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# A thirteen-year follow-up of respiratory effects of acute exposure to sulfur dioxide

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**Objectives** In 1977, nine men were accidentally exposed to sulfur dioxide in an explosion in a pyrite mine. The lung function of seven men was followed after the accident. A four-year follow-up has been published previously. The greatest decrease in forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_{1.0}$), and maximal midexpiratory flow (MMEF) was observed one week after the accident, after which all these parameters improved without reaching the preaccident level. Reversible bronchial obstruction was still present in three patients, and a positive reaction in the histamine challenge test was found for four. In the present paper, the lung function follow-up 13 years after the accident is reported for six men.

**Methods** The patients' clinical condition, chest X-ray, spirometry, and histamine challenge test were studied 13 years after the incident.

**Results** Spirometry was normal in one worker, two displayed obstruction, and three had a combined obstructive and restrictive, mainly obstructive, ventilatory impairment. In the histamine challenge test, four patients showed bronchial hyperreactivity, one with a nearly significant reaction. Because of bronchial obstruction one patient could not perform the challenge test.

**Conclusions** This 13-year follow-up showed that acute inflammatory obstruction caused by exposure to sulfur dioxide left, as sequelae, obstructive impairment of ventilatory function and permanent bronchial hyperreactivity. The clinical picture displayed by these patients was named the "reactive airways dysfunction syndrome" (RADS) in 1985. Four of the patients also showed symptoms of chronic bronchitis.

**Key terms** chronic obstructive pulmonary disease, follow-up of lung function, reactive airways dysfunction syndrome, sulfur dioxide exposure.

A four-year follow-up of the effects of pyrite ($FeS_2$) dust on the lung function of seven men trapped in a mine shaft after an explosion in the Pyhäsalmi mine in 1977 has been reported earlier (1). At the time of the explosion nine workers were descending into the mine in a cage that could not be stopped. They were exposed to explosion gases, mainly sulfur dioxide for 20—45 min. One man died and eight men were injured. The patients had had almost identical symptoms immediately after the accident: cyanosis, dyspnea, and thoracic pain. Moist rales had been heard in lung auscultation, and in the chest X-rays of three victims diffuse small opacities and light confluent shadows were seen.

After first aid and hospital treatment, seven men were followed at the plant's health care station, which had also followed them prior to the accident. One week after the accident the lung function profile was at its lowest. Partial improvement was seen in four weeks, although the preaccidental level was not reached. In the four-year follow-up examination, all the patients still complained of breathlessness during pronounced effort. Four showed bronchial hyperreactivity in the histamine challenge test, and three responded positively to a bronchodilator during spirometry. Only two men displayed no signs of altered bronchial response. Chronic bronchitis, chronic permanent obstruction, and bronchial reactivity seem to be late sequelae after massive accidental exposure to sulfur dioxide.

In 1990 we reexamined six of the men exposed in 1977. This report describes their clinical condition and lung function 13 years after the explosion.

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## Methods

The reexamination of six of the seven victims was undertaken in autumn 1990 at the Finnish Institute of Occupational Health. Since 1980, the methods of monitoring lung function had changed to some extent. Flow-volume spirometry was performed with a rolling seal spirometer (Mijnhardt, Vicatest 3) connected to a microcomputer (Medicro MR-3) and Viljanen's reference values were used (2). The interpretation of the spirometric results were based on the dispersion of the spirometric parameters in the Viljanen reference values (3). A bronchodilator test was performed with three puffs of rimiterol hydrobromide, 0.2 mg per puff at 1-min intervals. Spirometry was controlled 5 min later, and an increase in forced expiratory volume in 1 s ($FEV_1$) of 15% or 200 ml or an increase in maximum midexpiratory flow (MMEF) of 33% or at least 0.4 $l \cdot s^{-1}$ was considered significant. Histamine challenge tests were performed according to a modification of Laitinen's method (4). Four, eight and sixteen inhalations of 1.5% histamine diphosphate were given, and the $FEV_{1.0}$ values were measured with a Vitalograph® bellow spirometer. A $FEV_{1.0}$ decrease of 15% was considered significant.

The diffusion capacity measurement was made with a carbon monoxide single breath method (Transfer test, Morgan, England) using Viljanen's reference values (3). The total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV) were measured by helium steady-state volume spirometry (Transfer test, Morgan, England) using Grimby & Söderholm's reference values (5). Full-size thorax radiographs, posteroanterior and lateral projections, were interpreted by a single reader. The criteria for chronic bronchitis were those of the American Thoracic Society (6).

The patients took a graded submaximal exercise test with a bicycle ergometer (Monark, Sweden) with 50-W increments in steps of 4 min each. Their electrocardiogram was monitored continuously (Siemens-Elema Schonander, Mingocard, Germany 7). Maximal oxygen uptake was estimated with the extrapolation method of the World Health Organization (7). Arterial blood oxygen saturation was continuously monitored with an ear oximeter (Ohmeda Biox 3700 Pulse Oximeter, United States). The peak expiratory flow (PEF) was measured before and 5, 10, 20 and 30 min after the exercise with a Wright peak flow meter (Clement Clarke M286, Ferraris Medical Ltd). A decrease of at least 15% in the PEF value was regarded as significant.

## Results

In 1990, six of the seven men were examined at the Finnish Institute of Occupational Health. The ages, symptoms, and anthropometric and smoking data of the patients in 1990 are shown in table 1.

Patients numbered 1, 3, and 6 were still working in the same workplace, and patient 4 had retired five years earlier because of respiratory disability due to the accident. Patients 5 and 7 had been retrained for other worktasks; they did not work underground any longer. Patient 7, who had been an active athlete before the accident, had to give up sports after the accident because of dyspnea during exercise. All of the patients complained of shortness of breath during exercise, and four of them had had excess mucus production daily for several years. The symptoms of five patients had remained unchanged since 1980, whereas those of one had subjectively improved. Only patient 4 used sympathomimetics on demand.

In the chest X-rays no changes were found compared with the findings in 1980. The lung function data are given in table 2. One patient showed normal ventilatory function, two slight obstruction, two had moderate combined obstructive and restrictive (basically obstructive) impairment, and one had moderate obstructive ventilatory impairment. One reacted positively to a bronchodilator. The histamine challenge test showed bronchial hyperreactivity in four patients. In addition, one patient displayed an almost significant $FEV_{1.0}$ depression of 14% during the histamine challenge test. One patient did not do the histamine challenge test because of dyspnea, expiratory wheezing on auscultation, and moderate obstructive ventilatory impairment in spirometry. Diffusion ca-

**Table 1.** Anthropometric data, smoking habits, symptoms, and use of medication of the patients in 1990.

| Patient | Age (years) | | Weight (kg) | Height (cm) | Smoking | Dyspnea in exercise[a] | Dyspnea in cold weather[a] | Phlegm production[a] | Medication[a] |
|---|---|---|---|---|---|---|---|---|---|
| | In 1990 | In 1977 | | | | | | | |
| 1 | 39 | 26 | 62 | 168 | 15 years; 20 cigarettes a day | + | – | – | – |
| 2 | .. | 22 | .. | .. | .. | .. | .. | .. | .. |
| 3 | 35 | 22 | 78 | 185 | 16 years; 10—20 cigarettes per day | + | + | + | – |
| 4 | 48 | 34 | 70 | 179 | 17 years; 10 cigarettes per day | + | + | + | + |
| 5 | 39 | 25 | 68 | 173 | Never | + | + | – | – |
| 6 | 47 | 34 | 68 | 175 | Never | + | + | + | – |
| 7 | 38 | 25 | 80 | 172 | 20 years; 20 cigarettes per day | + | + | + | – |

[a] + = yes, – = no.

**Table 2.** Results of the spirometric lung function, bronchodilator tests, histamine challenge tests, and diffusion capacity 13 years after the explosion. ($FEV_{1.0}$ = forced expiratory volume in 1 s, FVC = forced vital capacity, FEV% = (100 · $FEV_{1.0}$)/FVC, MMEF = maximal midexpiratory flow, DL = diffusion capacity, DL/VA = specific diffusion capacity, TLC = total lung capacity, FRC = functional residual capacity, RV = residual volume, pred = predicted)

| Patient | $FEV_{1.0}$ (l,BTPS) | | FVC (l,BTPS) | | FEV% | | MMEF (l · $s^{-1}$) | | Response to bronchodilator[a] | Histamine challenge [($FEV_{1.0}$)%] | Diffusion capacity (% of pred) | | TLC | | FRC | | RV | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | l | % of pred | l | % of pred | l | % of pred | l | % of pred | | | DL | DL/VA | l | % of pred | l | % of pred | l | % of pred |
| 1 | 3.72 | 92 | 4.22 | 85 | 89.92 | 111 | 5.55 | 124 | – | –15 | 79 | 99 | 5.92 | 86 | 3.36 | 93 | 2.07 | 110 |
| 2 | | | | | | | | | | | | | | | | | | |
| 3 | 3.59 | 75 | 5.09 | 85 | 70.54 | 87 | 2.54 | 47 | – | –22 | 83 | 97 | 8.07 | 102 | 4.92 | 126 | 3.13 | 165 |
| 4 | 2.05 | 63 | 3.27 | 61 | 57.05 | 74 | 1.23 | 26 | + | –28 | 79 | 103 | 8.31 | 115 | 5.22 | 159 | 4.57 | 243 |
| 5 | 2.65 | 63 | 4.46 | 85 | 59.52 | 73 | 1.32 | 28 | – | –19 | 118 | 138 | 7.16 | 105 | 4.49 | 122 | 3.23 | 171 |
| 6 | 2.76 | 68 | 4.78 | 85 | 63.01 | 78 | 1.59 | 35 | – | not done | 106 | 126 | 7.19 | 98 | 3.89 | 99 | 3.21 | 150 |
| 7 | 3.32 | 79 | 4.73 | 91 | 68.03 | 85 | 2.03 | 43 | – | –14 | 95 | 101 | 6.99 | 102 | 3.26 | 105 | 2.16 | 131 |

[a] + = yes, – = no.

pacity was marginally lowered in two patients and within normal limits in four. The transfer coefficient was normal for all of the patients. The TLC was 7.27 (SD 0.85) l or 101 (SD 9.5)% of the predicted value, and the FRC was 4.19 (SD 0.82) l or 117 (SD 24)% of the predicted value. The residual volume was 3.06 (SD 0.91) l or 162 (SD 46)% of the predicted value.

The development of the spirometric parameters FVC, $FEV_{1.0}$, and the MMEF percentage of the predicted values during the 13-year follow-up of patients 3 through 7 are presented in figure 1. Thirteen years after the accident the FVC was 4.46 (SD 0.71) l or 81% of the predicted value, that is, 14.7 (SD 11.9)% lower than the preaccident level. The $FEV_{1.0}$ was 2.87 (SD 0.60) l, 67% of the predicted value, 33.57 (SD 12.3)% lower than the preaccidental level. The MMEF was 1.74 (SD 0.54) l · $s^{-1}$, 36% of the predicted value. No further improvement had occurred since 1980. In addition the $FEV_{1.0}$ [(100 · $FVC_{1.0}$)/FVC] was at the same level as in 1990 (figure 2).

All the patients displayed a normal exercise capacity. One showed a slight decrease in his ear oximeter saturation value during exercise (97—94%); none had an asthmatic reaction during exercise. The maximal oxygen uptake ranged from 31.8 to 55.4 ml · $min^{-1}$ · $kg^{-1}$ [mean 41.2 (SD 9.2) ml · $min^{-1}$ · $kg^{-1}$].

## Discussion

The acute clinical picture after the pyrite explosion met all the criteria proposed for the reactive airways dysfunction syndrome (RADS). RADS is inflammatory bronchial obstruction combined with bronchial hyperreactivity

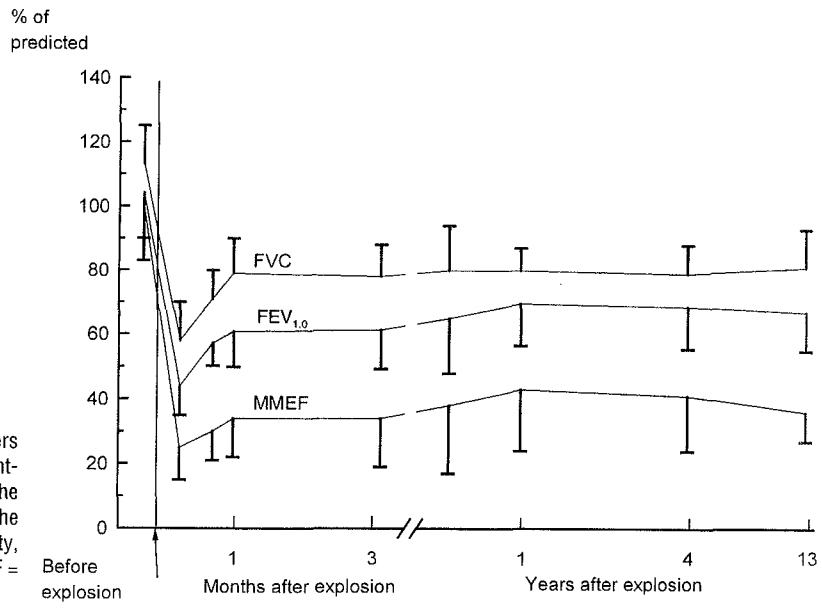


**Figure 1.** Spirometric parameters of five miners 13 years after exposure to pyrite in 1977, presented as the percentage of the predicted values. The time scale is logarithmic; the arrow indicates the time of the explosion. (FVC = forced vital capacity, $FEV_{1.0}$ = forced expiratory volume in 1 s, MMEF = maximal midexpiratory flow)

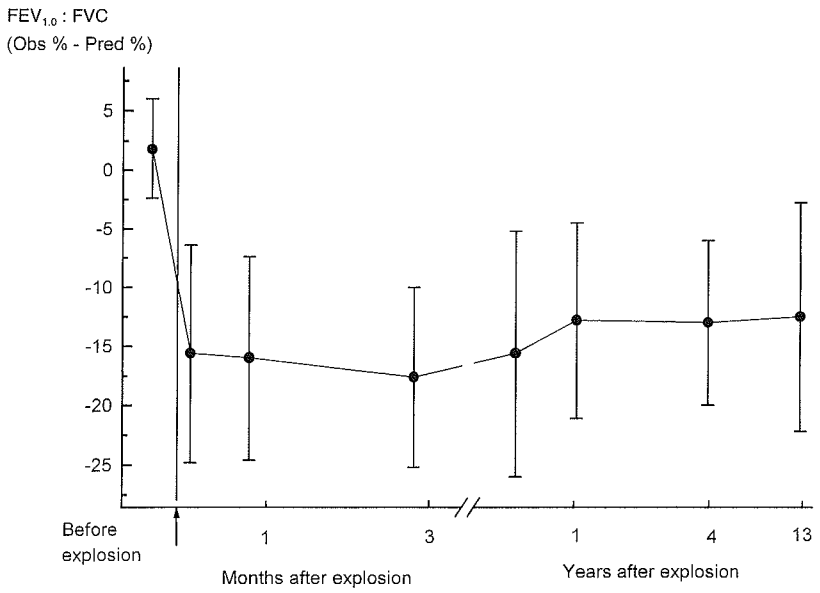


**Figure 2.** Ratio of the forced expiratory voluve in 1 s to the forced vital capacity ($FEV_{1.0}$:FVC) for five miners, presented as the difference of the observed values minus the predicted values. The time scale is logarithmic; the arrow indicates the time of the explosion. (obs = observed, pred = predicted)

caused by single exposure to high concentrations of an irritant (8). Long-term follow-up studies on RADS have so far been lacking. This report shows that the bronchial hyperreactivity seen in RADS can develop into a permanent pathological state.

Exposure to high concentrations of sulfur dioxide may have fatal consequences (9, 10). Bronchitic symptoms have been shown to develop from long-lasting exposure to sulfur dioxide (10, 11). Rabidovitch et al (12) used two years to follow two men accidentally exposed to high concentrations of sulfur dioxide; they concluded that exposure to high concentrations of this compound resulted in severe airway obstruction. The disturbances in pulmonary function were partly reversible, and most of the improvement occurred within 12 months after the injury. These authors did not measure bronchial hyperreactivity or response to a bronchodilator. Their observations are comparable with ours, although the major improvement in our patients took place within four weeks of the accident and thereafter the improvement in the spirometric values has been minimal.

Although chronic bronchitis usually takes decades to develop in humans, experimentally it has been shown in canine models that high exposure to sulfur dioxide can cause chronic bronchitis to develop in four to six months (13). The chronic bronchitis syndrome caused in dogs by exposure to high concentrations of sulfur dioxide gas closely resembles human chronic bronchitis (13—16); chronic cough and mucus hypersecretion occur along with histologically determined airway epithelial inflammation hypertrophy, and hyperplasia of the mucous secretory apparatus and airway obstruction. Repeated exposure of dogs to sulfur dioxide has also been shown to cause persistent lung inflammation without a bacterial infection component (15).

The responsiveness to bronchoconstrictors after exposure to sulfur dioxide varies in animal experiments. Decreased responsiveness to inhaled methacholine (15) or histamine (17) has been shown in some studies in which high concentrations of sulfur dioxide have caused the chronic bronchitis syndrome in dogs. This decreased responsiveness has been explained as due to increased mucus secretion. The thickened mucoepithelial barrier causes dilution of the inhaled bronchoconstrictors and results in decreased bronchial hyperreactivity (15, 17). In some animal studies, exposure to sulfur dioxide has also increased bronchial hyperreactivity (16, 18). In these studies, the follow-up times have not been very long, however.

The present study demonstrates that bronchial hyperreactivity persists in persons accidentally exposed to sulfur dioxide. Even 13 years after the accident all six patients studied displayed altered bronchial response. The histamine challenge test showed a significant reaction in four, being nearly significant for one, and bronchial hyperreactivity was likely in the one for whom the challenge test could not be performed because of pulmonary obstruction. Our patients' bronchial hyperreactivity was classified as slight (four patients) or moderate (one patient). Patients with chronic bronchitis are usually known to be hyperreactive, but to a less degree than asthmatics (19, 20).

Since 1980, the histamine challenge method has called for the follow up of $FEV_{1.0}$ instead of PEF. This change may have increased the sensitivity to disclose bronchial reactivity over the studies in 1980. In 1980, two patients with a negative histamine challenge test result had performed the rimiterole bronchodilation test 4 h before the histamine challenge test on the same day. This procedure could have also influenced the result of

the histamine challenge test. The lung function profile of the patients indicated bronchial obstruction 13 years after the accident. The MMEF value was prominently depressed, but the total capacity, functional residual capacity, and residual volume levels were normal or slightly elevated in all the patients, indicating that no volume restriction had developed. The lung function data of the patients has been recorded as a percentage of the reference values, and therefore the influence of aging during the 13-year interval has been taken into account. Only one patient used beta-sympathomimetics on demand. This result tallies with the results of our lung function tests. The patient was the only one who showed reversibility in the bronchodilation test.

At the time of the accident, the patients were 22—34 years of age and they were physically active. The most notable negative effect of the accident on all the patients was the markedly decreased exertion tolerance.

In the present study, none of the victims had a previous history of asthma or atopy. Although the men were not studied with histamine until four years after the incident, the decline of lung function, compared with the preaccident level, and the beginning of respiratory symptoms connected with the accident indicate that the altered bronchial response had developed as a result of the exposure to sulfur dioxide in the pyrite explosion. In some reports (21, 22) an asthma-like syndrome has developed as a result of repeated exposure to high concentrations of irritants. We were unable to ascertain any previous high exposures to sulfur dioxide among these workers.

Four workers had a smoking history of about 15 years, and two (patients 5 and 6) were nonsmokers. The criteria for chronic bronchitis were met by three smokers and one nonsmoker. All of them claimed that the symptoms had started in conjunction with the accident. Patient 5 had a moderate combined ventilatory impairment and showed an increased bronchial reactivity to histamine. Patient 6 showed moderate obstructive ventilatory impairment, but the histamine challenge test could not be done due to the degree of pulmonary obstruction (table 2). In these patients, the bronchial hyperreactivity and, in one of them, chronic obstruction had developed independently of smoking. The study does not clarify to what extent smoking has maintained the hyperreactivity and chronic bronchitis.

In conclusion, exposure to high concentrations of sulfur dioxide primarily causes severe obstruction and restriction in spirometry. The main improvement occurred within four weeks, but there was a slight further improvement during the first year after the incident. The preaccident level was never reached, however. Chronic obstructive pulmonary disease developed as a sequela of exposure to high concentrations of sulfur dioxide, as documented also in case reports (10, 12, 18) and as induced experimentally in animals (13, 14, 15, 16). Bronchial hyperresponsiviness seems to persist for years in humans exposed to high concentrations of sulfur dioxide. Permanent bronchial obstruction seems to develop also in nonsmokers and persons without a previous history of atopy.

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