

## Occupational Asthma Due to Formaldehyde

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Formaldehyde is a low molecular weight chemical and can elicit acute and chronic health related problems. Most of the inhaled formaldehyde is retained in the upper respiratory tract due to its extraordinary solubility. Therefore, cases of formaldehyde-induced occupational asthma are sporadic despite its widespread use in industrial processes. We herein report upon a case of occupational asthma due to formaldehyde, which was confirmed by workplace challenge including working environmental assessments, and by formaldehyde inhalation challenge using a specially designed closed-circuit apparatus. To investigate the possible involvement of an IgE-mediated mechanism, both *in vitro* and *in vivo* tests were done. IgE antibody specific for formaldehyde-human serum albumin conjugate (F-HSA) was not detected by ELISA, and no specific cutaneous reactivity to F-HSA was noted by either skin prick or intradermal test. The patient was diagnosed with formaldehyde-induced occupational asthma not associated with an IgE mediated mechanism.

**Key Words:** Occupational asthma, formaldehyde

### INTRODUCTION

Formaldehyde (HCHO) is a low molecular weight organic chemical. It has widespread industrial applications in the manufacturing of plastics, rubber, resins, plywood, fabric coatings, and adhesives. It is also used as a disinfecting, preserving, and embalming agent.<sup>1</sup>

Formaldehyde has been reported to cause acute

and chronic health-related problems.<sup>1</sup> However, due to its high water solubility, more than 95% of inhaled formaldehyde is absorbed in the upper respiratory tract and comparatively small amounts reach the alveolar membranes of the lung.<sup>2-4</sup> The most frequent symptoms resulting from exposure to formaldehyde are irritation of eye and the upper respiratory tract, and headache, which are associated with high concentration exposure.<sup>1</sup>

Formaldehyde can also act as a sensitizer at low concentrations, but despite its widespread use in industrial processes, formaldehyde only sporadically causes occupational asthma and it cannot be regarded as a potent asthmogenic agent. Here, we report the first case of occupational asthma due to formaldehyde in Korea, which was confirmed by workplace challenge supported by working environmental assessments, and by specific inhalation challenge using a specially designed closed-circuit apparatus.

### CASE REPORT

A 39-year-old Korean-Chinese male had been working since December 1997 in a factory that produced crease resistant trousers. His previous job in China was a public servant. He had no previous history of asthma or atopy and had never smoked.

In the factory, his work involved a heat-treatment process, which was performed in large heating chamber maintained at a temperature between 165 to 170°C. Six months after beginning this work, he developed episodic wheezing, shortness of breathing and chest tightness. He had

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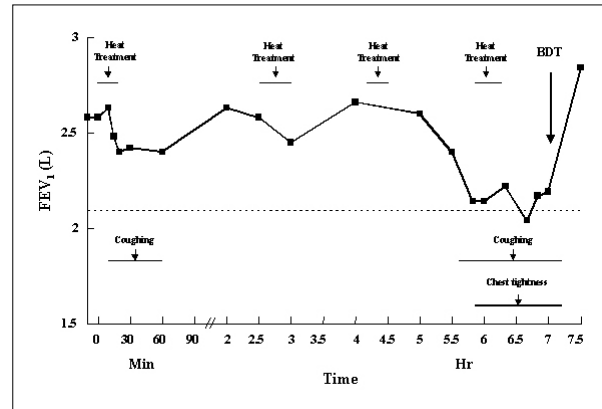
looked for emergency care 4 times due to severe attacks of dyspnea. He stopped working and his symptoms improved slightly, but when he returned to work one month later, within two days he was transferred to an emergency center because of a severe attack of asphyxia. He experienced another asphyxia attack and was suspended from the factory. He was referred to the Allergy Clinic at the Severance Hospital, Yonsei University for the assessment of possible occupational asthma.

When initially evaluated, the patient had been treated with fenoterol 5 mg orally 3 times and inhaled fenoterol, 200 mcg as needed. Hemoglobin, white blood cell count and differential counts were normal and the serum total IgE was 240 U/ml. Allergy skin prick tests with 50 common inhalant allergens were all negative. Chest X-ray film findings were normal. His forced expiratory volume in one second (FEV<sub>1</sub>) was 1.30 L (36.3% pred.) with a forced vital capacity (FVC) of 2.67 L (61.7% pred.) and a normal carbon monoxide diffusing capacity. After a short course of systemic corticosteroids treatments, his FEV<sub>1</sub> and FVC were to 2.94 L (81.9% pred.) and 3.43 L (80.3% pred.) respectively. The provocative concentration of methacholine causing a fall of 20% in FEV<sub>1</sub> (PC<sub>20</sub>) was 0.33 mg/ml, reflecting severe bronchial hyperresponsiveness.

#### Workplace challenge and working environment measurement

Workplace challenge was carried under the guidance of a physician. One hour after working, the subject complained of coughing, and six hours and 30 minutes after starting the work, his FEV<sub>1</sub> had reduced 21% from baseline (2.58 L to 2.04 L) (Fig. 1). Nonspecific bronchial hyperresponsiveness increased after workplace challenge (PC<sub>20</sub> at 3 days before workplace challenge -0.96 mg/ml; PC<sub>20</sub> at 1 day after workplace challenge -0.11 mg/ml).

In the factory, several chemical agents were used that were imported from Japan. The exact components of these agents were unknown, but, included glyoxal containing formaldehyde, phenol, urea, silicon, metal catalyzers, polyethylene emulsions and small amounts of polyurethane.



**Fig. 1.** Changes in lung function during workplace challenge. A late reaction is shown with recovery after inhalation of a short acting beta2-adrenergic agents (BDT). Arrows indicate the time of the heat-treatment process. Refer to the text for details. FEV<sub>1</sub>: forced expiratory volume in one second.

Formaldehyde can directly cause occupational asthma, and polyurethane can also cause asthma through generation of isocyanate. Therefore, the levels of formaldehyde and isocyanate were measured during working hours in the factory.

The formaldehyde level was measured by the chemical analytic method proposed by the National Institute for Occupational Safety and Health (NIOSH).<sup>5</sup> Briefly, samples were collected by drawing air through a silica gel tube coated with 2,4-dinitrophenylhydrazine (2,4-DNPH). Collected samples were extracted with solvent and levels of the formaldehyde derivative, formaldehyde-2,4-DNPH, were determined by high pressure liquid chromatography-ultraviolet (HPLC-UV). Isocyanate levels were measured by the method proposed by the Occupational Safety and Health Administration (OSHA).<sup>6</sup> Samples were collected by drawing air through glass fiber filters coated with 1-(2-pyridyl)piperazine. Collected samples were extracted with solvent and levels of the isocyanate derivative, isocyanate-1-(2-pyridyl)piperazine, were measured by HPLC-UV.

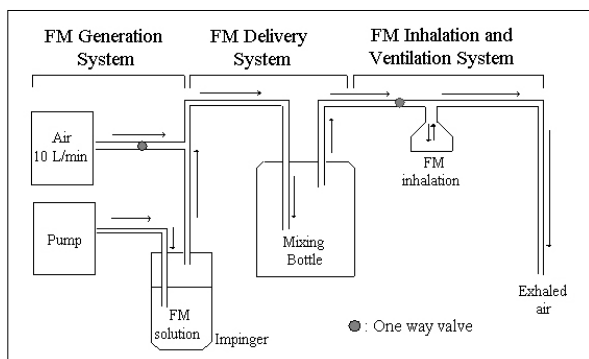
The mean level of formaldehyde was 0.06 ppm in the area around the heating chamber and the individual short-term exposure level of workers in this area was 0.12 to 0.13 ppm. No isocyanate was detected, which might have been the result of very small amounts of polyurethanes used (2 to 3% of total chemicals). Relative humidity and temperature at the area around the heating

chamber were 5 to 15% lower and 2 to 8°C higher than in other parts of the factory (44 - 55% relative humidity, 27-32°C temperature).

### Specific inhalation challenge with closed-circuit apparatus

A specialized closed-circuit apparatus was designed for formaldehyde inhalation challenge. The apparatus consisted of three parts: (1) a generation system; (2) a delivery system; and (3) an inhalation and ventilation system (Fig. 2). A saturated solution of formaldehyde diluted with distilled water was poured into the impinger, and formaldehyde gas was generated by bubbling formaldehyde solution. The pumping rate was fixed at 0.46 L/min, and concentration of generated gas was controlled by changing the dilution ratio of the formaldehyde solution in the impinger. Generated gas was then mixed with a constant flow of compressed air at 10 L/min. In order to exposure constant concentrations, preliminary experiments were done to determine the dilution ratio for 0.1, 0.5, 1 and 3 ppm of formaldehyde gas. After repeated experiments, it was confirmed that the concentration of formaldehyde, which was measured by UV spectrophotometry at 580 nm, was constant, and that an adequate amount of formaldehyde was delivered to the inhalation system for set periods of time, namely, 5, 10 and 20 minutes respectively.

Specific inhalation challenges with formaldehyde were then performed. On the first day, which was used as a control, the patient was exposed to distilled water for 20 min. No significant

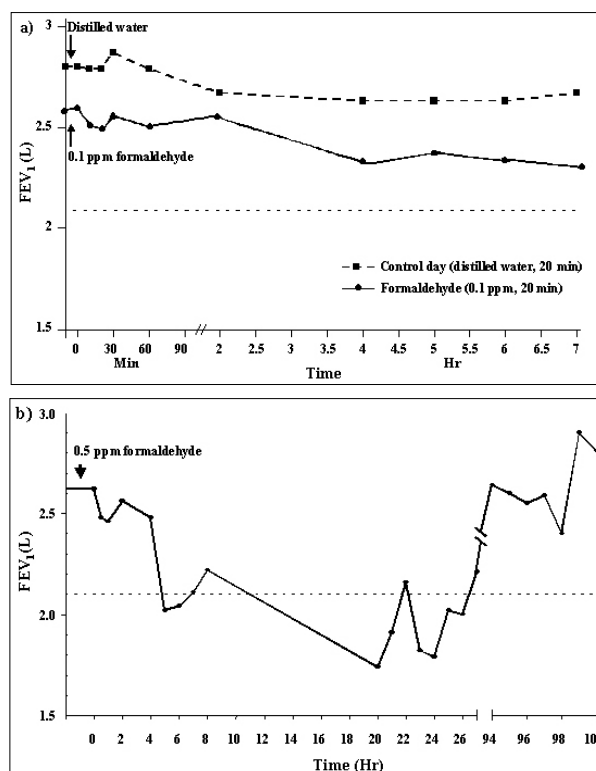


**Fig. 2.** Schematic presentation of the closed-circuit apparatus used for the formaldehyde (FM) inhalation challenge test. See text for details of the apparatus.

change in FEV<sub>1</sub> was noted over the next 7 hours. On the second day, he was exposed to 0.1 ppm of formaldehyde for 20 min, again without producing significant changes in FEV<sub>1</sub>. The subject was then exposed to 0.5 ppm of formaldehyde for 20 min. Five hours after the inhalation, his FEV<sub>1</sub> decreased from 2.62 to 2.02 L (23% fall) and the patient began to complain of dyspnea, chest tightness and wheezing (Fig. 3). The FEV<sub>1</sub> decreased to 1.74 L (34% fall) 22 hours after inhalation, and then improved slowly on serial monitoring of pulmonary function. He was confirmed to have formaldehyde-induced occupational asthma.

### Measurement of specific antibodies to formaldehyde by *in vitro* and *in vivo* methods

To investigate the possible involvement of an IgE mediated mechanism, both *in vitro* and *in vivo*



**Fig. 3.** Specific inhalation challenges by exposing the subject to control or formaldehyde for 20 min. a) No significant changes in FEV<sub>1</sub> after exposure either to control (distilled water) or to formaldehyde (0.1 ppm) for 20 min. b) Prolonged late asthmatic reaction with significant fall in FEV<sub>1</sub> was noted after the inhalation of formaldehyde (0.5 ppm) for 20 min. FEV<sub>1</sub>: forced expiratory volume in one second.

tests were performed using formaldehyde-human serum albumin conjugate (F-HSA). F-HSA was produced using a previously reported method with slight modification.<sup>7</sup> Briefly, HSA (Green Cross Co., Youngin, Korea) in PBS was exposed to formaldehyde in equal amount. The mixture was incubated for 30 minutes at 37°C and then extensively dialyzed against PBS. The F-HSA was sterilized with a 0.2 µm filter (Millipore Corp., Bedford, Mass., USA). Conjugation was proved by different electrophoretic mobility of F-HSA compared with HSA, and the specificity of antibody response to F-HSA was confirmed by inhibitory ELISA using positive control serum (data not shown).

Specific IgE antibody to F-HSA was measured by ELISA. F-HSA was coated onto a 96-well polyvinyl microtiter plate at a concentration of 100 µg/ml in carbonate buffer (pH 9.6). After washing, the antigen-coated plate was incubated with 50 µL of undiluted serum for 1 hour at 37°C. The plate was then incubated with 1:500 biotinylated anti-human IgE (Vector) followed by incubation with 1:500 streptavidin-peroxidase (Sigma). After washing, 100 µL of ABTS solution (25 mg of 2,2'-azino-bis-ethylbenzthiazoline sulfonic acid in 50 mL of 50 mmol/L citrate buffer [pH 4.2] containing 50 µL of 0.03% hydrogen peroxide) was added as a substrate, and after 5 minutes, 100 µL of 2 mmol/L NaN<sub>3</sub> was added to stop the reaction. The colorimetric reaction was measured by the absorbency at 405 nm on an ELISA reader (Dynatec).

IgE antibody specific for F-HSA was not detected in the patient and detected in only one of ten medical students, who were exposed to formaldehyde during an anatomy dissecting course and used as positive controls. IgG antibody to F-HSA was detected in the patient, but considered to be nonspecific because IgG responses were detected not only in positive controls but also in negative controls who are not occupationally exposed to formaldehyde.

Cutaneous reactivity to formaldehyde was determined by prick and intradermal (ID) tests with F-HSA, HSA, and formaldehyde. Concentrations used for the prick and ID test, respectively, were F-HSA (1, 5, and 10 mg/ml and 10, 100 and 500 µg/ml), F-HSA (1, 5, and 10 mg/ml and 10,

100 and 500 µg/ml), and formaldehyde (0.01, 0.1 mg/ml and ID test was not done with formaldehyde alone).

No specific cutaneous reactivity to F-HSA, HSA, or formaldehyde was noted in the patient and the positive control group, even though one positive control showed weak IgE antibody reaction to F-HSA by ELISA.

### Clinical course

The patient was advised to discontinue exposure to formaldehyde and to take anti-asthma medication including inhaled corticosteroid. Despite the avoidance of formaldehyde exposure and the continuous administration of anti-asthma medication, he frequently experienced chest symptoms, such as cough, chest tightness and dyspnea, and severely decreased pulmonary function was noted [FEV<sub>1</sub> 1.51 L (42.0% pred) and FVC 2.84 L (65.7% pred)] after 1 year.

### DISCUSSION

High exposure to formaldehyde can occur in occupational settings. However, the general public is now subjected to increased formaldehyde exposure because it is now a ubiquitous chemical that is found at low levels in homes, offices, and in the general urban environment.

In general, cases of occupational asthma demonstrate typical features of specific reactions. Only a small proportion of exposed workers develop the disease, and there is a latent period, which extends from weeks to years before symptoms begin. Reactions are then provoked by concentrations that were previously well tolerated and that have little effect on the majority of fellow workers.

Our patient's previous job was not associated with exposure to formaldehyde. He had six months period of latent period, and no other workers in his workplace had similar lower respiratory symptoms except nasal and ocular irritation symptoms by interview. Environmental assessment showed that the mean level of formaldehyde was 0.06 ppm in the patient's working area and that individual short-term exposure reached 0.12 to 0.13 ppm. These results are some-

what different to the reported exposure level, range of 0.2 to 1.2 ppm, in similar garment manufacturers using crease-resistant cloth,<sup>8,9</sup> but such differences are not surprising because of the diverse working processes and chemical agents used by each manufacturer. In addition, the factory was working at a low level when the environment assessment was performed. So it is considered that the mean exposure level had been much higher when the patient had suffered asthmatic attacks in workplace.

In spite of continuing to take low dose oral corticosteroids (prednisolone 5 mg, daily) during the workplace challenge, patient's FEV<sub>1</sub> was reduced after 6.5 hours in postshift spirometry compared to preshift, and airway hyperresponsiveness was increased after workplace challenge. Late asthmatic reaction was reproduced by specific bronchoprovocation test, moreover, such a late reaction is typical of formaldehyde induced asthmatic reactions. However, there was some discrepancy between the formaldehyde concentrations, which induced asthmatic reaction in the workplace challenge and in the specific challenge tests. A lower concentration of formaldehyde was required to induce asthmatic reactions in the workplace, which might have been the result of the different patient's condition. And other factors, such as long duration of exposure, high temperature and dried air around the patient's working area might also have aggravated or contributed to his asthmatic reaction at lower formaldehyde concentrations.

The simplest method of challenging with formaldehyde is to paint solutions onto nonreactive surfaces. Alternatively, formaldehyde can be vaporized into an exposure chamber or can be inhaled through a breathing circuit.<sup>10,11</sup> But, it was found to be difficult to maintain a constant concentration of formaldehyde or to determine accurately the atmospheric end target concentration of formaldehyde during inhalation. Recently, Lemiére et al.<sup>12</sup> developed a closed-circuit apparatus that could generate formaldehyde as a vapor. With such apparatus, they obtained safe and nonirritant concentrations of formaldehyde by on-line assessment and control. Their apparatus may be an ideal device for specific inhalation testing. However it requires specific control and

monitoring systems, and such requirements are not feasible for routine challenge tests with unusual agents. For this reason we designed an apparatus for formaldehyde inhalation challenge. By repeated experiments, it was confirmed that the equipment delivered a constant level of formaldehyde. The apparatus is simple and doesn't require any specialized devices or machines, and can be used generally by those with sufficient experience of inhalation challenge testing. Nevertheless, further studies and applications will be needed to certify and standardize our equipment.

The mechanism of formaldehyde induced asthma remains unclear. Immunologic hypersensitivity to formaldehyde in the form of allergic contact dermatitis is well recognized. Formaldehyde administered parenterally can frequently stimulate the formation of antibodies, but there are no conclusive data that prove the development of de novo IgE-mediated respiratory tract symptoms secondary to formaldehyde inhalation.<sup>1,7,13,14</sup> IgE antibody specific for formaldehyde was not detected in our patient. Further studies are needed to determine the exact pathophysiologic mechanism of formaldehyde asthma.

A small number of studies have been conducted on the prognosis of formaldehyde induced occupational asthma. According to the report by Hendrick et al.,<sup>15</sup> symptoms and airway hyperactivity can disappear following the complete cessation of exposure. Despite avoidance of exposure, however, our patient had persistent symptoms and showed decreased lung function after 1 year, which might have been the result of under-treatment of the asthma and/or incomplete avoidance. But, it is considered that delayed diagnosis from the onset of symptoms may be the most important cause of such a severe asthma state, because the patient had been continuously exposed to formaldehyde for more than 1 year after the symptoms onset and had been referred to our hospital after several experiences of near-fatal asphyxia and life threatening exacerbations of asthma. In fact the majority of studies about occupational asthma have reported that the outcome after diagnosis is often poor, and that the duration of exposure after the onset of symptoms and the severity of the asthma at the time of

diagnosis are determinants of the prognosis. Further study is needed to determine the exact prognostic features of formaldehyde-induced asthma.

In conclusion, we report upon a case of occupational asthma due to formaldehyde, and believe that there may be undetected cases of formaldehyde-induced occupational asthma because of the Korean industrial structure. So occupational history and details of environmental conditions should be carefully obtained whilst examining any suspected case, and inhalation challenge should be performed. It may be possible, using such active interventions, for prompt diagnosis and the avoidance of causative agents.

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