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## Pulmonary Function Test Trend in Adult Bronchiolitis Obliterans

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### ABSTRACT

**Background:** Some histopathologic patterns of bronchiolar disease may be relatively unique to a specific clinical entity, such as respiratory bronchiolitis caused by cigarette smoking and toxic fumes i.e. sulfur mustard (SM).

The aim of this study was to determine the trend of pulmonary function indices in SM-exposed patients with the diagnosis of bronchiolitis obliterans.

**Materials and Methods:** In this retrospective cohort study, 407 cases were evaluated. Patients were divided into 4 groups according to the time period from performing PFT: 1-3, 4-6, 7-10 and more than 10 years. The amounts of these changes amongst four PFT interval groups were compared by analysis of variance test. In addition, we used linear regression analysis to create a linear model of changes for each PFT index.

**Results:** The following equations imply a correlation between decrease in PFT indices and interval between the two tests plus index value of baseline PFT. 1:  $\Delta(\text{FVC \%}) = -2.23 - (0.76 \Delta T) - (0.23 \text{ FVC1 \%})$ , 2:  $\Delta(\text{FEV1\%}) = -1.43 - (0.95 \Delta T) - (0.10 \text{ FEV11 \%})$ , 3:  $\Delta(\text{PEF \%}) = -0.91 - (1.07 \Delta T) - (0.14 \text{ PEF1 \%})$ .

**Conclusion:** Better understanding of the nature of bronchiolitis obliterans, helps improve the treatment of this disease. Our study suggests a pattern of decline in pulmonary function indices directly proportional to the percentage of each index in the baseline PFT which was apparent during a 10-year observation period. (Tanaffos 2007; 6(3): 40-46)

**Key word:** Bronchiolitis Obliterans, Pulmonary Function Test, Sulfur Mustard

### INTRODUCTION

Bronchiolar abnormalities are relatively common and occur in a variety of clinical settings, including

infections, connective tissue diseases, other immunologic disorders, inhalational injuries, drug reactions, and allograft transplantations (1). Some histopathologic patterns of bronchiolar disease may be relatively unique to a specific clinical entity, such as respiratory bronchiolitis caused by cigarette smoking and toxic fumes i.e. sulfur mustard (SM) (2-4). To our knowledge there is little information

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regarding prognosis of patients with respiratory problems following inhalation bronchiolitis in comparison to bronchiolitis obliterans due to lung transplant. SM, a chemical warfare agent, was frequently used against Iranian troops and civilians by the Iraqi regime during the Iraq-Iran war (1980-1988) (5). Beside horrible casualties, these chemical attacks resulted in disabling chronic diseases among survivors (6). Respiratory involvement, which is shown to be the most common chronic health problem experienced by SM survivors (7), represents itself by a triad of cough, shortness of breath and sputum (8,9). Several studies have shown that the main diagnosis of long-term effect of SM on the lungs is bronchiolitis obliterans (10,11,12).

Pulmonary function tests are frequently used to assess the progression of lung disease in various respiratory conditions such as COPD following cigarette smoking or occupational exposure to noxious fumes and dusts (13). Therefore, enormous efforts have been made to measure the declining rate of pulmonary function test (PFT) values among these populations (14). The main goals of these studies were to calculate the speed of lung function loss, to find factors hastening or slowing this declining trend and consequently, to design interventional strategies to inhibit further respiratory disabilities and as a result to decrease the mortality in these patients.

In this regard, the main question of the present study is whether pulmonary function indices in SM-exposed patients, as a toxic fume induced bronchiolitis obliterans, are declining, and if so, what is the rate of PFT decrease in these patients.

## **MATERIALS AND METHODS**

In a retrospective cohort study documents were selected from veteran's organization. The study was conducted in accordance with the principles embodied in the declaration of Helsinki and the

project design was approved by the institutional ethics committee. Our estimation of the number of SM-injured patients was 5000. However, some deficiencies exist in this regard such as uncontrolled conditions in obtaining PFT from SM-exposed patients and the fact that the number of PFT records existing within each patient's file is not more than 2 or 3. Therefore, we had to implement rigid exclusion criteria to increase the validity of the study. In this regard, we decided to conduct the project as a census study of all files kept in these provinces to reach our desired sample size.

A standard questionnaire was designed. This questionnaire included history of chemical exposure and other war injuries, general medical history of the patients, history of cigarette smoking, PFT data and any abnormal lung examination finding. All spirometry tests performed during the last ten years were used to complete the questionnaire. PFTs were first reviewed by an expert physician with adequate knowledge about validity assessment of PFT records. Lung problems were divided into 3 subgroups: mild, moderate or severe based on a Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Compatibility of each PFT with our criteria was noted.

### **Inclusion criteria:**

- a) Documented evidence of chemical exposure by military health services;
  - b) Having at least 2 PFT records with an interval of more than a year;
  - c) ATS (American Thoracic Society) criteria.
- Since many spirometries had been performed under uncontrolled conditions, we pursued a very rigid manner to include only valid spirometries in our study. In this regard, we followed ATS criteria to enter cases for final analysis (15).

### **Exclusion criteria:**

All previously diagnosed patients with lung cancer, suspected cases of pneumonia or acute

infective bronchitis, history of cigarette smoking, presence of any form of malignancies or other chronic diseases were excluded from the study.

#### **Data analysis:**

While entering PFT data in the questionnaire, we also recorded the machine created predicted value of each PFT index. Therefore, we were able to eliminate the effect of age and BMI changes on PFT changes by applying the percentage of every PFT index (i.e. measured value/predicted value\*100) in our analysis.

Since the number of excluded cases were somehow much more than included cases, we made demographic analysis in both groups (included and excluded groups) to find out whether there are significant differences between the two groups (in terms of age, sex, date of SM exposure).

When analyzing the PFT data, we selected two PFTs of each patient with the longest time interval between them. In this regard, we had patients who had two PFTs with different interval times. According to these intervals, we divided our cases into 4 groups: 1-3 years, 4-6 years, 7-10 years and more than 10 years. We omitted cases with interval times less than 1 year (57 cases). As it was mentioned earlier, we used alteration of percentages of four PFT indices: FVC, FEV1, PEF and MMEF to determination of PFT trend. We compared the amount of these changes amongst our four PFT interval groups by analysis of variance test. LSD was used to obtain within group comparison. In addition, we used linear regression analysis to create a linear model of changes for each PFT index.

## **RESULTS**

### **Demographic Analysis**

A total of 2463 questionnaires were completed; among them 407 cases were included and the remaining (2056 patients) were excluded from the final analysis. All 407 included cases were males with the mean age of  $42.6 \pm 7.6$  years (Mean  $\pm$  SD).

The mean time between the first exposure to SM and this study was  $18.3 \pm 1.4$  yrs (range 15-21 years). 93.3% of patients had only one exposure to SM, 4.4% were exposed twice and 1.7% three times. 87% of patients were in an open environment when exposed to chemical attack. 39.7% of included cases had concomitant war injuries and 9.6% cases had a history of medical chronic diseases not related to respiratory system. In 35.2% of cases there was a simultaneous report of abnormal clinical findings in lung examination. According to GOLD criteria, severity of lung lesions was classified as normal spirometry group (48.6%, 198 patients), mild group (44.7%, 182 patients), moderate group (4.7%, 19 patients) and severe group (2.0%, 8 patients).

### **Excluded Cases**

Data analysis revealed a slight difference between included and excluded groups; the mean age in the included group was 42.8 (SD 7.8) years and 41.5 (SD 7.9) years in the excluded group ( $P = 0.03$ ). The mean time elapsed after exposure was 18.3 (SD 1.4) years for the included and 17.7 (SD 1.4) years for the excluded group ( $P < 0.0001$ ). Due to the large sample size in each group, especially in the excluded group, the differences between two groups were statistically significant. However they were not significant in clinical differences.

### **PFT changes amongst PFT interval groups**

The mean time between exposure and the first PFT in included cases was 9.3 (SD 2.4) years. Also, the mean time between first and second PFTs in included patients was 4.1 (SD 2.5) years. The trend of PFT changes in different PFT interval groups is shown in Figures 1-4.

Statistical tests showed that the declining differences among the four PFT interval groups were significant for FVC, FEV1 and PEF, but not for MMEF. The chronological trend of these alterations in each group is depicted in Table 1.

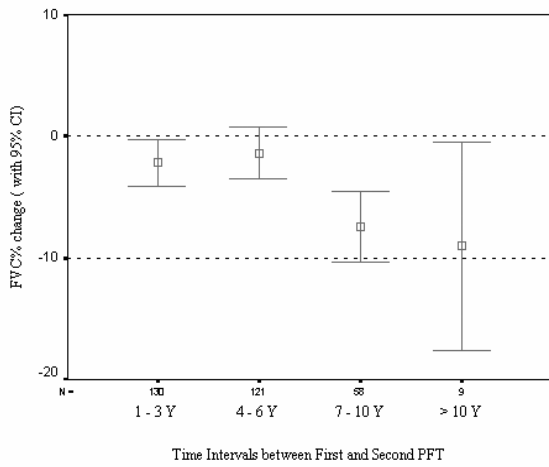


Figure 1. FVC changes in different PFT interval groups

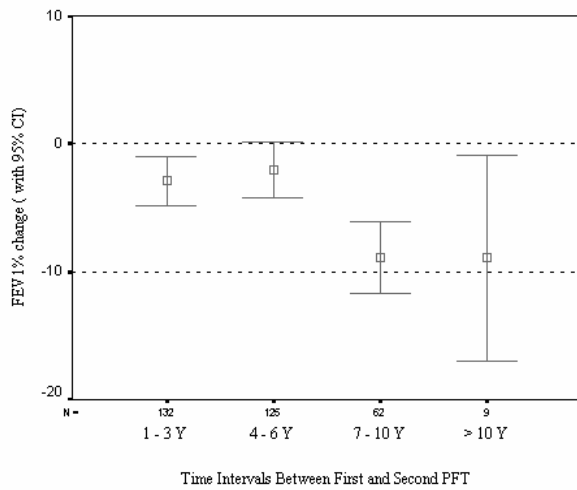


Figure 2. FEV1 changes in different PFT interval groups

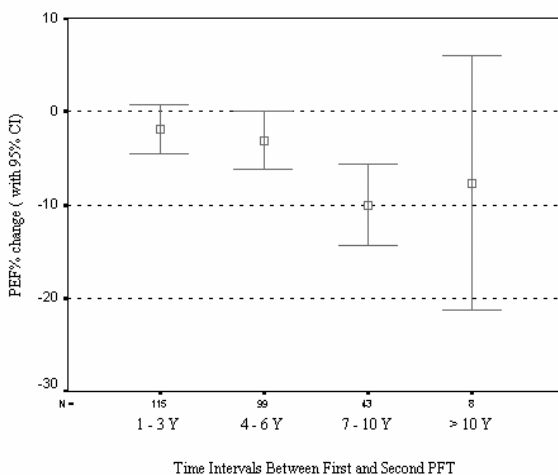


Figure 3. PEF changes in different PFT interval groups

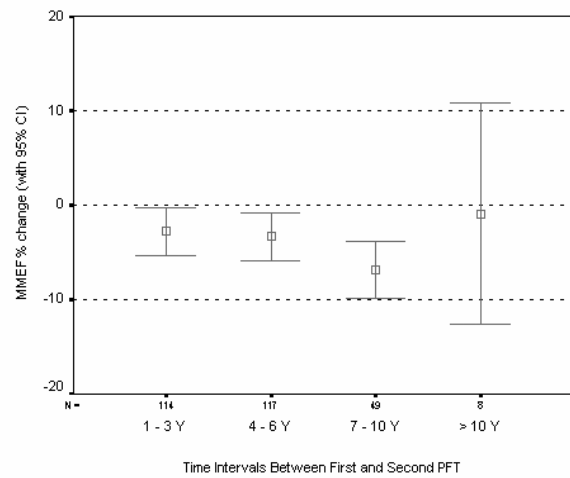


Figure 4. MMEF changes in different PFT interval groups

Table 1. Comparison of PFT changes (mean±SD) in different PFT interval groups

Interval between PFTs	1-3 years	4-6 years	7-10 years	> 10 years	p-value
FVC (L)	2.2 (±11.0)	1.4 (±11.7)	7.4 (±11.1)	9.0 (±11.1)	0.002
FEV1(L)	2.9 (±11.2)	2 (±12.4)	8.9 (±11.0)	8.9 (±10.4)	0.001
PEF(L)	1.9 (±14.3)	3.1 (±15.6)	10 (±14.1)	7.7 (±16.3)	0.018
MMEF(L)	2.8 (±13.6)	3.4 (±13.7)	6.9 (±10.6)	0.9 (±13.9)	0.3

Equations 1, 2 and 3 are linear models which imply correlation between decrease in PFT indices and the interval between the two tests plus index value of baseline performed PFT (Table 2; Δ shows changes of index percentage, ΔT shows interval between the two tests, and index 1% shows percent of index in the baseline PFT).

Table 2. Correlation between inter-PFTs interval and PFT indices.

Equation 1: $\Delta (FVC \%) = - 2.23 - (0.76 \Delta T) - (0.23 FVC_1 \%)$
Equation 2: $\Delta (FEV1\%) = - 1.43 - (0.95 \Delta T) - (0.10 FEV1_1 \%)$
Equation 3: $\Delta (PEF \%) = - 0.91 - (1.07 \Delta T) - (0.14 PEF_1 \%)$

We also analyzed the probable correlation between decrease in PFT indices and other factors

including age, place of residence, number of exposures to SM, time interval between exposure to SM and the study, time interval between the exposure to SM and first PFT, environmental situation when exposed to SM (open or closed environment), existence of nonchemical war injuries or other medical diseases and abnormal respiratory findings upon medical examination. However, we did not find any significant correlation between any of these variables and declining of PFT indices in our patients. Therefore, we omitted them from these equations.

## DISCUSSION

Bronchiolitis obliterans syndrome is the main cause of late morbidity and mortality in SM exposed patients and also in lung transplantation (11, 16). Better understanding of the nature of this syndrome can promote treatment of this disease.

A pattern of decline in pulmonary function indices directly proportional to the percent of each index in the baseline PFT was apparent over a 10-yr observation period. This effect was independent of other patients characteristics such as place of residence, number of exposures to SM, time between exposure to SM and study, time between exposure to SM and first PFT, environmental situation when exposed to SM (open or closed environment), coexistence of non-chemical war injuries or other medical diseases and abnormal respiratory findings revealed during medical examination. However, by using machine-produced predicted values in our analysis (percentage of each PFT index), we managed to eliminate effects of factors like age, sex and BMI on the changes of PFT. These data strongly support the concept that despite all therapeutic measures used for treatment, the pulmonary function of these patients still deteriorates. These observations are in agreement with our previous studies and also other works which have suggested an increased

morbidity in patients with lung complications due to SM intoxication (6,7). Zarchi et al. reported that the estimated risk of pulmonary complications from war exposure to mustard gas in soldiers who had not worn masks increased with age (9). They believe that the smoking history and frequency of gas exposure were not associated with a significant rise in the risk of lung injury; this may be explained by ambient gas concentrations and duration of exposure and temperature. Thus, smoking history and frequency of gas exposure may not be the only main risk factors, and the role of age and gas mask protection may be more important (17). Similar ailments have also been reported following accidental inhalation of other toxic fumes (18). Known causes of bronchiolitis include toxic fume inhalation, tobacco smoke, mineral dust inhalation, penicillamine, collagen vascular diseases, and infections (19). Bone marrow, heart-lung, and lung transplantation have also been associated with this complication (20). Clinically apparent infectious bronchiolitis is generally considered to be a pediatric disease, rarely being recognized in adults (21). Bronchiolitis obliterans is usually an irreversible process (in contrast to the reversibility of granulation tissue) and therefore has a strong correlation with diminished pulmonary function test indices and primary forced expiratory volume in one second. Obviously the extent of injury to the airways would have some effect on pulmonary function alterations. In the experience of the University of Pittsburgh, the response of BO patients (following lung transplant) to interventional therapy was disappointing. Approximately two thirds of the patients experienced a progressive unrelenting loss of pulmonary function which continued for several years. Currently the progressive nature of BO due to lung transplant which is also associated with significant mortality has been confirmed (22). Pathologic studies on BO patients have shown that there are two stages in the process of the disease. In

the first phase, the disease is initiated by attendant lymphocytic inflammation of the airways, which is followed by fibrous obliteration of bronchioles (23).

Another significant finding in our study is a continuous decrease in FVC of mustard-exposed patients, though with a rate less than FEV1 or PEF. This phenomenon can be explained by two mechanisms. The first is that the obstruction has led to significant air trapping, a condition which is also called pseudorestriction (13). The second is that there may be a mixed pattern with both an obstructive and a restrictive component. There are some reports that air trapping is an important finding in chest HRCT of BO patients (24). Nevertheless, since we are not aware of total lung capacity (TLC) and its trend in our patients, we should not overlook the probability of a simultaneous restrictive component.

While there is little information about PFT changes (trend) amongst SM-exposed patients, many cohort studies have been conducted about the effects of smoking and long-term exposure to air pollutants on lung function. These studies have shown more rapid deterioration in lung function in these groups (25, 26). Similar studies have been done in people who have had occupational exposure to dust and other fumes. These studies were also confirmative of accelerated decline of pulmonary function indices in these groups in comparison to the normal population (27). In comparison to these studies, our study gives us only an initial clue to design and conduct more comprehensive prospective studies to determine the precise rate of PFT decline in our patients and evaluate the role of suggested factors involved in this process. Special focus on FEV1/FVC which can distinguish obstructive pattern would be more helpful. While this was a limitation of our study it is obvious that FEV1/FVC can help future studies to study PFT changes more precisely.

In summary, we present strong evidence of a

declining trend of PFT in toxic fume-induced BO patients. Therefore, further studies are necessary to elucidate the extent of respiratory failure and consequently design effective therapeutic strategies for these patients.

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