Late Respiratory Complications of Mustard Gas Poisoning in Iranian Veterans

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Mustard gas or sulfur mustard (SM) is an alkylating chemical warfare agent that was widely used during the World War I and the Iran–Iraq conflict. We aimed to study late toxic effects of SM on the respiratory system of severely intoxicated Iranian veterans. Respiratory examination, spirometry, arterial blood gas (ABG) analysis, and high-resolution computed tomography (HRCT) of the chest were performed on all severely SM-poisoned veterans in the province of Khorasan, Iran. HRCT abnormalities were classified into four grades based on the number of lung lobes involved. ABG and spirometric results were compared with each other, as well as with the severity grades of HRCT abnormalities, using Spearman’s rank correlation test. Forty male subjects with confirmed SM poisoning 16 to 20 yr ago were studied. Main respiratory complications were diagnosed as chronic obstructive pulmonary disease (COPD) (35%), bronchiectasis (32.5%), asthma (25%), large-airway narrowing (15%), pulmonary fibrosis (7.5%), and simple chronic bronchitis (5%) patients. While there was a significant correlation ($p < .05$) between ABG and spirometric results, the severity grades of HRCT abnormalities revealed a significant correlation ($p < .05$) only with $\text{PaO}_2$. We concluded that SM-induced respiratory complications tend to progress over the years. While spirometry is a valuable diagnostic tool for evaluation of pulmonary impairment during regular follow-ups, ABG and HRCT are more objective and should be more considered for evaluation of the severity and for diagnosis of the respiratory complications.

The mustard gas or sulfur mustard (SM) was the most widely used chemical warfare agent (CWA) in the past century. It was responsible for almost 400,000 chemical casualties during World War I and was employed extensively in various regions of the world thereafter (Prentiss, 1937; SIPRI, 1971). The most recent use of sulfur mustard a large scale was made by Iraqi forces against Iranian soldiers and even on the civilian population, resulting in over 100,000 medical casualties between 1983 and 1988 (United Nations Security Council, 1988).

Mustard gas acts as an alkylating agent with both short- and long-term toxic effects on the skin, eyes, and respiratory system (Balali, 1984; Crathorn & Roberts, 1966; Gilman & Philips, 1946). When absorbed in large amounts, it can also produce a wide range of systemic toxicities, including hematologic, immunologic, digestive, and neuropsychiatric disorders (Balali & Navaeian, 1986; Willems, 1989).
Acute SM inhalation can lead to hoarseness, coughing and sputum production, as well as pulmonary edema and respiratory failure in the severely intoxicated patients (Balali-Mood, 1986; Iwaszkiewicz, 1996; Willems, 1989). Delayed respiratory complications, which are the greatest cause of long-term disability, occur between a few months to several years after exposure and mainly include chronic bronchitis, bronchiectasis, asthma, large airway narrowing, and pulmonary fibrosis (Balali-Mood, 1986; Emad & Rezaian, 1997).

We conducted this study to evaluate delayed complications of SM poisoning in the respiratory system of the severely intoxicated Iranian veterans and to make a comparison between gasometric, spirometric, and roentgenographic findings in these patients.

METHOD

Patients and Study Design

The Veteran Foundation provided us with the files of all CWA injured patients in the province of Khorasan, Iran. We reviewed the files and selected the patients who met the following criteria: (1) documented exposure to SM, as confirmed by toxicological analyses of their urine and vesicular fluid during the war, and (2) significant clinical complications of SM poisoning in the respiratory system of the patients. Those with a known respiratory disease before their exposure to SM, cigarette smokers, and those with proven systemic illness were excluded. All these patients had their initial admissions in Imam Reza University Teaching Hospital between 1983 and 1988 and have had regular follow-ups since then.

Forty seven male subjects fulfilled these criteria. Of these, 40 patients volunteered to participate in the study and signed the informed written consent. After approval by the medical ethics committee of the university, the patients were hospitalized in the Toxicology Ward of Imam Reza Hospital, where they underwent a thorough history and physical examination by the experienced pulmonologist of our research team. A uniform series of paraclinical investigations was then performed for all the patients as described next.

Procedures

Pulmonary function tests (PFT) were measured according to the spirometric assessment standards of the American Thoracic Society (American Thoracic Society, 1987), using a flow-sensing spirometer (FUDAC 50; FUKUDA Sangyo, Chiba, Japan). An experienced physician performed all the spirometric measurements and recorded slow vital capacity (SVC), forced vital capacity (FVC), forced vital capacity in the first second (FEV1), FEV1/FVC ratio (FEV1%), and peak expiratory flow (PEF) before and 10 min after 2 puffs of salbutamol (100 µg/puff). Arterial blood gas (ABG) analysis was performed with an AVL 995 blood gas analyzer (AVL Biomedical Instruments, Graz, Austria). High-resolution computed tomography (HRCT) of the chest was obtained from each patient, using a high-speed General Electric CT unit (General Electric Medical Systems, Milwaukee, WI). Patients were scanned at fully suspended inspiration with 1.5- to 2.0-mm sections taken at 10-mm intervals through the entire thorax. Bronchoscopy was performed by the pulmonologist for 24 of 40 patients, using a flexible fiber-optic bronchoscope (Olympus BF1T; Tokyo). The other 16 patients were not considered for bronchoscopy because they were at very high risk for the complications from this procedure. Supplemental oxygen and continuous cardiac monitoring were provided throughout the procedure.

ABG and spirometric results were interpreted by the pulmonologist, using the normal standards described by Andreoli et al. (2001) and Boskabadi et al. (2002), respectively. Chronic obstructive pulmonary disease (COPD) was defined when the following criteria were present: (1) history of cough and sputum production for at least 3 mo/yr for 2 yr, (2) an irreversible (<15% increase in FEV1 after bronchodilator inhalation) obstructive pattern in the results of spirometry, and (3) no evidence of bronchiectasis in the HRCT scans of the chest. Patients were labeled as having simple chronic bronchitis when they had history of coughing and sputum production but revealed no obstructive pattern in their spirometric results and no evidence of bronchiectasis in the HRCT scans of the chest. Asthma was defined when patients met the following criteria: (1) typical history of attacks of dyspnea, wheezing, or both, and nocturnal cough triggered either by irritants, respiratory infections, or exercise, and (2) reversible (>15% increase in FEV1 after bronchodilator inhalation) obstructive pattern in the results of spirometry. The HRCT scans were evaluated and interpreted by a chest radiologist who was not aware of the patients’ clinical data. Each individual section on the HRCT scans was assessed for the reticular densities and honeycombing, as well as for the radiologic evidences of bronchiectasis such as bronchial dilation, bronchial wall thickening, lack of normal bronchial tapering, gross airway irregularities, and air-fluid levels in distended bronchi (Luce, 2001). Large-airway narrowing was diagnosed according to the bronchoscopic and spirometric findings.

Severity Grading of Pulmonary Paraclinical Findings

The severity of pulmonary function impairment was classified into four grades based on the patients’ FEV1 and FVC, as shown in Table 1. Hypoxemia was reported to be absent (grade 1), mild (grade 2), moderate (grade 3), or severe (grade 4) when PaO2 was >85, 60 to 84, 45 to 59, or < 45 mm Hg, respectively. Hyper- and hypocapnia were defined when PaCO2 was >43 and ≤37 mm Hg, respectively. The severity of bronchiectasis was estimated according to the number of lung lobes showing this complication on HRCT scans. Patients without radiologic evidence of bronchiectasis were classified in grade 1 (no bronchiectasis), while those with bronchiectatic lesions in one, two, or at least three lung lobes were graded as mild (grade 2), moderate (grade 2), or severe (grade 4) bronchiectasis, respectively.
MUSTARD GAS POISONING

TABLE 1
Classification of pulmonary function impairment by category

<table>
<thead>
<tr>
<th>No impairment (grade 1)</th>
<th>Mild impairment (grade 2)</th>
<th>Moderate impairment (grade 3)</th>
<th>Severe impairment (grade 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC ≥ 80% and FEV1 ≥ 80%</td>
<td>80% &gt; FVC ≥ 60% or FEV1 ≥ 60%</td>
<td>60% &gt; FVC ≥ 50% or FEV1 ≥ 40%</td>
<td>50% &gt; FVC or FEV1 ≥ 40%</td>
</tr>
</tbody>
</table>

Note. Numbers are expressed as percentage of predicted values for the same sex, age, and height.

Statistics
All data are expressed as mean (±SD) unless otherwise indicated. Differences among groups were ascertained, using the Kruskal–Wallis test. The Spearman rank test was also performed to find out the correlation between ABG and spirometric parameters and also to compare the severity grades of bronchiectasis with ABG and PFT parameters. SPSS version 11.5 (SPSS Inc., Chicago) was used throughout, with the minimum level of significance set at \( p = .05 \) for all the comparisons.

RESULTS
The age range of the patients was 32 to 76 (43.8 ± 9.8) yr. Their exposure to mustard gas was 16 to 20 (18.0 ± 1.5) yr prior to the study. At the time of this study, all patients complained of coughing, 95% of sputum production, 85% of dyspnea, and 60% of hemoptysis. The main objective clinical findings were wheezing (95%), crackles (50%), and stridor (10%).

Diagnosed Respiratory Complications
Based on clinical and paraclinical findings, main respiratory complications were diagnosed as COPD in 14 (35%), bronchiectasis in 13 (32.5%), asthma in 10 (25%), large-airway narrowing in 6 (15%), pulmonary fibrosis in 3 (7.5%), and simple chronic bronchitis in 2 (5%) patients. Thirty-five patients revealed these complications in their pure forms, while the other five patients had a combination of two or three complications. Pure forms of COPD, bronchiectasis, asthma, large-airway narrowing, simple chronic bronchitis, and pulmonary fibrosis were diagnosed in 14, 8, 7, 3, 2, and 1 patient, respectively.

Spirometric Findings
The results of FVC, FEV1 and FEV1% (expressed as percentages of predicted values) in 40 patients with late respiratory complications, 16 to 20 yr after exposure to SM, were 57.8 ± 17.2, 49.3 ± 18.0, and 64.1 ± 23.3, respectively. Comparison of the FVC and FEV1 in the patients with pure forms of COPD, bronchiectasis, and asthma revealed the lowest values in the patients with pure bronchiectasis, followed by pure COPD and asthma (Table 2). There were, however, no significant differences in PFT parameters among the three groups. The overall pattern of PFT was obstructive in 23 (57.5%), restrictive in 9 (22.5%), mixed in 6 (15%), and normal in 2 (5%) patients. The severity of pulmonary function impairment was graded as 2 (5%) in grade 1, 11 (27.5%) in grade 2, 14 (35%) in grade 3, and 13 (32.5%) in grade 4.

ABG Results
The \( \text{PaO}_2 \) and \( \text{PaCO}_2 \) in 40 patients with late respiratory complications, 16 to 20 yr after exposure to SM, were 63.1 ± 9.6 and 40.5 ± 3.8 mm Hg, respectively. Comparison of \( \text{PaO}_2 \) and \( \text{PaCO}_2 \) of the patients with pure forms of COPD, bronchiectasis, and asthma revealed the lowest \( \text{PaO}_2 \) in patients with pure bronchiectasis, followed by the patients with pure COPD and asthma (Table 2). The highest \( \text{PaCO}_2 \) was found in patients with pure COPD, followed by the patients with pure bronchiectasis and asthma. None of the ABG variables, however, revealed a significant difference among the three groups. Regarding all the 40 patients, \( \text{PaO}_2 \) was normal in only 2 (5%) cases. Based on \( \text{PaO}_2 \) results, mild, moderate, and severe hypoxemia were found in 27 (67.5%), 11 (27.5%), and 0 (0%) patients, respectively. Hyper- and hypocapnia were found in 12 (30%) and 6 (15%) patients, respectively.

HRCT Findings
HRCT revealed bronchiectasis and pulmonary fibrosis in 13 (32.5%) and 3 (7.5%) patients, respectively. Bronchiectatic

TABLE 2
Spirometric and ABG results in patients with pure COPD, pure bronchiectasis, and pure asthma, 16–20 yr after exposure to sulfur mustard

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>FVC (% of predicted)</th>
<th>FEV1 (% of predicted)</th>
<th>FEV1% (%)</th>
<th>( \text{PaO}_2 ) (mm Hg)</th>
<th>( \text{PaCO}_2 ) (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure COPD (( n = 14 ))</td>
<td>56.7 ± 16.6</td>
<td>47.7 ± 14.85</td>
<td>62.0 ± 12.7</td>
<td>63.0 ± 11.3</td>
<td>41.9 ± 3.7</td>
</tr>
<tr>
<td>Pure bronchiectasis (( n = 8 ))</td>
<td>49.0 ± 17.2</td>
<td>42.1 ± 22.9</td>
<td>64.3 ± 21.7</td>
<td>59.8 ± 6.7</td>
<td>41.7 ± 3.1</td>
</tr>
<tr>
<td>Pure asthma (( n = 7 ))</td>
<td>67.2 ± 19.6</td>
<td>57.8 ± 14.2</td>
<td>76.1 ± 11.2</td>
<td>66.7 ± 9.4</td>
<td>39.4 ± 4.0</td>
</tr>
<tr>
<td>( p ) Value</td>
<td>0.177</td>
<td>0.139</td>
<td>0.988</td>
<td>0.392</td>
<td>0.259</td>
</tr>
</tbody>
</table>
lesions were most commonly observed in the left and right lower lobes (8 and 7 patients, respectively), followed by the right middle lobe (6 patients) and the lingula (4 patients). Right and left upper lobes were involved in only one patient. This patient had bronchiectatic lesions in the right and left lower lobes 12 yr ago, while the present examination revealed lesions in all lung lobes, including the right and left upper lobes (Figure 1). Bronchiectasis was bilateral in eight patients and unilateral in five patients. One patient who had undergone left pneumonectomy due to extensive bronchiectatic lesions now revealed bronchiectatic lesions in the right lower and right middle lung lobes and was thus classified as grade 4 of bronchiectasis. The overall severity of bronchiectatic lesions was estimated as 27 (67.5%) patients in grade 1, 5 (12.5%) in grade 2, 4 (10%) in grade 3, and 4 (10%) patients in grade 4.

**Bronchoscopic Results**

From the 24 patients who underwent bronchoscopy, 6 patients revealed large-airway narrowing. Sites of narrowing were found in the main bronchus of the right middle lobe (3 patients), the lingual (1 patient), and the trachea (1 patient). Simultaneous involvement of the bronchus of the right middle lobe and the lingual was also found in one patient.

**Correlation Between Spirometric and ABG Parameters**

A significant positive correlation was found between PaO₂ and both FEV₁ ($r = .340$, $p = .032$) and FVC ($r = .422$, $p = .007$). There was also a significant negative correlation between these two parameters and PaCO₂ (Figure 2).
with PaO2, while PaCO2, FVC, and FEV1 revealed no significant correlation. 

**Comparison of Bronchiectatic Severity Grades With Spirometric and ABG Parameters**

As shown in Table 3, severity grades of bronchiectasis revealed a significant negative correlation ($r = -0.673, p = .012$) with PaO2, while PaCO2, FVC, and FEV1 revealed no significant correlation with the severity grades of bronchiectasis.

<table>
<thead>
<tr>
<th>Severity grades of bronchiectasis</th>
<th>$r$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>-0.029</td>
<td>0.925</td>
</tr>
<tr>
<td>FVC</td>
<td>-0.137</td>
<td>0.655</td>
</tr>
<tr>
<td>PaO2</td>
<td>-0.673</td>
<td>0.012</td>
</tr>
<tr>
<td>PaCO2</td>
<td>-0.010</td>
<td>0.973</td>
</tr>
</tbody>
</table>

**DISCUSSION AND CONCLUSIONS**

Despite several international conventions and treaties designed to prohibit the use of CWAs, SM was widely used during the Iran–Iraq War in the 1980s. Its highly long-lasting toxic effects may ensure its further use in future military conflicts as well as in terrorist attacks (WHO, 2004).

The first report of the delayed toxic effects of SM poisoning in 236 Iranian veterans revealed the most common effects on the respiratory system (78%), central nervous system (45%), skin (41%), and eyes (36%) (Balali-Mood, 1986). These effects were recorded between 2 and 28 mo after exposure. In a later study on 34,000 Iranians, 13–20 yr after exposure to SM, the most common complications were found in the lungs (42.5%), eyes (39%), and skin (24.5%) (Khateri et al., 2003). In the present report, we studied only cases with significant clinical complications of SM poisoning, 16–20 yr after exposure to mustard gas.

Delayed respiratory complications are known to be the greatest cause of long-term disability among SM-poisoned patients. Emad and Rezaian studied 197 Iranian veterans, 10 yr after exposure to mustard gas, and reported the main respiratory complications as chronic bronchitis (58.8%), bronchiectasis (8.6%), asthma (10.6%), large-airway narrowing (9.6%), and pulmonary fibrosis (12%) (Emad & Rezaian, 1997).

Comparison of Emad’s results with our findings demonstrates a higher frequency of bronchiectasis (32.5%) and large-airway narrowing (15%) in our patients. This can be due to either the progressive nature of SM’s toxic effects on the respiratory system or our strict patient selection which included only cases with more significant complications. Comparison of the spirometric results between the two studies, however, indicates that PFT parameters of the patients with pure COPD, pure bronchiectasis or pure asthma in our study are similar to those of the patients with moderate to severe complications in each diagnostic group of Emad’s study. Therefore, even patients with the same diagnosis have more severe complications in our study and pulmonary function impairment in SM-poisoned patients probably tends to escalate with time.

The study of 77 subjects, who were present in a contaminated area and had no signs and symptoms at the time of exposure to SM, revealed respiratory problems 18 yr later, indicating that subclinical exposure can be responsible for the development of delayed respiratory complications such as bronchiectasis and broncholithitis obliterans (Ghanei et al., 2004). Comparison of our patients’ spirometric results with those of the same patients studied 4 to 7 yr after their initial exposure (Keshmiri et al., 1992) revealed the percentage of patients with normal spirometric results has declined from 42% in their investigation to 5% in the present study. This shows that respiratory complications, recorded in our study, were both more frequent and more progressed compared with previous studies. Subjects who had bronchiectasis confined to few lung lobes during the earlier follow-ups now revealed this complication more extensively and in more lung lobes. The loss of normal ciliary activity, airway obstruction and, more importantly, the pathogenic status of the immune system with its subsequent increased risk of recurrent respiratory infections are known to be the major factors responsible for the development and progression of bronchiectasis over several years (Ghotbi & Hassan, 2002; Thompson et al., 1989).

Two recent studies have indicated COPD as the most frequent involvement resulting from SM exposure (Bijani & Moghadamnia, 2002; Emad & Rezaian, 1997). With an incidence of 35%, it was also the most common pulmonary sequel in our patients. However, compared to previous studies, the difference between the frequency of COPD and other respiratory problems, such as bronchiectasis, was less marked in our study. This probably reflects the clinical course of SM-induced complications, which gradually progress from simple chronic bronchitis to COPD and bronchiectasis. Although malignant respiratory complications of SM poisoning were previously reported in Iranian veterans (Balali, 1992), we found no such complications in this cross-sectional study.

Regarding the progressive course of SM-induced respiratory complications and the importance of early diagnosis and treatment of these patients, it is essential to rely on a sensitive but simple method for the evaluation of respiratory complications during follow-ups. The comparison of spirometry, ABG, and HRCT results in our patients demonstrated a significant correlation between ABG and spirometric variables, while the severity of HRCT findings had a significant correlation only with PaO2. Therefore, it is recommended to use spirometry for regular follow-ups of patients, provided that it is performed by an expert physician who is knowledgeable of common spirometric abnormalities, as well as the pitfalls in carrying out the procedure. ABG analysis yields invaluable information, but because of its relatively invasive procedure it would be better saved for more critical patients or for those with acute exacerbation.
of their disease. While HRCT is a powerful tool in detecting both parenchymal and airway abnormalities, it is not competent enough for estimating the severity of respiratory impairment or for determining the overall condition of patients. Therefore, all clinical and paraclinical investigations must be carefully considered for the diagnosis and severity assessment of complications.

REFERENCES


