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Pulmonary function and concentrations of α_1 -antitrypsin and immunoglobulin E in workers exposed to pancreatic enzymes

by Bengt Sjögren, MD,¹ Göran Hedenstierna, MD²

SJÖGREN B, HEDENSTIERNA G. Pulmonary function and concentrations of α_1 -antitrypsin and immunoglobulin E in workers exposed to pancreatic enzymes. *Scand j work environ health* 9 (1983) 385–390. Fourteen workers exposed to pancreatic enzymes in tanneries were studied by interview, spirometry, and the single-breath nitrogen washout technique. Blood concentrations of α_1 -antitrypsin and immunoglobulin E (IgE) were determined. For each exposed subject a nonexposed referent was selected, matched by sex, age, height and smoking habits. Symptoms in the airways were reported by four of the 14 subjects when weighing pancreatic enzymes. The exposed group did not show any deterioration in pulmonary volumes, forced expiratory flow, airway closure, or gas distribution when compared to the referents. The exposed group had significantly higher plasma levels of α_1 -antitrypsin than the referents. This elevation might be a compensatory response to increased levels of proteases within the lungs. The serum levels of IgE did not differ between the groups.

Key terms: tannery workers.

Occupational exposure to proteolytic enzymes such as subtilisin, papain, and pancreatic enzymes are known to produce allergic reactions mediated by immunoglobulin E (IgE) (3, 10, 11, 23). In animal studies the inhalation of papain and pancreatic elastase has generated emphysema (13, 15, 16, 18, 27). In a group of workers exposed to enzymes in a detergent industry an increased total lung capacity and a loss of elastic recoil were observed as a possible expression of pulmonary emphysema (12).

Some years ago a 47-year-old man was admitted to the Occupational Medicine Clinic at the Karolinska Hospital because of respiratory failure. During 1967–1975

he had worked in a tannery weighing powdered pancreatic enzymes. During exposure he had never experienced wheezing or dyspnea. He had smoked three to four cigarettes per day between 1945 and 1976. The results from spirometry, measurements of the transfer factor, and the mechanics of the lung, as well as radiospirometry, were suggestive of a severe obstructive pulmonary disease with emphysema (5). Thus the total lung capacity was 10.6 l (expected 7.3 l), the forced expired volume in 1 s (FEV_{1.0}) was 1.1 l (expected 4.0 l), the transfer factor was markedly reduced, and the static pressure-volume curve of the lung displayed a left shift and a steeper slope than normal. His concentration of α_1 -antitrypsin was 2.3 g/l (reference values 1.5–3.5 g/l), and his IgE was 19 μ g/l (upper limit value 290 μ g/l).

In view of the advanced destruction of the pulmonary tissue observed in this patient, the following study was undertaken. The purpose was to register the frequency of symptoms from the airways and any

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lung function impairment in a group of workers exposed to pancreatic enzymes.

Subjects

The exposed group consisted of 14 men who were working in tanneries at the time of the study or who had previously worked in tanneries. Their mean age was 52.4 (SD 9.3) years, and their mean height and weight were 174 (SD 6) cm and 74 (SD 7) kg, respectively. They worked or had worked weighing such chemicals as sodium chloride, sodium hydrosulfide, ammonia, sodium hydroxide, sodium hydrocarbonate; acids such as formic acid, acetic acid and sulfuric acid, and their salts; and also emulsifiers and chromium compounds. These chemicals were added to the hides which were treated in rotating vats. Only a minor part of the workday (5 min–2 h) was needed to weigh the powdered pancreatic enzymes Pellvit® and Oropon®. Some formation of dust was unavoidable during this work.

Eight subjects were exposed to pancreatic enzymes at the time of the study, and the other six subjects had been exposed until a few years ago. The exposure time varied from 2 to 18 years (median 7 years). Two years before the study local exhaust ventilation had been installed in four of the five tanneries visited.

Measurements of exposure were not performed because of the difficulty of assessing pancreatic enzyme activity.

One reference group worked with hides in the tanneries but was not exposed to chemicals. For each exposed subject a "tannery" referent was selected who was matched by sex, age, height, and smoking habits. The exposed subjects were, on the average, 2.0 (SD 2.2) years older and 0.1 (SD 3.5) cm shorter than their respective matched tannery referents.

Another reference group was formed from previously published reference values (4, 6, 8, 9, 14). The members of this group are called "external" referents in the present communication.

Methods

Interview

Clinical data were obtained for each subject from a standardized questionnaire

based on the 1976 revised version of the British Medical Research Council Questionnaire on Respiratory Symptoms. In this questionnaire "chronic bronchitis" was defined as a syndrome of cough and phlegm occurring on most days for at least three months for at least two years.

Spirometry

The forced vital capacity (FVC) was recorded by means of a rolling seal spirometer (Ohio 840). The maneuver was performed in the sitting position after careful instruction from the examiner. Tight clothing was loosened. Several tests were performed, and the best result for each variable, corrected to BTPS (37°C, ambient pressure, saturated with water vapor at 37°C) was used for the statistical analysis. Thus results for different variables could be chosen from different recordings. The variables analyzed were FVC, FEV_{1.0}, FEV_{1.0} divided by FVC times 100 (FEV%), and maximal midexpiratory flow rate (MMFR), which is the mean flow during the middle two quarters of FVC. The recordings were performed in the morning after some hours of work and thus reflect possible effects of some hours of exposure, as well as the effects of long-term exposure.

Gas distribution, airway closure and total lung capacity

Gas distribution, airway closure, and total lung capacity were measured by a single breath nitrogen washout technique (8, 9). The nitrogen concentration was assessed by an analyzer according to an ionization technique (Ohio 720), and the volume by the aforementioned spirometer. The gas concentration and volume were displayed on an X-Y recorder (Bryans 26 000). At least two measurements were performed with an intermission of 7–10 min; thus a stable nitrogen concentration within the lungs was assured before a new nitrogen washout. The mean values were used for the statistical analysis. These recordings were also performed in the morning after some hours of work.

The onset of airway closure was defined as that point at which consistent departure began from a best-fit line through the

alveolar plateau. This volume was expressed as the percentage of the expired vital capacity.

The slope of the alveolar plateau (phase III) was calculated as the difference in nitrogen gas concentration between two points on the alveolar plateau. One point was chosen as 30 % of the expired vital capacity, and the other was defined as the onset of airway closure. The slope was expressed as the percentage of expired nitrogen per liter of expired gas (% N₂/l).

Total lung capacity was assessed from the nitrogen washout curve after a maximal inspiration of oxygen. Thus the gas dilution technique was used to determine the total lung capacity, the expired volume of nitrogen being obtained by planimetry of the nitrogen washout curve (8).

Alpha₁-antitrypsin and immunoglobulin E

The blood samples were immediately centrifuged and kept cold during transportation. The plasma concentrations of alpha₁-antitrypsin were assessed by a quantitative electroimmuno rocket technique (19). The serum concentrations of IgE were determined by paper radioimmunoassay (17). All the determinations were performed at the Clinical Chemical Laboratory at the Karolinska Hospital.

Statistical methods

The pulmonary function values of the exposed individuals were compared to the values of their respectively matched tannery referents and to the values of the ex-

ternal referents. In the study of the concentrations of alpha₁-antitrypsin the groups were treated as independent. Differences were tested by Student's t-test. The concentrations of IgE were compared by Wilcoxon's ranking test. Two-tailed tests were used. Statistical significance occurred when $p < 0.05$.

Results

Interview

Half of the exposed subjects (7 of the 14) described symptoms in the airways, such as cough, and irritation of the nose when weighing chemicals. Four persons complained of symptoms when weighing pancreatic enzymes.

None of the tannery referents had any symptoms related to work, but one of them suffered from chronic bronchitis. He had previously become allergic to hides but had been subjected to desensitization.

Pulmonary function

The data from the spirometry and nitrogen washout measurements for the exposed subjects, the tannery referents, and the external referents are given in table 1. The exposed group and the tannery referents did not differ with respect to any variable. However the exposed subjects had significantly lower FVC values than the external referents (4) and also a lower total lung capacity (14).

When the exposed group was divided into one currently exposed group and one previously exposed group, no differences

Table 1. Spirometry and nitrogen washout measurements from the exposed subjects and the two reference groups, one from the same tannery as the exposed subjects and the other made up of previously published reference values, the external referents.

Measurement	Exposed subjects (N = 14)		Tannery referents (N = 14)		External referents ^a	
	Mean	SD	Mean	SD	Mean	SD
Forced vital capacity (FVC) (l)	4.5 ^b	0.7	4.4	0.9	5.0	0.3
Forced expired volume in 1 s (FEV _{1.0}) (l/s)	3.4	0.7	3.1	0.6	3.6	0.4
FEV _{1.0} /FVC · 100 (%)	75.1	9.2	71.0	7.5	72.3	3.8
Maximal midexpiratory flow rate (l/s)	3.4	0.8	2.8	1.0	3.4	0.4
Closing volume (%)	18.8	5.1	21.0	5.7	19.4	3.2
Phase III (% of nitrogen/l of gas)	1.4	0.7	1.8	0.9	1.2	0.1
Total lung capacity (l)	6.8 ^c	0.8	6.8	1.0	7.1	0.4

^a Matched to the exposed subjects by sex, age, and height.

^b Significant difference from the external referents ($p < 0.01$).

^c Significant difference from the external referents ($p < 0.05$).

Table 2. Levels of α_1 -antitrypsin in the exposed subjects and the tannery referents.

Group	Exposed subjects			Tannery referents		
	Mean	SD	N	Mean	SD	N
Smokers	1.58	0.20	6	1.36	0.40	5
Nonsmokers	1.50	0.15	8	1.26	0.28	8
All	1.54 ^a	0.17	14	1.30	0.32	13

^a Significant difference between the groups ($p < 0.05$).

were seen. Neither were any differences revealed when the exposed group was divided according to length of exposure, ie, one group with short exposure time (two to five years) and another with long exposure time (7–18 years).

The referents from the tanneries, being nonexposed to any agent known to be harmful to the pulmonary system, had somewhat low values for FVC and FEV_{1.0} in comparison with the external referents.

Alpha₁-antitrypsin and immunoglobulin E

The exposed subjects had significantly higher concentrations of α_1 -antitrypsin than the tannery referents (table 2). The levels of α_1 -antitrypsin were not influenced by current or previous exposure to pancreatic enzymes. The smokers had higher α_1 -antitrypsin concentrations than the nonsmokers, but the differences were not significant.

The median IgE concentration was 87 μ g/l among the exposed subjects and 35 μ g/l among the tannery referents. This difference was however not statistically significant.

Discussion

Symptoms and pulmonary function

The exposed subjects of our study had more frequent symptoms of the airways in comparison to the tannery referents; this result was not surprising as several of the chemicals used are known to irritate the airways. Despite symptoms related to exposure to pancreatic enzymes, no effect on pulmonary function could be seen when the exposed group was compared to their matched tannery referents. The pul-

monary function tests used in the present study were selected in an attempt to detect early changes in the peripheral airways, the area where early emphysematous changes are to be found.

The exposed group did not show any sign of airway obstruction in comparison to the external referents. Their FVC was lower in comparison with that of the external referents, but it did not differ from that of Swedish office clerks matched for smoking habits (1). A restrictive impairment could be associated with a decrease in FVC but should concomitantly be associated with a decrease in total lung capacity. The presently used technique for assessing total lung capacity, ie, single-breath nitrogen washout, is not as accurate as other methods, especially in the event of uneven gas distribution. It was primarily used because it added no extra time to the study, a factor considered to be important for a field study like the present one. It has been shown that total lung capacity measured by single-breath nitrogen washout is underestimated by about 5 % when compared to corresponding determinations made by body plethysmography or the helium equilibration technique (20, 24). The exposed group displayed a somewhat low total lung capacity in the present study. However, when the value for total lung capacity is multiplied by the factor 1.05, to correct for the underestimation inherent with the single-breath nitrogen washout technique, the value thus obtained does not differ from that determined by helium equilibration for the external referents (14). It can thus be concluded that there were no clear signs of any restrictive impairment.

Some of the pulmonary variables of the tannery reference group were lower than expected. This fact cannot be satisfactorily explained, as this environment is not known to cause impairment of pulmonary function.

Alpha₁-antitrypsin

The exposed group had significantly higher concentrations of α_1 -antitrypsin in plasma; this change might be a compensatory response to increased concentrations of proteases, pancreatic enzymes being such proteases, within the lungs. The observed increase in α_1 -antitryp-

sin was small in comparison with the concentrations seen during inflammation, tumor disease, pregnancy, or estrogen therapy (21, 22).

Previous studies have shown smokers to have higher levels of α_1 -antitrypsin than nonsmokers (2, 25). Such a tendency was also observed in our study. This increase can probably be explained by an increase of elastase, coming from polymorphonuclear leucocytes and alveolar macrophages, within the lungs (7, 26). Ex-smokers have lower concentrations of α_1 -antitrypsin than current smokers (2); however, the normalization of the level has been shown to be slow in exsmokers and extended over about five years (25).

The level of α_1 -antitrypsin did not differ between subjects currently and previously exposed to pancreatic enzymes. Almost all previously exposed subjects (five out of six) had been exposed within the last three years before the study. If the normalization of the level of α_1 -antitrypsin after pancreatic enzyme exposure is congruent with the normalization after the smoking of cigarettes, a nonexposure period of three years could be too short to create a significant decrease.

Immunoglobulin E

Exposure to pancreatic enzymes has been related to IgE-mediated allergic reactions in previous studies (10, 28), but the present study did not reveal any significant increase in IgE among the exposed subjects.

Conclusion

The marked pulmonary function deterioration previously described in one individual must be regarded as an exception rather than as the rule for subjects exposed to pancreatic enzymes. However, subjects exposed to such enzymes must be observed in the future because of the possible risk of their developing IgE-mediated hypersensitivity reactions and the theoretical risk of their developing pulmonary emphysema.

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