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Retrospective analysis of lung function abnormalities of Bhopal gas tragedy affected population

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***Background & objectives*: A large numbers of subjects were exposed to the aerosol of methyl isocyanate (MIC) during Bhopal gas disaster and lung was one of the most commonly affected organs. The aim of the present study was to analyze retrospectively the lung function abnormalities among the surviving MIC exposed population (gas victims) and to compare it with the non-MIC exposed (non gas exposed) population.**

***Methods*: The spirometry data of both gas victims and non gas exposed population who attended the Bhopal Memorial Hospital & Research Centre for evaluation of their respiratory complaints from August 2001 to December 2009, were retrospectively evaluated and compared.**

***Results*: A total 4782 gas victims and 1190 non gas exposed individuals performed spirometry during the study period. Among the gas victims, obstructive pattern was the commonest (50.8%) spirometric abnormality followed by restrictive pattern (13.3%). The increased relative risk of developing restrictive abnormality among gas victims was observed in 20-29 yr age group only (adjusted relative risk: 2.94, *P*<0.001). Male gas victims were more affected by severe airflow obstruction than females and the overall increased relative risk (1.33 to 1.45, *P*<0.001) of developing obstructive pattern among gas victims was observed.**

***Interpretation & conclusions*: The present study showed that the relative risk for pulmonary function abnormalities in gas victims was significantly more among those who were young at the time of disaster. Increased smoking habit among gas victims might have played an additive effect on predominance of obstructive pattern in spirometry.**

Key words Bhopal gas tragedy - Lung function - MIC - spirometry - obstructive - respiratory

In December 1984, the residents of Bhopal at Madhya Pradesh, India experienced one of the worst chemical disasters of the world. The exact nature of the toxic substance responsible for this disaster is disputed and multiple chemical substances are attributed[1]. It is suspected that the disaster was mainly due to leakage of methyl isocyanate (MIC), an intermediate product in the manufacturing of carbamate pesticide from the Union Carbide plant. The MIC aerosol was also super-added with its pyrolytic products *i.e*. hydrogen cyanide, nitrogen oxides and carbon monoxide and contaminants such

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as phosgene and monomethylamine which were also used for manufacturing of MIC[2].

Eyes and respiratory system were mainly affected by the MIC. Acute respiratory symptoms were primarily due to inhalation of volatile and irritant fumes of MIC causing severe necrotizing lesions on the lining of the upper and lower respiratory tract[3]. Most of the immediate deaths after the disaster were due to involvement of lung. Within 5 days of the disaster, more than 3800 deaths were occurred and the rest became disabled[4].

Various studies have documented the high incidence of respiratory morbidity among the surviving population (gas victims) due to single high level exposure of MIC[5,6]. Chronic inflammation of the respiratory tract is attributed for the long-term morbidity and respiratory function abnormality. Study conducted within a few months after the disaster had demonstrated the presence of bronchiolitis obliterans[5]. Subsequent study reported the presence of pulmonary fibrosis that was also confirmed histopathologically by the presence of interstitial pneumonia in autopsy sample[3,6]. One year after the disaster, Rastogi *et al*[7] evaluated spirometry of gas victims and observed that the mixed pattern was the commonest lung function abnormality.

Ten years after the disaster, Cullinan *et al*[8] assessed the respiratory morbidity in surviving population. After this study, no study was carried out to evaluate the extent and nature of long-term sequelae of MIC on respiratory system. Bhopal Memorial Hospital and Research Centre (BMHRC), a multi-specialty centre was set up in 2000 to provide tertiary care facility to the gas victims as well as to non MIC exposed population. Approximate 3,80,000 gas victims are registered with this hospital for free treatment and these patients are first evaluated at the primary care level in the eight mini units (satellite health centres) spread around the city and then referred to specialized departments of BMHRC, if required.

The purpose of the present study was to analyze the patterns of lung function abnormalities among gas victims (surviving MIC exposed individuals) and to compare with the non-MIC exposed population (non gas exposed).

Material & Methods

The records of spirometry data of gas victims and non gas exposed subjects from the Pulmonary Medicine department of BMHRC that were done as part of evaluation of their respiratory complaints from August 2001 to December 2009, were analyzed retrospectively. The non gas exposed individuals included both the MIC unexposed population of Bhopal and also the surrounding areas. Only the acceptable and reproducible spirometric data were included in the analysis. If spirometry was performed more than once on a subject during this period, initially performed spirometric recording was included in data analysis. This study was approved by the local ethics committee.

Study population: Age, gender, height, weight, smoking status and spirometry results were noted from the records. The indications for spirometry were as part of evaluation of their respiratory symptoms.

Pulmonary function test: Jaeger Masterscope PC (Jaeger Co, Germany) was used for the spirometry and it was calibrated daily before use. Three acceptable and at least two reproducible maximal expiratory flow volume curves were obtained from each subject and the highest forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were recorded as per American Thoracic Society guideline[9]. Each patient was given two puffs of salbutamol (200 µg) and second spirometry was performed 15 min after the administration of salbutamol. The bronchodilator reversibility was defined as change of FEV_1 and/or FVC 12 per cent and 200 ml compared with the baseline value.

Predicted values for FVC, FEV_1 and FEV_1/FVC were generated separately for men and women based on age and height using the north Indian reference equation[10]. 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. Any observed value lower than its corresponding LLN was considered abnormal. If the FEV_1/ FVC ratio and FVC values were more than LLN, these were categorized as normal pulmonary function.

If the FEV_1/FVC was less than the LLN, it was categorized as an obstructive pattern and the severity of obstruction was classified as per American Thoracic Society (ATS/ERS) guideline[11] *i.e.* mild obstruction if predicted >70, moderate if 60-69, moderately severe if 50-59, severe if 35-49 and very severe if FEV_1% predicted <35.

If the FEV_1/FVC value was above the LLN with FVC less than LLN, then it was categorized as restrictive pattern. American Thoracic Society guideline recommended that if the total lung capacities were not measured in restrictive pattern, the severity of restriction can be classified on the basis of largest value of FVC (pre- or post-bronchodilator FVC)[9]. Classification of severity of restriction was as follows: mild if % FVC is <LLN but >70 per cent; moderate if %FVC <70 and >60; moderately severe if %FVC <60 and >50; severe if %FVC <50 and >34, and very severe if %FVC <34.

Reversibility tests were not performed in 53 obstructive patterns and these cases were excluded while analyzing the reversibility of obstruction.

Statistical analysis: The SPSS for Windows version 9.0 software package (SPSS Inc, Chicago IL, USA) was used for statistical analysis. The study population was categorized in six age groups. For each age group, adjusted relative risks of developing restrictive and obstructive pattern in spirometry were computed by logistic regression analysis and $P<0.05$ was considered significant.

Results

A total of 7412 spirometry procedures were performed in our pulmonary function laboratory between August 2001 and December 2009. After excluding the unacceptable and repeat tests, 5972 spirometry were included in the analysis. Of the 4782 gas victims who performed spirometry during this period, 3324 (69.5%) were males (Table I).

Obstructive pattern was the commonest abnormality observed in 2430 (50.8%) cases, restrictive pattern in 638 (13.3%) cases and normal spirometry was observed in 1714 (35.8%) cases. Irreversible and reversible obstruction was seen in 24 and 26.8 per cent, cases, respectively.

A total of 1190 non gas exposed individuals and 770 were male (64.7%) performed spirometry during the same period. Obstructive pattern was the commonest abnormal pattern among this group also and was observed in 515 (43.3%) cases, restrictive

Table I. Demographic characteristics of the study population

	Male (%)		Female (%)	
Age groups (yr)	Gas victims	Non gas exposed	Gas victims	Non gas exposed
10-19	38 (1.1)	55 (7.1)	27 (1.9)	27 (6.4)
20-29	206 (6.2)	74 (9.6)	129 (8.8)	58 (13.8)
30-39	298 (9.0)	98 (12.7)	201 (13.8)	80 (19.0)
40-49	537 (16.2)	116 (15.1)	327 (22.4)	79 (18.8)
50-59	749 (22.5)	153 (19.9)	337 (23.1)	68 (16.2)
60+	1496 (45)	274 (35.6)	437 (30.0)	108 (25.7)
Total	3324 (100)	770 (100)	1458 (100)	420 (100)

Table II. Prevalence of smoking habit of the study population according to age#

Age group (yr)	Type of patients	Non smoker (%)	Ex-smoker (%)	Current smoker (%)
10-19	Gas victims	63 (96.9)	-	2 (3.1)
	Non gas exposed	81 (98.8)	-	1(1.2)
20-29	Gas victims	273 (81.5)	3 (0.9)	59 (17.6)
	Non gas exposed	112 (86.8)	2(1.6)	15 (11.6)
30-39	Gas victims	375 (75.2)	22 (4.4)	102 (20.4)
	Non gas exposed	148 (83.6)	6 (3.4)	23 (13.0)
40-49	Gas victims	582 (67.4)	56 (6.5)	226 (26.2)
	Non gas exposed	137 (70.3)	12 (6.2)	46 (23.6)
50-59	Gas victims	588 (54.2)	115(10.6)	382 (35.2)*
	Non gas exposed	128 (57.9)	31 (14)	58 (26.2)
60+	Gas victims	830 (43.0)	291 (15.1)	810 (41.9)*
	Non gas exposed	234 (61.9)	56 (14.8)	86 (22.8)
Total	Gas victims	2711(56.7)	487 (10.2)	1581 (33.1)*
	Non gas exposed	840 (71.1)	107 (9.1)	229 (19.4)

*$P<0.001$ compared to non gas exposed individuals in the same age group, # Smoking history was not captured in seven cases

pattern in 163 (13.7%) cases and normal spirometry was observed in 512 (43%) cases.

Forty three per cent gas victims (59.4% male and 6.4% female) were either active or ex-smoker and obstructive pattern was observed in (48.6%) of them. The age wise distribution of smoking status among study population showed that the gas victims especially those 50 yr or more of age were more active smoker (P<0.001) than the non gas exposed individuals of same age (Table II).

The age wise distributions of different spirometric abnormalities of study population were compared (Table III). The relative risk with 95 per cent confidence interval (CI) of developing different spirometric abnormalities among gas victims were assessed by logistic regression analysis. No overall increase in relative risk for developing restrictive abnormality among gas victims was observed except for 20-29 yr age group (adjusted relative risk: 2.94, P<0.001). The overall adjusted relative risks of developing reversible and irreversible obstruction among gas victims were 1.45 (95% CI 1.23 to 1.71, P<0.001) and 1.33 (95% CI 1.12 to1.58, P<0.001) respectively.

The distribution of severity of restriction among gas victims were as follows: mild 29.3 per cent, moderate 30.7 per cent, moderately severe 22.1 per cent, severe 13.8 per cent and very severe 4.1 per cent. The severity of obstruction among the gas victims were: mild 19.5 per cent, moderate 13.1 per cent, moderately severe 15.6 per cent, severe 26.7 per cent and very severe 25.1 per cent.

Among the gas victims, presence of mild restriction and severe obstruction (reversible or irreversible) were more among males than in females (Figs 1 & 2). The obstructive pattern remained the predominant spirometric abnormalities among the newly registered gas victims during the entire study period.

Discussion

Immediately after the disaster and during the subsequent years epidemiological studies were carried out to evaluate the respiratory symptoms and spirometric abnormalities among the surviving gas victims. Kamat *et al*[12] carried out spirometry on 113 persistently symptomatic gas-victims between 7 to 90

Table III. Comparison of different spirometric abnormalities of study population according to age group#

Age group (yr)	Type of patients	Normal (%)	Restriction (%)	Reversible obstruction (%)	Irreversible obstruction (%)
10-19	Gas victims	25 (44.6)	14 (25)	10 (17.9)	7 (12.5)
	Non gas exposed	33 (46.5)	23 (32.4)	6 (8.5)	9 (12.7)
	RR (95% CI)	1	0.85 (0.38 to1.92)	2.22 (0.76 to 6.33)	1.41 (0.52 to 3.78)
20-29	Gas victims	182 (52.9)	55 (16)	71 (20.6)	35 (10.2)
	Non gas exposed	94 (65.7)	9 (6.3)	22 (15.4)	17 (11.9)
	RR (95% CI)	1	2.94 (1.39 to 6.22)*	1.60 (0.92 to 2.78)	0.96 (0.50 to 1.85)
30-39	Gas victims	245 (49.1)	63 (12.6)	123 (24.6)	65 (13)
	Non gas exposed	109 (61.2)	19 (10.7)	24(14.5)	26 (14.6)
	RR (95% CI)	1	1.48 (0.84 to 2.58)	2.28 (1.39 to 3.73)*	1.11 (0.67 to 1.85)
40-49	Gas victims	363 (42.0)	112 (13.0)	232 (26.9)	147 (17.0)
	Non gas exposed	81 (41.5)	23 (11.8)	50 (25.6)	41 (21.0)
	RR (95% CI)	1	1.09 (0.65 to1.80)	1.04 (0.70 to 1.53)	0.80 (0.53 to1.22)
50-59	Gas victims	376 (34.6)	173 (15.9)	279 (25.7)	247 (22.7)
	Non gas victims	85 (38.5)	32 (14.5)	53 (24.0)	51 (23.1)
	RR (95% CI)	1	1.22 (0.78 to 1.91)	1.19 (0.82 to 1.73)	1.10 (0.75 to1.61)
60+	Gas Victims	524 (27.1)	220 (11.4)	568 (29.4)	599 (31.0)
	Non gas victims	110 (28.8)	57 (14.9)	109 (28.5)	103 (26.9)
	RR (95% CI)	1	0.81 (0.57 to 1.16)	1.09 (0.82 to 1.46)	1.22 (0.91 to1.64)
Total	Gas victims	1715 (35.9)	637 (13.3)	1283 (26.8)	1100 (23)
	Non gas victims	512 (43)	163 (13.7)	264 (22.2)	247 (20.8)
	RR (95% CI)	1	1.17 (0.96 to 1.42)	1.45 (1.23 to 1.71)*	1.33 (1.12 to1.58)*

RR= Adjusted relative risk, CI= confidence interval; *P<0.001. #For each age group, adjusted relative risk was computed using logistic regression analysis

Fig. 1. Sex wise distribution of severity of restriction.

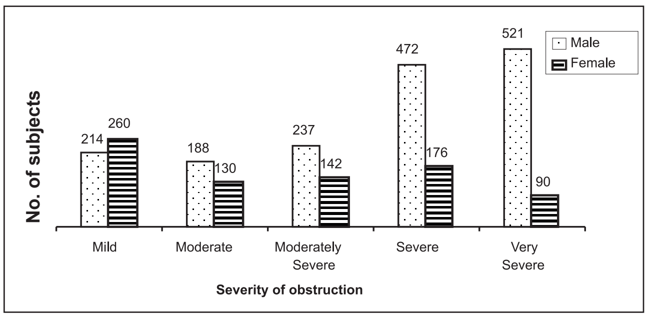

Fig. 2. Sex wise distribution of severity of obstruction.

days after the disaster and found no significant changes in FVC and FEV_1 during the three months follow up. The same group[13] evaluated spirometry of 82 subjects between 7 and 53 days after the disaster and observed restrictive pattern in 78 per cent cases. Four weeks after the disaster, Bhargava *et al*[14] conducted spirometry on 224 gas victims and observed normal spirometry in 56.3 per cent, obstructive pattern in 10.7 per cent, restrictive and mixed pattern in 17 per cent and 16 per cent, respectively.

Fifteen weeks after the disaster, Naik *et al*[15] carried out spirometry of 326 subjects who were residing within 0.5-2 km from the Union Carbide plant. Restrictive pattern was observed as the commonest abnormality (49.1%), followed by obstructive pattern (21.2%). During the same period, another group evaluated spirometry in pediatric population residing within 2 km and 8-10 km from the factory and observed obstructive pattern in 84.8 and 66.6 per cent of cases, respectively[16]. A study conducted on 1109 gas victims in 1985 found abnormal findings on chest X-ray in 4.3 per cent due to exposure to MIC[17].

Acquilla *et al*[18] conducted spirometry on 476 subjects and observed abnormalities of FVC, FEV_1 and FEV_1/FVC ratio in 15.5 per cent cases. Dhara *et al*[19] in 1994 had evaluated the exposure-response relationship among 1618 gas victims and observed largest difference in FEF_{25-75} between high and low exposed groups.

Several studies were carried out by various investigators from 1985 to 1994[20,21]. Within three months after the disaster, spirometry of 129 symptomatic patients residing within 2 km from the Union Carbide plant was done. Using the cut-off points 75 per cent for FVC and FEV_1/FVC, spirometry data showed 55.8 per cent had normal, 10.1 per cent had obstructive pattern, 12.4 per cent had restrictive pattern and 21.7 per cent had mixed pattern. In another study 119 very severely affected gas victims were evaluated and 22.2 per cent had restrictive, 11.8 per cent had obstructive and 25.2 per cent had mixed pattern (based on 75% as the cut-off point for FVC and FEV_1). These patients were first followed after 6-12 months and then at 4-5 years after the initial visit and no further deterioration of lung function was detected. From mid October 1985 to April 1988, spirometry of 4938 gas victims showed normal spirometry in 36 per cent cases, restrictive pattern in 50 per cent cases, obstructive pattern in 7 per cent cases and mixed pattern in 7 per cent cases (cut-off point between normal and impaired lung function was 80% of predicted). No deterioration in spirometric abnormalities was observed among severely affected gas victims during five year follow up.

The last study that evaluated the respiratory morbidity of gas victims was conducted by Cullinan *et al*[8] in 1995. They evaluated spirometry of 74 subjects and observed that FVC, FEV_1, FEV_1/FVC ratio and FEF_{25-75} were reduced due to exposure of MIC. They did not categorize the pattern of spirometric abnormality, but observed that obstructions were mostly irreversible[8].

The studies that were carried out more than one year after the disaster documented the reduction in prevalence of restrictive pattern[20]. The prevalence of restrictive disorders across the studies were variable due to use of different cut off value of FVC. The distributions of severity of restrictive pattern in our study was similar to an earlier study[15]. The increased relative risk of restrictive abnormality among gas victims was limited in 20-29 yr age group only. So, the gas victims who were infants at the time of disaster were possibly more affected by the residual fibrotic changes in lung. Infant mortality rate among gas victims was high in initial two years. Subsequently, the mortality rate among >50 yr of age was increased[21]. The gas victims who were exposed to massive to sub-massive MIC developed severe restrictive defects *i.e.*

interstitial lung disease and probably died within a few years of the disaster. The gas victims with restrictive abnormalities in present study might have exposed to lesser amount of MIC and thus no overall increase in relative risk for development of restrictive pattern was observed. Earlier studies also failed to detect any further deterioration of lung function during follow up[20,21]. The registrations of new restrictive abnormalities remained static throughout our nine year study period suggesting that restrictive defects were possibly non progressive.

The prevalence of obstruction in gas victims varied from 10.1 to 21.2 per cent[14,15,20]. We observed obstructive pattern in 50.8 per cent gas victims and among whom 51.8 per cent were suffering from severe to very severe obstruction and 29.3 per cent had mild obstruction. So, the present study showed that with the passage of time, both the incidence and the severity of obstruction among gas victims had increased. The overall relative risks of developing reversible and irreversible airflow obstruction among gas victims were 1.45 and 1.33, respectively. These observations suggest that the gas victims irrespective of their age are at higher risk of developing obstructive lung disease. Without any pre-existing respiratory illness, single exposure to high levels of an irritating vapour, fume, or smoke may cause asthma like symptoms known as reactive airways dysfunction syndrome (RADS)[22]. The increased relative risk for reversible obstructive pattern in 30-39 yr age group are may either be due to development of RADS as a consequence of MIC inhalation or MIC might have reactivated the latent asthma or worsened the pre existing asthma[23].

Smoking is an important risk factor for developing airflow obstruction; 9.9 per cent gas victims were found to be smoker during the survey conducted by ICMR in 1985[21]. Earlier studies failed to observe any effect of smoking on pulmonary function[7,19,20]. In the present study, 43.3 per cent gas victims were current or ex-smokers, and smoking was significantly more among those >50 yr age. Our study also showed a significant relationship between smoking and presence and severity of obstruction ($P<0.001$).

Socio-economic status is a known risk factor for the development of airflow obstruction[24]. In 1985, the monthly income of 96 per cent gas victims was below ₹ 300/month, and only 1.25 per cent earned more than ₹ 1000/month and 73 per cent had no occupation[21]. Gupta *et al*[17] also reported that per capita income 89.5 per cent gas victims was ₹ 300/month or less. So the poor socio-economic status might also played a role in development of predominance of obstructive pattern among the surviving gas victims.

Rastogi *et al*[7] observed more respiratory impairments in female population. Present study showed that the restrictive defects were more common in males than in females, but as the severity of restriction increased, the difference of prevalence between males and females were lost. In case of obstructive defects, severe obstructions were more among males than in females and this could be possibly due to additive effect of smoking.

The use of reference equations for Caucasian leads to misinterpretation of spirometric data in a significant proportion of Indian population[25]. There is no uniform predicted equation for the Indian population. In comparison to north Indian reference equation for spirometry, the south Indian and west Indian reference equation under predict the LLN of FEV_1 and FVC and hence we had used north India reference equation in our study[10]. Lower limit of FEV_1/FVC 70 per cent results in a significant false-positive result in male >40 yr of age and female >50 yr age and there is increased risk of over-diagnosis of obstruction in asymptomatic elderly never-smoker subjects[26,27]. Use of different cut-off value and reference equations leads to variable interpretation of spirometry. Previous studies had used the value of FEV_1 and FVC less than 75 or 80 per cent of predicted as abnormal. In the present study, the predicted equation for north Indian was used to define the normal and LLN of FVC, FEV_1 and FEV_1/FVC and thus reduced the risk of over diagnosis.

The limitation of this study was that the study population was hospital based and only those who had respiratory symptoms were evaluated. The collection of spirometric data was started 16 yr after the disaster and severely affected gas victims might have died by then or were incapable to visit this hospital due to severity of their disease status. During the long interval between the disaster and data collection, many affected individuals might have migrated out. The actual recall of the disaster after 16 yr was difficult and thus the exposure history might be unreliable. To avoid the recall bias, the exposure-effect relationship was not attempted. The presence of RADS among the patient with normal spirometry and chronic respiratory symptoms was not evaluated in present study. The hospital had no paediatrics department, so very few paediatric patients were enrolled in study. The socio-economic status of the study population was not collected. Even excluding smoking status and advanced lesion on chest X-ray, previous history of pulmonary tuberculosis is a risk factor for developing obstructive pattern in spirometry. Some of our study population had prior pulmonary tuberculosis, but the effect of tuberculosis on lung function was not explored.

The diagnosis of restrictive defects in present study was based on the results of spirometry. In spirometry, reduced vital capacity with a normal or even slightly increased FEV_1/FVC may be observed due to sub maximal effort or patchy airflow obstruction. The predictive value of spirometric diagnosis of restriction *i.e.* FVC < LLN and $FEV_1/FVC \geq$ LLN varies from 26.3 to 73.9 per cent[28]. Thus, the confirmation of restrictive defect requires the measurement of total lung capacity (TLC) and that was not measured in all cases of our restrictive pattern. So, all mild restrictive patterns observed in the present study might not have the actual restriction.

A mixed pattern in spirometry is co-existence of both obstructive and restrictive defects and is characterized by reduction of both FEV_1/FVC and TLC below the 5th percentiles of predicted values. FVC can be reduced in both obstructive and restrictive defects. So the presence of a restrictive component in obstructive pattern required measurement of TLC by body plethysmography. Since TLC was not evaluated in the present study, the presence of mixed pattern cannot be ruled out.

In conclusion, this study showed that the obstructive pattern was the commonest spirometric abnormality among the surviving gas victims with respiratory symptoms and the prevalence of it (either reversible or irreversible) was more in gas victims compared to non-exposed subjects. Tobacco smoking and poor socio-economic condition might have played a significant role in development of predominant obstructive pattern.

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