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Case Report

Persistent and Unusual Respiratory Findings after Prolonged Glutaraldehyde Exposure

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Abstract

Glutaraldehyde is commonly used in endoscopy labs to clean and disinfect instruments. It can cause direct irritation of the skin and the upper and lower airways. Health care workers are also at risk for the development of irritant-induced or sensitizer-induced occupational asthma when exposed to this chemical. Herein, we report on a patient who had frequent exposures to glutaraldehyde over one year while working in an endoscopy lab and developed chronic upper and lower respiratory tract symptoms. Multiple spirometric tests during her evaluation revealed variable results including restrictive pattern with a response to bronchodilators, obstructive pattern with a paradoxic bronchoconstrictive response to bronchodilators, and obstructive pattern with a partial response to bronchodilators. These results indicate that the distribution of inflammation and bronchial responsiveness can vary in a single patient with glutaraldehyde-induced occupational asthma. Therefore, the evaluation may be more difficult than might be expected in patients with occupational asthma, and some patients will need multiple pulmonary function tests to characterize their airway disease.

Keywords: Glutaral; Asthma, occupational; Occupational exposure; Inhalational exposure; Health personnel

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Introduction

Occupational asthma (OA) is defined by "variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment."[1] It is the most prevalent occupational lung disease in developed countries, and Dykewicz has suggested that OA "may account for 25% or more of *de novo* adult asthma."[2] OA is particularly important in the medical field, as health care workers are the second most exposed population subset, accounting for 9% of reported cases.[3] Glutaraldehyde has been used as a disinfectant since 1966.[4] It is commonly used in endoscopy and bronchoscopy labs because of its wide spectrum of microbicidal activity and its non-corrosive action. Unfortunately, glutaraldehyde has been identified as a frequent cause of OA and was reported at 6% in a list of the most common offending agents.[3] The actual number is probably higher due to the under-recognized and unreported incidents.[5,6] There are two major types of OA—sensitizer-induced (*ie*, work-related asthma associated with exposure to one or more sensitizing agents and appearing after a latency period), and irritant-induced (which may occur after single or multiple exposures to nonspecific irritants).[7] Irritant-induced OA includes three subcategories that predominantly

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Table 1: Serial spirometry testing

PFT Analysis	Study 1*	Study 2	Study 3
Pre-FVC (L, %predicted)	2.08 (75.8%)	3.53 (128.8%)	3.56 (129.8%)
Pre-FEV_1 (L, %predicted)	2.02 (89.6%)	1.52 (67.4%)	1.93 (85.4%)
Pre- FEV_1/FVC	0.97	0.43	0.54
Post-FVC (L, %predicted)	3.27 (119.5%) ↑	3.11 (113.6%) ↓	3.92 (143.25) ↑
Post-FEV_1 (L, %predicted)	1.47 (65%) ↓	1.33 (58.8%) ↓	2.14 (94.8%) ↑
Post-FEV_1/FVC	0.45	0.43	0.54
%Change FVC	57.6%	-11.8%	10.3%
%Change FEV_1	-27.5%	-12.8%	11.0%
Effect of bronchodilator	Improved FVC, reduced FEV_1	Reduced FEV_1 and FVC	Mildly improved FEV_1 and FVC

*These three studies were done at weekly intervals.

differ according to the concentration of irritants in the workplace atmosphere.[6] OA diagnostic testing depends on spirometry, workplace evaluation, and detailed data logs of four times daily peak expiratory flow rates (PEFR), when possible.[2] Airway hyperresponsiveness is common in OA, and methacholine challenge tests have been used in confirmatory testing. Testing is often performed at the end of a work week with a repeat trial after the patient has been removed from the suspected offending agent.[2] However, some authors have noted the lack of consistent functional changes with glutaraldehyde exposure. Vyas reported that workers with suspected OA from glutaraldehyde exposure generally complained of symptoms without objective evidence of pulmonary disease.[8] All workers in this study had spirometric values in the normal range.

Case Presentation

A 55-year-old woman referred to our center for evaluation for chronic cough. The patient had enjoyed excellent health until approximately one year prior to her presentation to our clinic. She complained of chronic persistent non-productive cough and episodic shortness of breath, especially with moderate exertion. She noted exacerbation of symptoms when she was exposed to perfumes, natural smoke, and tobacco smoke. She was a lifetime non-smoker, did not live with any smokers, and had no obvious exposures to environmental allergens. She previously was employed at an endoscopy lab where part of her job included cleaning the scopes. She was routinely exposed to Rapicide (Medivators: Minneapolis, MN, 2.5% glutaraldehyde solution) throughout her employment. The particular lab at work did not have special ventilation or hoods, and she did not wear a respirator. She cleaned up to 38 scopes per day in an open area using a five gallon and a four gallon container of glutaraldehyde. She worked in this lab for approximately one year, but she was forced to quit work secondary to respiratory symptoms.

On physical examination, her vital signs were within normal limits, including oxygen saturation of 97% by pulse oximetry. She had frequent non-productive cough throughout the interview. Her nares were

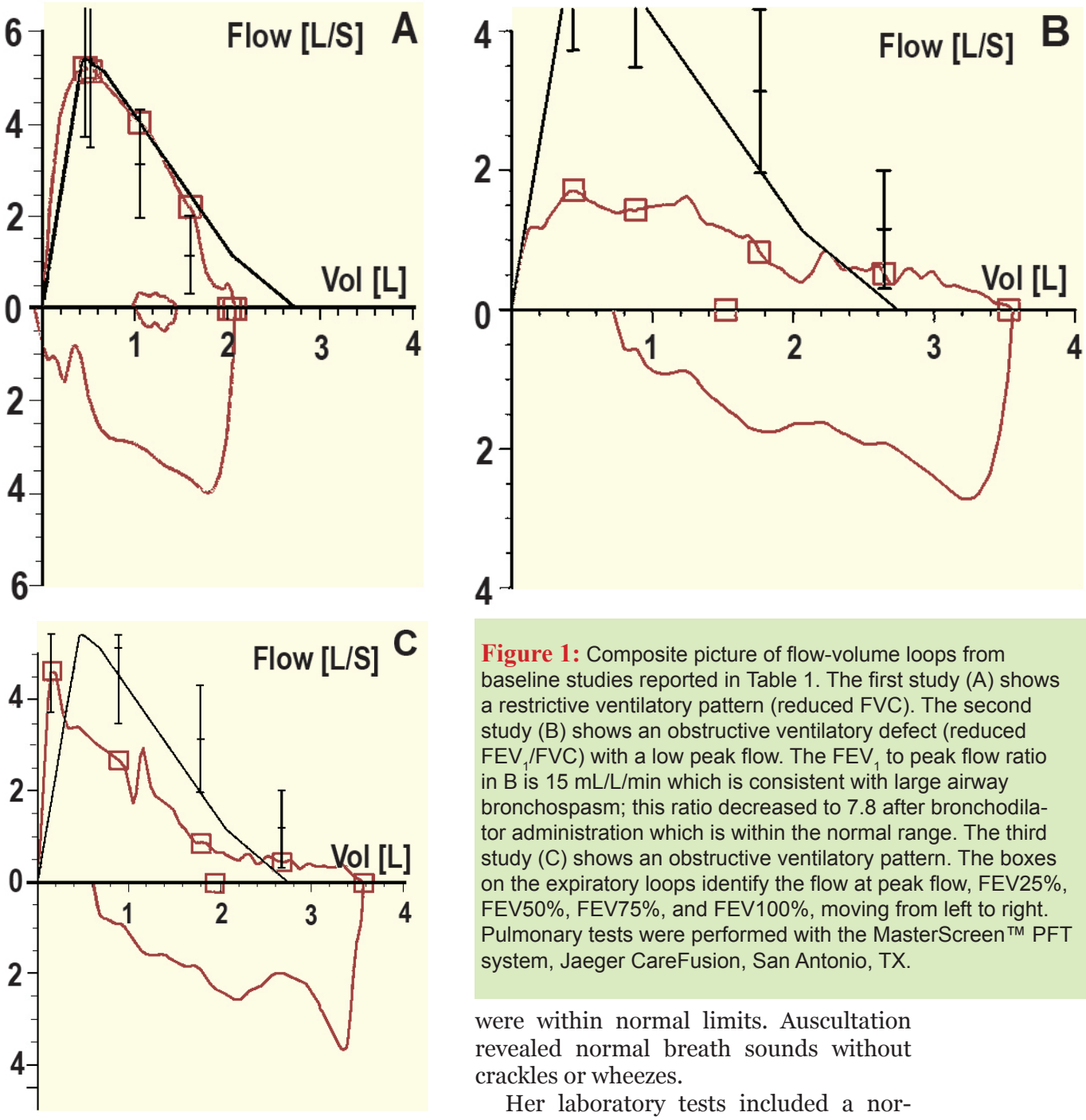

Figure 1: Composite picture of flow-volume loops from baseline studies reported in Table 1. The first study (A) shows a restrictive ventilatory pattern (reduced FVC). The second study (B) shows an obstructive ventilatory defect (reduced FEV_1/FVC) with a low peak flow. The FEV_1 to peak flow ratio in B is 15 mL/L/min which is consistent with large airway bronchospasm; this ratio decreased to 7.8 after bronchodilator administration which is within the normal range. The third study (C) shows an obstructive ventilatory pattern. The boxes on the expiratory loops identify the flow at peak flow, FEV25%, FEV50%, FEV75%, and FEV100%, moving from left to right. Pulmonary tests were performed with the MasterScreen™ PFT system, Jaeger CareFusion, San Antonio, TX.

patent without inflammation of the turbinates or increased secretions; the pharyngeal mucosa had mild cobblestoning without exudate. The chest wall moved symmetrically, and percussion notes were within normal limits. Auscultation revealed normal breath sounds without crackles or wheezes.

Her laboratory tests included a normal complete blood count and differential and a normal complete metabolic panel. Her chest x-ray revealed normal cardiac silhouette without pulmonary infiltrates, nodules, or hyperinflation. Spirometry on the initial presentation revealed an abnor-

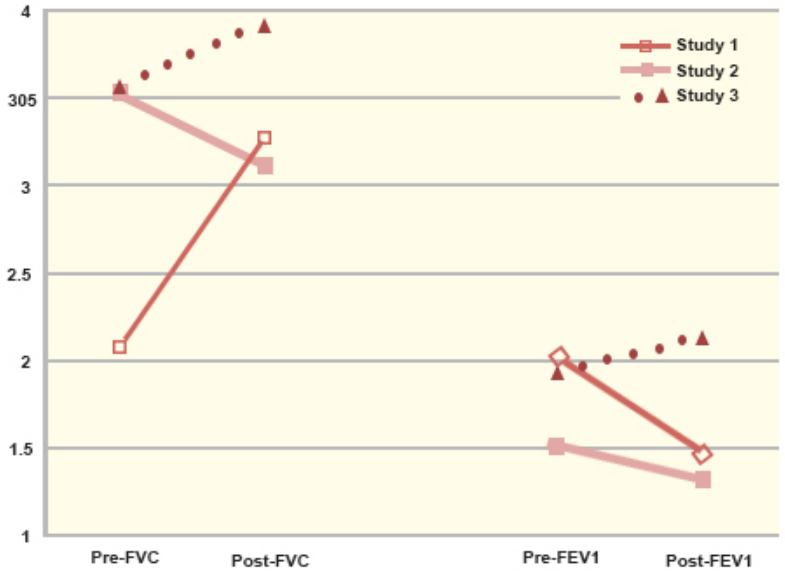

Figure 2: This is a graphic representation of the changes in FVC and FEV_1 after bronchodilator administration in the three consecutive studies. See Table 1 for more detail

mal flow-volume loop characterized by reduced peak expiratory flow and a reduced peak inspiratory flow. The forced expiratory volume in one second (FEV_1) was 2.59 L (112% of predicted). The forced vital capacity (FVC) was 3.54 L (124% of predicted). The FEV_1/FVC ratio was 0.73. At the initial follow-up repeat spirometry showed a normal flow-volume loop. The FEV_1 was 3.28 L (143% of predicted). The FVC was 3.76 L (134% of predicted) and the FEV_1/FVC ratio was 0.87.

The patient was started on fluticasone propionate (100 µg/inhalation) with one inhalation twice daily and albuterol (two inhalations as needed for cough, dyspnea, or wheeze). At follow-up at six weeks, the patient felt better on therapy. However, at subsequent follow-up visits she noted chronic episodic upper respiratory symptoms, including rhinorrhea, sore throat, and cough, and chronic episodic lower respiratory symptoms with cough, shortness of breath, and chest tightness, especially when exposed to fumes and chemicals. At the six-month follow-up the patient was started on salmeterol xinafoate with fluticasone propionate and as needed albuterol. At subsequent follow-up the patient felt better. She had normal levels of physical activity with the exception of an average of two episodic pulmonary exacerbations per week.

The patient had several pulmonary function test (PFT) evaluations requested by her workers compensation physician approximately 10 months after her initial clinic visit (Table 1, Figures 1 and 2). During the first testing session, she had cough during the pre-bronchodilator testing. The baseline spirometry revealed a mild restrictive ventilatory defect. There was a significant increase in FVC with a bronchodilator (albuterol) and a reduction in the FEV_1. After bronchodilator administration she had a mild obstructive ventilatory defect. Repeat of pulmonary function seven days later revealed a moderate obstructive defect. After the administration of a bronchodilator, both the FEV_1 and FVC fell. A third pulmonary function test revealed a mild obstructive ventilatory defect with FEV_1 of 1.93 L (85% of predicted). The FEV_1/FVC ratio was 0.54. The FEF 25%–75% was markedly decreased at 34% predicted. She had a partial response to bronchodilators. Table 1 provides a detailed summary of pulmonary function testing. The patient was taking fluticasone/salmeterol (250/50 µg/inhalation) combination inhaler twice daily and albuterol (90 µg/inhalation) as needed for symptoms at the time of testing. All testing was performed in the morning between 9:00 and 10:00 am. All efforts during spirometry lasted at least six seconds, and she was considered cooperative throughout testing.

Discussion

Glutaraldehyde, a known cause of OA, is frequently used in the health care industry. Symptoms of glutaraldehyde-associat-

ed OA typically include chest tightness and persistent cough.[8] These nonspecific symptoms coupled with a delay in symptoms after exposure can hamper diagnosis. Vyas reported that ex-employees with glutaraldehyde exposure had significantly lower lung function than current employees, however their mean spirometric results were in the normal range.[8] Di Stefano and coworkers studied 24 health care workers with symptoms consistent with OA due to glutaraldehyde exposure.[9] All patients had upper and lower respiratory tract symptoms, and 16 had peak flow measurements consistent with work-related changes in lung function. Seven workers had specific IgE antibodies to glutaraldehyde. Eight workers had normal spirometric results, 12 had obstructive pattern, and four had restrictive indices. Eight underwent specific bronchial challenge with glutaraldehyde exposure. Three had an early and late response defined by a 20% fall in FEV_1; five had only a late response. All developed increased sensitivity to histamine following glutaraldehyde challenge.

The pathophysiology of OA includes IgE-mediated and non-IgE-mediated immunological reactions and direct irritative injury. High molecular weight occupational agents typically induce specific IgE antibody production, which leads to airway inflammation and hyperresponsiveness.[10-12] Low molecular weight agents can induce specific IgG antibodies with airway inflammation involving activated T lymphocytes. Late asthmatic responses occur in 90% of patients with OA associated with low molecular weight sensitizing chemicals.[13] Direct irritative agents can cause airway injury with loss of the epithelial surface and airway inflammation with infiltration of both eosinophils and lymphocytes. All three pathophysiologic processes can cause airway remodeling with chronic inflammation and bronchial hyperresponsiveness. Some patients may have more than one pathological process causing airway injury and hyperresponsiveness.

Glutaraldehyde, a low molecular weight agent, may induce an immunologic response or cause a direct injury with low grade chronic airway injury. Dearman and coworkers studied the cytokine profile from cultured lymph nodes from mice treated with topical glutaraldehyde and formaldehyde.[11] The lymphocytes from glutaraldehyde-treated mice produced interleukins 4 and 10 (IL4 and IL10) but little interferon gamma (INFγ). This is a type-2 T-helper lymphocyte cytokine profile and supports the hypothesis that glutaraldehyde has the potential to cause allergic sensitization of the respiratory tract. Azadi used a mouse model to study the effect of glutaraldehyde on the induction of immediate hypersensitivity and delayed hypersensitivity.[14] Glutaraldehyde had a dose-dependent effect on the activation of lymph nodes in sites draining the topical application of glutaraldehyde. Phenotypic analysis of the lymph cells revealed IgE-positive cells; the total IgE levels were increased in blood. Higher concentrations of glutaraldehyde caused immediate ear swelling and lower concentrations caused delayed reactions at 48 hours. These studies indicate that glutaraldehyde can produce both contact dermatitis and OA and that the concentration of chemical exposure may have an important role in the resulting immune response. Takeda studied 10 patients with chronic irritant-induced asthma using both the bronchoalveolar lavage and bronchial biopsies.[15] The lavage fluid contained increased numbers of eosinophils and neutrophils in 30% and 60% of patients, respectively. There were significant increases in eosinophilic cationic protein, IL8, basic fibroblast growth factor, and matrix metalloproteinase 1 in lavage fluid. Biopsies revealed increased basement membrane thickness, epithelial detachment, and chronic inflammation.

We think our patient had OA. She did not report respiratory symptoms before working in the endoscopy center where she was exposed to glutaraldehyde for an extended period of time and then developed respiratory symptoms. The workers compensation physician ordered confirmatory testing, which yielded highly variable and unusual results. She initially exhibited a restrictive defect on spirometry with a response to bronchodilators in the FVC measurement. We suggest that she had small airway bronchospasm resulting in a high residual volume, which reversed with a bronchodilator. In the second test, an obstructive defect with a paradoxic drop in FEV_1 and FVC post-bronchodilator was noted. A reduction in the FEV_1 following forced exhalation might be explained by bronchoconstriction challenge maneuvers, namely deep inspirations with repeated forced exhalations. Another possible explanation is a paradoxic response to β-agonists, in which β_2-AR polymorphisms might alter the response to the use of β-agonists.[16] In the third trial, abnormal spirometry was recorded with some improvement post-bronchodilator therapy. This would be the typical response in OA. These three tests in a cooperative subject on treatment suggest that the location of bronchoconstriction and the response to β-agonists and airway maneuvers can vary in these patients. Consequently, pulmonary function testing may be difficult to interpret. In addition, she had normal spirometric results at her initial visits, which might lead to an incorrect assessment of her symptoms. Her serial tests provided results similar to the individual patient results in the cohort reported by Di Stefano.[9]

Glutaraldehyde remains a commonly used disinfectant. Our patient had episodic symptom and highly variable pulmonary function after prolonged exposure to glutaraldehyde in a health care worksite. These results indicate that normal results on one set of pulmonary tests may not provide an adequate understanding of the pulmonary status. A systematic study of workers with glutaraldehyde exposure with serial tests would help physicians evaluate diagnostic testing results in these cases. These fluctuations in PFT may occur in other types of OA and warrant consideration when evaluating workers.

Conflicts of Interest: None declared.

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