ decline before and after removal from exposure. Intra-individual variability in spirometric measures tend to be large over short periods of time and accurate estimates of individual FEV₁ decline require monitoring over long periods of time, preferably over at least five years. Particularly with respect to the exposed period, few subjects have measurements over this period of time and it was necessary to specify a shorter minimum period that measurements were made over. Although a shorter period would make individual estimates of FEV₁ decline less reliable, group estimates ought to still be reasonably reliable. A minimum of a one-year period of spirometric measurements for determining FEV₁ decline was felt to be a reasonable compromise in allowing inclusion of more subjects but at the same time trying to minimise the error of individual regression estimates. Inclusion of only subjects with longer periods of

follow-up would also introduce bias because of the “healthy survivor” effect, i.e. the result would probably underestimate the true FEV₁ decline of the group as a whole, as those with more severe disease and rapid FEV₁ decline were more likely to have been removed from exposure and thus excluded from analysis. FEV₁ measurements made before the age of 25 years were not included in regression estimates for any individual as maximally attained lung function is not reached until about this age, hence a linear model is inappropriate.

Estimates of decline in FEV₁ after removal from exposure were even less reliable than whilst exposed. There are several possible reasons for this. Firstly, follow-up tended to be less intensive after removal from exposure and there were less data points over any given period of time. Secondly, the model estimated a linear decline following the step-up period. It is likely that there is considerable intra-individual variation in the pattern of recovery that would make this model incorrect for many subjects. As there were fewer data points in the post-removal period, data points after 6 months removal from exposure were included in the regression estimates in order to minimise the standard error of the regression estimates. Assuming the step-up occurred in a non-linear manner, this would lead to a small underestimate in calculating the step-up value and possibly the post-removal regression slope.

There are several difficulties with using individual regression estimates to calculate FEV₁ decline for the whole group. All the data are not used (such as in subjects with only one FEV₁ measurement within an exposed or unexposed period), thus reducing the power of the analysis. Each regression coefficient is given equal weighting within the analysis, despite the fact that subjects who have more data points are likely to have less error in their estimates than those with fewer data points. There are other models that might overcome some of the disadvantages of simple regression estimates, e.g. multi-level hierarchical linear models (mixed models). Unfortunately, they are also biased by weighting in favour of those who are exposed for longer (these subjects are likely to be less seriously affected).

For the group as a whole, FEV₁ decline appeared to be very rapid whilst exposed in the workplace with a mean rate of decline of about 100 ml per year. The actual rates of decline have large confidence intervals and lack precision. With a standard error of 17.7 this means that at best this value is likely to be at least 65.5 ml per year, which is a considerably faster rate of decline than that reported in non-occupational asthma [2] and at least as bad as that reported in COPD.[3] Potential confounders such as gender, age and baseline FEV₁ did not influence rate of decline nor did current smoking, though ex-smokers declined significantly less rapidly, possibly related to ongoing benefits from having stopped smoking. The lack of effect of current smoking is perhaps not surprising considering the relatively small additional influence this has on FEV₁ decline in asthmatic subjects (an additional 9-14 ml/year in asthmatic men). [8]

There was a high degree of variability in the step-up in FEV₁ but amongst those in whom both a pre-removal decline and an up-step in FEV₁ could be calculated, the up-step in the year after removal was significantly better than the prior rate of decline. Rate of change in FEV₁ thereafter was significantly better than whilst exposed. There were a small number of workers with pre-existing asthma, the pattern of FEV₁ decline whilst exposed and then following removal was not significantly different from the rest (data not shown).

In conclusion, in this group of workers with occupational asthma, FEV₁ declined rapidly at about 100 ml per year whilst they were exposed in the workplace. Removal from exposure

was associated with an up-step in FEV₁ of about 12 ml in the first year, following which FEV₁ declined at a rate similar to healthy non-smoking adults.

ACKNOWLEDGEMENTS

The authors would like to thank Sally Spencer for statistical advice. The project was funded by the European Chemical Industry Council (CEFIC). Dr Anees was also supported by a grant from the COLT foundation.

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Table 1. Main causative agents

High molecular weight agent 21 (13.5%)
 (including 5 cases to flour, 5 to latex, 4 to wood dust)
 Isocyanates 35 (22%)
 Metal agents 21 (13.5%)
 Biocidal agents 17 (10.9%)
 Colophony 13 (8.3%)
 Oil mists 9 (5.8%)

Table 2. Demographic data of whole and subgroups of follow-up study population

	Whole group n=156 (50 females)	Subjects with FEV ₁ change data				
		Exposed ≥ 1 year n=90	Step-up n=114	Post- removal n=86	Exposed ≥ 1 year and step-up n=63	Exposed ≥ 1 year and post-removal n=44
Age at first symptoms	40.2	40.4	40.2	40.3	39.6	40
Baseline FEV ₁ % pred	89.4	88.4	88.7	87.5	89.9	86.3
Atopic (%)	45	45.5	39	37.3	39.2	30.6
Current/ Ex-/ Never smokers (%)	24 / 28 / 48	20.5 / 30.7 / 48.9	21.6 / 28.8 / 49.5	22.9 / 30.1 / 47	18 / 31.1 / 50.8	21.4 / 33.3 / 45.2
On inhaled steroids at time of removal from exposure	82.7	80	77.2	80.2	81	86.4
Increased bronchial hyperresponsiv eness at diagnosis (%)	63.6	62.8	61.5	65.2	51.1	67.6
Median latent interval between first exposure and symptoms (months)	64	72	64	72	72	66
Duration of symptomatic exposure (months)	45	57	42	41	57	55

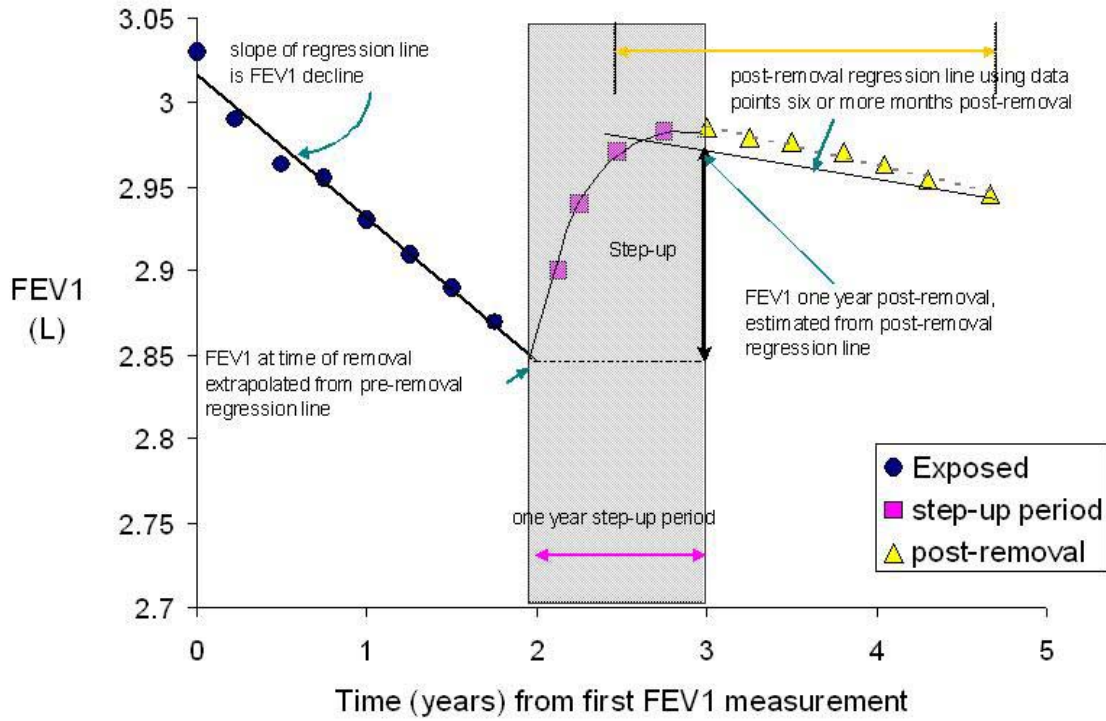
Figure 1. Model of change in FEV₁ over time in response to exposure and removal from exposure.

Figure 2. Subject inclusion diagram showing numbers according to sufficiency of data to determine FEV₁ decline during exposed, step-up and follow-up periods

Figure 3. Individual regression estimates of average annual FEV₁ decline in subjects with measurements over at least one year (median 2.9 years) whilst exposed according to class of causative agent.

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No data	Exposed	Step-up year	Post exposure
13	27		
	19		
	44		
		40	
		11	
			2

