Original Article

Annual change in spirometric parameters among patients affected in Bhopal gas disaster: A retrospective observational study

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ABSTRACT

Background: The involvement of respiratory system due to inhalation of methyl isocyanate (MIC) during Bhopal gas disaster was particularly severe. We retrospectively evaluated the annual changes in spirometric parameters among those who were affected in this disaster (exposed survivors) and had respiratory symptoms. **Materials and Methods:** Spirometry reports of exposed survivors that were carried out in our institution were retrospectively reviewed and we identified 252 subjects who had performed spirometry at least twice with interval of more than one year. The annual changes in spirometric indices of them were calculated. **Results:** The average age of study population was 55.7 years and 72% were male. Annual decline of $FEV_1 \geq 40$ ml/yr was observed among 48% exposed survivors. The mean annual decline of FEV_1 among symptomatic exposed survivors with initial normal spirometry was 91 ml (95% CI: 52 ml to 130 ml) and this was more than the patients with initial obstructive pattern. Among fifty four patients with initial normal spirometry, ten patients (18.5%) developed obstructive and two patients (5%) developed restrictive lung function abnormalities during follow up spirometry. **Conclusion:** The exposed survivors with chronic respiratory symptoms had accelerated decline in lung function and they are at higher risk of developing obstructive lung function.

KEY WORDS: Annual changes, Bhopal gas disaster, inhalational injury, Methyl isocyanates, spirometry

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INTRODUCTION

2nd December 1984 night, residents of Bhopal (capital of state Madhya Pradesh, India) experienced one of the worst chemical disasters in the world. This disaster was due to accidental leakage of approximately 40 tons of highly toxic Methyl Isocyanate (MIC) and its reaction products from nearby pesticide plant of Union Carbide Corporation.[1] It was estimated that two-third population of Bhopal was exposed to MIC during this disaster. Approximately 2000 exposed subjects died within the first 72 hours, and a large numbers survived with residual multi-organ injury especially lung.[1]

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After the disaster, epidemiological studies were carried out by different investigators to assess the effects of MIC on lung function of exposed survivors. Lung function abnormalities among them was first reported by Kamat *et al*.[2] They observed restrictive pattern in 78% cases with significant bronchodilator response in 24% of them. Other lung function studies that carried out immediately after the disasters also showed high prevalence of restrictive abnormality, subsequent studies demonstrated decline in prevalence of restrictive abnormality and reported increasing prevalence of obstructive abnormality among exposed survivors.[1-4] However, the longitudinal spirometries that were carried out during first six years after the disaster had not observed progressive deterioration in lung function.[1] The purpose of the present study was evaluation of annual changes in spirometry parameters among exposed survivors with respiratory symptoms.

MATERIALS AND METHODS

The spirometry records of exposed survivor from

pulmonary medicine department of Bhopal Memorial Hospital and Research Centre (BMHRC) during August 2001 to December 2009 were retrospectively analyzed. BMHRC was set up in year 2000 at Bhopal to provide free tertiary care to exposed survivors. The indication for spirometry was part of investigation to evaluate of their respiratory symptoms. The individual spirometry records were looked for acceptability and reproducibility. The inclusion criteria was those exposed survivors who did spirometry at least twice during this period and the interval between two test was at least more than one year apart. If anyone did spirometry more than twice, the records of first and last spirometry were included in analysis. This study was approved by the Institutional Review Board, BMHRC.

Jaeger Masterscope PC (Jaeger Co, Germany) was used for the spirometry. The highest value of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were recorded as per American Thoracic Society guideline.[5] Each patient was given two puffs of 100μg salbutamol and second spirometry was performed 15 minutes after its administration. The bronchodilator reversibility was defined as a change in FEV_1 and/or FVC of 12% and 200 ml compared with the baseline value.

Predicted values for FVC, FEV_1 and FEV_1/FVC were calculated separately for men and women based on age and height using the north Indian reference equation.[6] Lower limits of normal (LLN) for FVC, FEV_1 and FEV_1/FVC were calculated as the difference between the predicted value and 1.645 times the standard error of estimate of the regression equation.

If the FEV_1/ FVC ratio and FVC values were more than LLN then it was categorized as normal. If the FEV_1/FVC was less than the LLN then it was categorized as an obstructive pattern. If the FEV_1/FVC value was above the LLN with FVC less than LLN, then it was categorized as restrictive pattern. The severity of obstruction and restriction were classified as per American Thoracic society guideline.[7]

The enrolled subjects were categorized on four groups i.e., normal, restriction, reversible obstruction and irreversible obstruction on the basis of initial spirometric results. The intervals between the two spirometry tests were calculated in years. Annualized change in FEV_1 and FVC were obtained by subtracting the baseline evaluation from subsequent evaluation, and divide by the time in years between two evaluations. Wherever available, we used post bronchodilator value of FEV_1 and FVC for calculations. The annual decline in $FEV_1 \geq 40$ ml was defined as rapid decline in FEV_1.

The characteristics of the patients are presented as number (percentages) and mean±SD. A logistic regression model was used to determine variables responsible for rapid decline in FEV_1. Statistical analysis was carried out with SPSS for Windows version 17.0 software package (IBM).

RESULTS

We retrospectively reviewed 6195 spirometry reports of exposed survivors that were carried out during the study period and identified spirometry reports of 252 exposed survivors that meet our inclusion criteria. The age of study population was 55.7±13.2 years and 181 (71.8%) of them were male. In our cohort, 93(36.9%) were current smoker and 29 (11.5%) were former smoker and only 4.2% female had smoking history.

Abnormal spirometry was observed in 78.6% cases during initial spirometry and obstructive pattern was the commonest (68.7%) abnormality, followed by restrictive pattern (9.9%). The characteristics of study population are compared according to spirometry results in Table 1. Smoking habit was not different across the different spirometric groups. The distributions of severity of obstruction during initial visit were as follows: Mild 48 (28.1%), moderate 21 (12.3%), moderately severe 29 (17%), severe 49 (28.7%) and very severe 24 (14%). The distributions of severity of restriction were as follows: Mild 4 (16%), moderate 7 (28%), moderately severe 7 (28%), severe 5 (20.0%) and very severe 2 (8%).

The median interval between initial and last spirometry of study population was 3.05 years (range, 1.01 to 8.14 years). No changes in pattern of spirometric abnormality were observed in 195 (77.4%) cases during median follow up of 3.1 years. During follow-up (median duration, 3.0 yrs), new airflow obstruction was developed among 19 (7.6%) patients, out of them 10 had initial normal spirometry and 9 had initial restrictive pattern. New restrictive abnormality was developed among 5 (2%) patients with initial normal spirometry during median follow up of 4.1 years. Twenty one patients (8.3%) with obstructive pattern became normal with treatment and 11 (4.4%) developed mixed pattern during 3.4 years of follow up. The annual changes in FEV_1 across the different spirometric abnormalities were shown in Figure 1. The mean annual decline in FEV_1 among exposed survivors with initial normal spirometry, restrictive pattern, reversible obstruction and irreversible obstruction was 91 ml, 18 ml, 5 ml and 27 ml respectively. The mean annual decline in FEV_1 exceeded the annual decline of FVC among exposed survivors with initial normal spirometry and restrictive pattern, indicates these patients are at risk for developing obstructive pattern [Table 2]. The annual decline in FEV_1 and FVC were more among patients with irreversible obstruction than reversible obstruction and patients with irreversible obstruction were at higher risk of developing mixed pattern. The annual decline in FVC are shown in Figure 2.

The influence of age group (<40, 40-60 years and >60 years), sex, change of BMI during two visit, smoking habit and initial FEV_1 on accelerated decline in FEV_1 (≥40ml/year) were examined separately for different spirometric groups by step wise multiple logistic regression

Table 1: Comparison of baseline characteristics of study population according to spirometry result[#]

Variables	Normal (*n*=54)	Restriction (*n*=25)	Reversible obstruction (*n*=111)	Irreversible obstruction (*n*=60)
Age, yr	51.8±12.2	59.4±14.2	54.9±13.9	59.3±11.0
Male (%)	42 (77.8)	15 (60.0)	78 (70.3)	45 (75)
BMI, kg/m^2	24.3±5.5	25.3±5.4	22.5±5.2	21.3±5.4
Never smoker	29 (53.7)	16 (64.0)	54 (48.6)	29 (48.3)
Former smoker	4 (7.4)	3 (12.0)	13 (11.7)	9 (15)
Current smoker	21 (38.9)	6 (24.0)	44 (39.6)	22 (36.7)
Annual decline in FEV_1 ≥40 ml	33 (61.1)	13 (52.0)	43 (38.7)	30 (50)
Annual improvement in FEV_1>20 ml	10 (18.5)	8 (32)	34 (30.6)	18 (30)

[#]bronchodilator response was not assessed in 2 cases of obstructive pattern

Table 2: The mean annual change of spirometric parameters in different groups

Variables	Normal	Restriction	Reversible obstruction	Irreversible obstruction
Change in FVC, ml/yr	-84 (-134 to -34)	45 (-50 to 139)	2 (-31 to 34)	-48 (-102 to 7)
Change in FEV_1, ml/yr	-91 (-130 to -52)	-18 (-75 to 40)	-5 (-35 to 25)	-27 (-66 to 12)

Data are presented as mean (95% confidence interval)

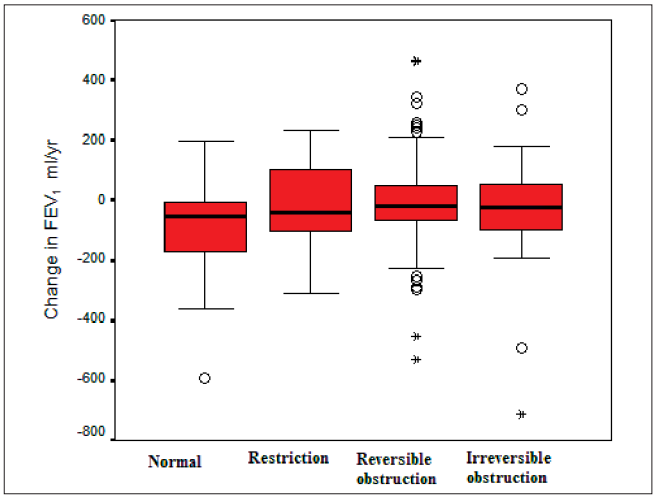

Figure 1: Box-and-whisker plot of annual changes in FEV_1 in different spirometric groups

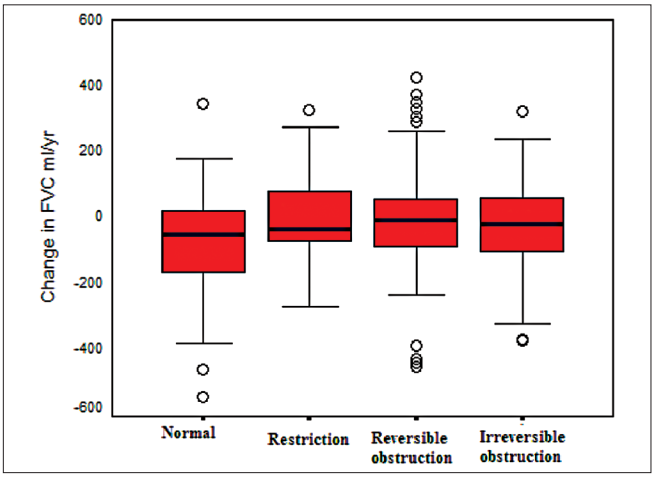

Figure 2: Box-and-whisker plot of annual changes in FVC in different spirometric groups

analysis. No relationship between these variables in either spirometric group was observed.

DISCUSSION

This retrospective study was carried out to assess the annual change in FEV_1 and FVC among exposed survivors of Bhopal Gas Tragedy who had respiratory symptoms and were evaluated by repeat spirometry during their visit to BMHRC.

In healthy individuals, FEV_1 increases up to age of 25 years and then gradually decline. Genetic factors contribute modestly to the overall population variance in rate of lung function decline.[8] Community based study had demonstrated the mean rates of decline in FEV_1 for 50-year old male and female never smokers were 27.9±2.8 mL/yr and 22.1±0.9 mL/yr respectively.[9] In our study, the mean annual decline in FEV_1 among patients with initial normal spirometry was more than this. Cigarette smoking is an important exogenous risk factor for rapid decline in lung functions. FEV_1 decline approximately 10 to 13 ml/yr and FVC 8 to 11ml/yr for each pack per day of smoking.[8] Smoking cessation reduces the smoking induced accelerated decline of FEV_1. Lung Health Study had demonstrated a significant improve of FEV_1 during the first year after smoking cessation among sustained quitters, followed by a steady decline as compared to never-smokers.[10] The annual rate of decline in FEV_1 among intermittent quitters was intermediate between that of sustained quitters and those who continued smoking. The rate of decline in FEV_1 among mild-to-moderate chronic obstructive pulmonary disease (COPD) patients who continued smoking are only influenced when smoking amount is reduced ≥85%.[11] In our study, smoking amount was not recorded in spirometry reports. Some exposed survivors changed their smoking habit in between two spirometric evaluations and some possibly had also changed their smoking amount. This may be the reason for which we failed to observe the effect of smoking on rate of change in spirometric parameters.

The airflow obstruction develops gradually over a long period and small change in FEV_1 may be obscured by either

biological variation or measurement error. Larger changes in FEV_1 can be identified by 1-2 years of monitoring and longer follow up is required to correctly identify the small changes.[12] Rescue workers of New York Fire Department were exposed to dust and combustion/pyrolysis products during World Trade Center collapse. During first year, the FEV_1 decreased significantly for all workers and the mean fall was 439 ml.[13] Longitudinal follow up spirometry documented elevated rate of spirometric abnormalities and rapid decline in lung function among them.[13] These declines were persistent and not recovered during next six years and leaving a substantial proportion of workers with abnormal lung function. So, acute severe inhalational injury even by dust was sufficient to cause progressive accelerated deterioration of lung function. Earlier studies had demonstrated acute deterioration of lung function among exposed survivors following acute and massive exposure to MIC.[1-3] But, no further deterioration of lung function among 119 very severely affected exposed survivors was observed during five year follow up from 1985 to 1990.[1] Misra *et al.* evaluated pulmonary function of 250 exposed survivors from 1984 to 1989 and observed no changes in FEV_1 and TLC till the end of study.[1] However, FVC were improved significantly at second year and subsequently no further changes were detected. So, progressive decline of lung function among exposed survivors was not observed in previous longitudinal studies. Our study documented accelerated annual decline of FEV_1 (≥40 ml/year) among 33 (61%) symptomatic exposed survivors with initial normal spirometry and 18.5% of them developed obstructive airway disease during follow up. The study of World Trade Centre collapse showed that the intensity of the initial inhalational exposure was critical determinant of acute inflammation and early reductions in lung function; however, the long-term course was more related to the population that was exposed than to the exposure.[13] The severity of exposure to MIC may not be the only responsible factor for progressive deterioration of lung function for which meticulously designed earlier studies failed to demonstrate the decline among severely exposed survivors. The individual susceptibility of exposed population probably played an important role for which we observed the rapid decline of lung function among exposed survivor with respiratory symptoms.

The development of COPD or bronchial asthma accelerates the annual decline of FEV_1. Longitudinal study demonstrated statistically significant decline of FEV_1 among adult asthmatics (38 mL/yr) as compared to non asthmatics (22 mL/yr).[14] Three year follow up study had documented the rate of annual decline in post bronchodilator FEV_1 among COPD patient is 33 ± 2 ml.[15] We classified annual decline in FEV_1 ≥ 40 ml as rapid decline in FEV_1 to compare our result with COPD patients. During 3-year follow up, Vestbo *et al.,* observed that 38% COPD patients had annual decline of FEV_1 ≥ 40 ml and 8% had increase in FEV_1 > 20 ml while on treatment.[15] We observed similar decline in FEV_1 among 43% and similar improvement in FEV_1 among 30% exposed survivors with obstructive airway disease. The improvement in FEV_1 among more exposed survivors was possibly due to inclusion of reversible airflow obstruction i.e. bronchial asthma. The FEV_1 in obstructive airway disease improves with treatment of inhaled corticosteroid (ICS) therapy due to anti-inflammatory effects of ICS. ICS reduces the percentage of neutrophils and other inflammatory cells in bronchial lavage fluid.[16] An abnormal accumulation of inflammatory cells (lymphocytes and neutrophils) in bronchoalveolar lavage fluid of exposed survivors and its correlation with the intensity of lung inflammation and reduction in pulmonary function had been demonstrated.[17] In our study, exposed survivors with obstructive airway disease were treated with ICS, inhaled short and long acting bronchodilator and oral theophylline. So, the treatment with these medications produces annual change in FEV_1 similar to COPD patients. Mishra *et al.,* observed annual decline in FEV_1 more than 50 ml among 20% exposed survivors with irreversible obstruction; out of them 17 (73%) were non-smokers and 50% had history of severe MIC exposure.[1] At least 20% of their cohort developed irreversible airflow obstruction and 12% cases developed bronchial asthma during follow-up. More number of exposed survivors (43%) with irreversible obstruction in our study demonstrated similar decline in FEV_1 while on treatment.

The annual decline in FVC varied from 43 ml to 54 ml depending upon smoking habit.[18] In our cohort, the mean annual decline of FVC (84 ml/yr) among symptomatic exposed survivors with normal spirometry was more than this. The etiology of development of new restrictive abnormalities among exposed survivors were postulated due to MIC induced inflammation of airways and alveoli with subsequent healing of injury resulted in alveolo-pleural fibrosis and constricting lesions in smaller airways and leaving behind residual scars in lungs.[1] Like earlier studies,[1] we also failed to demonstrate any accelerated annual decline of FVC among exposed survivors with restrictive pattern, indicating non-progressive nature of restrictive abnormality.

Our study had major limitations which includes the potential for selection bias as the study was hospital based and only symptomatic subjects were enrolled. The number of subjects was small and their exposure to MIC history based on their address during the accident was not collected. The wide variability in annual decline in spirometric parameters may be due to variable severity of exposure to MIC. Total lung capacity and carbon monoxide diffusing capacity are most useful to quantify the progression of restrictive abnormality and these were not carried out in this study. No long-term follow up study has been carried out to evaluate the annual decline in FEV_1 and FVC among Indian population and we didn't have non-MIC exposed cohort in our study to compare. This study was retrospective in nature and hence the intervals between the two spirometry were variable. The periodic

monitoring of lung function will be able to identify the subjects with accelerated decline in lung function and possible risk factors. The spirometric marker of smaller airway function i.e., $MEF_{25-75\%}$ were effort dependent and hence not analyzed in this study.

Our study documented exposed survivors with respiratory symptoms demonstrated accelerated annual decline in lung function and they are at higher risk for developing obstructive airway diseases. The treatment with inhaled corticosteroid and bronchodilator reduces decline in FEV_1 among exposed survivors with obstructive airway disease especially reversible obstruction. Longitudinal study involving large number of symptomatic exposed survivors will be useful to identify the risk factors for developing obstructive airway disease.

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