Tracheobronchomalacia and Air Trapping after Mustard Gas Exposure

Mostafa Ghanei, Farhad Akbari Moqadam, Mehdi Mir Mohammad, and Jafar Aslani

Research Center of Chemical Injuries and Department of Radiology, Baqiyatallah Medical Sciences University, Tehran, Iran

Rationale: **Mustard gas primarily affects the eyes, skin, and particularly the respiratory tract. Tracheobronchomalacia (TBM) and air trapping are often observed in high-resolution computerized tomography (HRCT) scans of the chest of mustard gas–exposed patients.**

Objectives: **To examine the frequency and severity of TBM in a group of Iranian wartime mustard gas–exposed victims, and to investigate the correlation between TBM and air trapping in these cases.**

Materials and Methods: **Chest HRCT films obtained from 300 randomly selected subjects who had been exposed to mustard gas 15.5 yr previously were reviewed to determine the existence of TBM and air trapping. The HRCT films of a healthy control group were also analyzed for comparison.**

Results: **Out of 300 reviewed cases, 13 had TBM. From these 13 TBM cases, 11 (85%) showed air trapping with mean score of 5.5. In the control group, 5 (25%) of 20 subjects showed air trapping, with mean score of 0.6. The total air trapping was significantly higher in the TBM group ($p < 0.001$). There was an association between the severity of tracheomalacia and air trapping in the TBM group ($p = 0.01$, $r = 0.69$), but no association was observed between severity of bronchomalacia and air trapping.**

Conclusion: **The results show that air trapping and TBM are correlated, both as long-term sequelae in mustard gas–exposed cases. Because air trapping is highly suggestive of bronchiolitis obliterans, we conclude that both bronchiolitis obliterans and TBM are caused by a single underlying process affecting small and large airways, respectively, in this group of patients.**

Keywords: air trapping; bronchiolitis obliterans; high-resolution computerized tomography; mustard gas; tracheobronchomalacia

Mustard gas was extensively used against Iranian civilians and military forces during the Iran–Iraq war of the 1980s (1). Mustard gas or sulfur mustard, bis(2-chloroethyl) sulfide, is a highly reactive agent that alkylates cellular components. The acute toxic effects of mustard gas result from irreversible alkylation of proteins (2, 3) and nucleic acids (4–6). Collectively this causes loss of structural and functional integrity of cells and tissues, resulting in intense pain and burning, with blister formation (7). Sulfur mustard primarily affects the eyes, skin, and respiratory tract. Symptom onset ranges from 1 to 12 h after exposure (8). Eye symptoms include erythema, edema, lachrymation, and discomfort, with more severe exposures resulting in severe pain, blepharospasm, iritis, and blindness (either temporary or permanent) (9). Effects on the skin range from erythema and edema to necrosis and vesicles. Although blisters generally are formed by 16 to 24 h after exposure, they can form as late as 7 to 12 d. Tracheobronchitis usually results several hours after exposure. Other respiratory manifestations can range from bronchospasm and bronchial obstruction to hemorrhagic pulmonary edema. Lethal exposures result in death from respiratory failure, secondary pneumonia, and occasional hemorrhagic pulmonary edema (10).

Sulfur mustard is stored as a liquid and is not likely to change into a vapor immediately if it is released at ordinary temperatures. However, with a concomitant explosion, it transforms into aerosols with particle sizes of 1 to 5 μm. As a liquid, it is colorless when pure and it is brown when mixed with other chemicals. It is odorless when pure, but can have a slight garlic smell when mixed with other chemicals. It dissolves easily in fats, oils, alcohol, and gasoline. Sulfur mustard dissolves slowly in unstirred water, but within minutes in stirred water (10).

Because ordinary chest X-rays and pulmonary function tests (PFTs) are normal in a considerable number of mustard gas–exposure cases, high-resolution computerized tomography (HRCT) of the chest is routinely performed to evaluate the respiratory condition of mustard gas–exposed victims. During clinical studies of these victims (11–13), we discovered a high proportion of symptomatic and asymptomatic subjects with features of air trapping on chest HRCT (14, 15), which is a fairly common finding. Moreover, several mustard gas–exposed subjects exhibited features of tracheobronchomalacia (TBM), which is relatively rare.

TBM is a condition characterized by excessive central airway collapsibility due to weakness of the airway wall and supporting cartilage (16–18). Two types of this disorder, primary and secondary, have been identified. Primary tracheomalacia has been well described in the literature and can present with stridor and pulmonary infection in infancy. The secondary or acquired type is often accompanied by bronchial involvement as well; hence the term "tracheobronchomalacia" is more commonly used in this case. The etiology of this disorder is unknown in most cases; however, apart from idiopathic causes, it is often associated with trauma, surgical procedures, chronic irritation tracheostomy, endotracheal intubation, and endotracheal tumors (19). It has been shown that chronic airway inflammation with diffuse panbronchiolitis might play a role in exacerbation of this disorder (20). The acquired form of TBM has been increasingly recognized as an important cause of chronic respiratory symptoms in recent years (16, 17). For example, in a bronchoscopic series of patients who did not smoke and were evaluated for chronic cough, TBM was found to be a cause in 14% of cases (17).

A recent study has shown a high frequency and severity of air trapping in expiratory HRCT scans of subjects afflicted by TBM (21). Air trapping on HRCT scans is defined as a decreased attenuation of pulmonary parenchyma after expiration (21) and is caused by excessive retention of gas in the lung. Previous studies have noted that air trapping on expiratory HRCT scans can be seen in association with various airway diseases, including bronchiolitis obliterans (BO) (22–26), asthma (27, 28), emphysema (29, 30), bronchiectases, and chronic bronchitis (29). In addition, air trapping can be seen in healthy subjects with normal PFTs (31–34). Although the severity of air trapping has been shown to be high in the presence of TBM, to date the reverse relationship has not been examined.

(*Received in original form February 16, 2005; accepted in final form October 26, 2005*)

Correspondence and requests for reprints should be addressed to Mostafa Ghanei, M.D., Research Center of Chemical Injuries, Baqiyatallah Medical Science University, Mollasadra Street, Tehran, 14359151371, Iran. E-mail: m.ghanei@bmsu.ac.ir

Am J Respir Crit Care Med Vol 173. pp 304–309, 2006
Originally Published in Press as DOI: 10.1164/rccm.200502-247OC on October 27, 2005
Internet address: www.atsjournals.org

The aim of the present study was to determine the frequency and severity of TBM and of air trapping in a group of Iranian victims of the wartime use of mustard gas. Because the pathogenesis of TBM is not well established, and because it has been suggested that TBM may be caused by air trapping, our population offered a unique opportunity to investigate whether and how these two phenomena might be related.

METHODS

Subjects

Currently in Iran, there are more than 30,000 people with documented exposure to mustard gas during the Iran–Iraq war of the 1980s (12). We had access to the medical information of nearly 12,000 cases. Because findings from PFTs and ordinary chest X-rays are often nonspecific, even in cases with respiratory symptoms, chest HRCT is among the routine medical examinations done for all cases with documented mustard exposure. During 2003–2004, the HRCT films of 300 documented mustard gas–exposure cases were chosen randomly using the following inclusion and exclusion criteria.

Inclusion criteria:

1. Exposure to mustard gas, documented by military health services records, and defined as a single, high-dose exposure to a chemical agent that causes skin blisters and subsequent transient or permanent disability in the exposed people.
2. Medical records documenting the care received for chemical exposure. This includes records of the injured victims being transferred to local military hospitals, where the type of chemical agent was determined based on signs and symptoms and also by detection of mustard gas on the clothing.

Exclusion criteria:

1. History of cigarette smoking or occupational exposure to pulmonary toxic agents.
2. Evidence of prior pneumonia, tuberculosis, lung cancer, or other respiratory infection.
3. History of cough, dyspnea on exertion, or any respiratory difficulty before mustard gas exposure.

The HRCT films were obtained during 2001–2002, hence the mean time since exposure was 15.5 yr. There is no overlap between the cases enrolled in this study and those from our previous publications (12–15, 22, 35).

Twenty healthy individuals were also enrolled in the study as a control group to compare the severity of air trapping. We advertised for healthy volunteers to participate in the study. They had no history of smoking, chronic cough, asthma, recurrent viral respiratory infection, or any specific respiratory disorder. After physical examination and routine clinical tests, the control subjects underwent the same imaging protocol as the cases. Written consent has been obtained from each volunteer. The study was approved by the medical ethics committee of our institute.

Imaging Technique and Assessment of TBM and Air Trapping

All patients were imaged on an axial GE Hi-speed Advantage CT scanner (FXI-plus; GE Medical Systems, Milwaukee, WI) at 120 kVp and 200 to 250 mA with 1-mm collimation and 10-mm intervals from proximal trachea to the diaphragm. The scans were obtained in the supine position in deep inspiration and also in deep expiration at the supraaortic arch, aortic arch, carina, and 5 to 10 cm below the carina according to the method used by Aquino and colleagues (36). The HRCT films, without identification of case and control status, were reviewed by three expert radiologists, and the reported values in this study are based on their consensus. The HRCT films were reviewed using eFilm workstation (eFilm Medical, Toronto, ON, Canada) and the anteroposterior diameter of the trachea and bronchi in each cut was measured by this program with a precision of 1 mm. TBM was considered to be present if the airway diameter decreased by more than 30% during expiration at the same level (36). Air trapping was evaluated in three of the four obtained anatomical levels in each case: upper lung zone, defined as the level of superior aspect of aortic arch; middle lung zone, defined as the level of carina; and lower lung zone, defined as the level 5 to 10 cm below the carina, according to the method used by Zhang and colleagues (21). Air trapping was defined as the presence of a radiolucent region of the lungs on expiratory images (31, 37). The degree of air trapping was assessed by comparing end inspiratory and expiratory images from the same anatomic level and grading each of the three levels on a 5-point scale: 0, no air trapping; 1, 1–25% cross-sectional area affected; 2, 26–50% cross-sectional area affected; 3, 51–75% cross-sectional area affected; and 4, 76–100% cross-sectional area affected. A total air-trapping score was obtained by summing the individual grades for the three levels (maximum possible score, 12 for each lung and 24 for both) (21).

PFT

Spirometry was performed according to American Thoracic Society criteria (38). The FVC and FEV_1 were measured, under the direction of physicians, using a standard spirometer (Jaeger, Hochberg, Germany). Subjects were seated with a nose clip in place and were asked to perform at least three forced expiratory maneuvers. Both the patients and the technician received visual feedback from a monitor during the test, which was repeated until three technically satisfactory curves with reproducible contour were obtained. All the indices used for the analysis were derived from the same maneuver, which was the one with the largest FVC. A constant-volume body plethysmograph was used to determine residual volume and total lung capacity (39).

Statistical Analysis

Fisher's exact test and Pearson's correlation test were used to show the association of tracheomalacia and bronchomalacia with air trapping. The Mann-Whitney test was used to compare the air trapping score between TBM cases and the control group. The software used is SPSS, version 11 (SPSS, Inc., Chicago, IL), and the threshold for significance was set to $p < 0.05$ (40).

RESULTS

Of the 300 reviewed patients, 13 subjects (12 males and 1 female, aged 35 to 52 yr; mean age, 42 yr) had HRCT evidence of tracheal collapse, with nine of these also showing bronchial collapse (Table 1). There was a poor correlation between the percentages of tracheal collapse and bronchial collapse in these patients ($p = 0.8$, $r = -0.08$). There was one severe case of tracheomalacia with more than 75% collapse of the trachea in expiration (case 9, Figure 1). Also, one case (case 11) presented with severe bronchomalacia. In the control group, consisting of 20 men with an age range of 30 to 49 yr (mean age, 31 yr), no sign of TBM was found. Table 2 depicts the PFT results of the patients with TBM. The most significant PFT finding is an increased residual volume. Predicted values are according to Morris/Polgar (41, 42).

Out of 300 reviewed patients, 137 cases (45.7%) had HRCT evidence of air trapping (score > 0). The observed pattern of air trapping was heterogeneous in all cases. There were 45 cases (15%) with air trapping of more than 25% (score > 6), which is suggestive of bronchiolitis obliterans (BO) (22, 37, 43, 44). A remarkable example of air trapping was seen in case 9 (Figure 2) in the patient who also had typical tracheomalacia.

In the TBM group, 11 (85%) of 13 patients were among the 137 cases with air trapping (with a median score of 7, first quartile median of 1, third quartile median of 8; mean, 5.5, and range, 0–14). There was a significant association between the presence of air trapping and presence of TBM in the case group ($p = 0.004$). Moreover, in the TBM group, 8 (62%) of 13 patients had more than 25% air trapping (BO-suggestive) in their expiratory HRCT (cases 3, 4, 5, 8, 9, 11, 12, 13) (22, 37, 43, 44). A significant association between the presence of BO-suggestive air trapping and presence of TBM was observed in this group ($p < 0.0001$). In the control group, 5 (25%) of 20 persons showed some air

TABLE 1. PATIENT CHARACTERISTICS AND CHEST HIGH-RESOLUTION COMPUTERIZED TOMOGRAPHY FINDINGS

	Patient Characteristics		Collapse Seen on Scan (%)		
Patient No.	Sex	Age (*yr*)	Trachea	Main Bronchus	Air-Trapping Score
1	M	41	40	40	1
2	M	52	47	60	2
3	M	39	44.5	36	7
4	M	41	62.5 (aortic arch)	NP	8
5	F	45	47 (aortic arch)	60	8
6	M	36	55.5	NP	1
7	M	35	52.5	NP	0
8	M	43	50	57	7
9	M	43	79	58	14
10	M	35	47.5	54.5	0
11	M	45	65	77	7
12	M	52	65	NP	8
13	M	42	63	40	8

Definitions of abbreviations: F = female; M = male; NP = not present.

trapping (with a median score of 0, first quartile median of 0, third quartile median of 0.75; mean, 0.6, and range, 0–5). The total air-trapping score was significantly higher in the TBM group compared with the control cases ($p < 0.001$).

There was an association between severity of tracheomalacia (percentage of tracheal collapse) and severity of air trapping (air-trapping score) in the TBM group ($p = 0.01$, $R = 0.69$), but there was only a poor association between severity of bronchomalacia and severity of air trapping ($p = 0.45$, $R = 0.23$).

DISCUSSION

Sulfur mustard is a potent alkylating and blistering agent that reacts with membranes, RNA, and proteins (45). When delivered in a small-droplet size (1–5 μm), sulfur mustard may reach the small bronchioles (10). Pulmonary complications, including asthma, chronic bronchitis, and bronchiectasis, have been reported as late complications of mustard exposure (46, 13). Structural damage of the respiratory tract has been described since the very earliest investigations on mustard-exposed victims (47). Extensive stenotic processes of the entire tracheobronchial tree have been detected in some of these cases (35, 48, 49). In line with these findings, the current study shows the presence of TBM in mustard-exposed cases.

Some limitations of this study should be mentioned. TBM was detected here by means of chest HRCT; however, bronchoscopy is the gold standard for diagnosing TBM (19), and dynamic CT scan images are more sensitive than the conventional static HRCT (36, 50). Also, although the presence of significant air trapping on expiratory HRCT is suggestive of BO (22), this diagnosis should be corroborated with histopathologic studies. Apart from a few case reports (51, 52), a large-scale pathologic study on the respiratory complications of mustard exposure is still missing. In the current study, the score of air trapping was assessed subjectively and visually, and concomitant PFT results of all the cases but one were available for analysis. Some researchers have argued that dynamic cine-CT scan is more sensitive in evaluating air trapping than the conventional HRCT used in this study (53, 54). In absence of the above alternative CT modalities, the extent of TBM and air trapping might have been underestimated in the present study, thus these complications may be in fact be more prevalent than the data indicated.

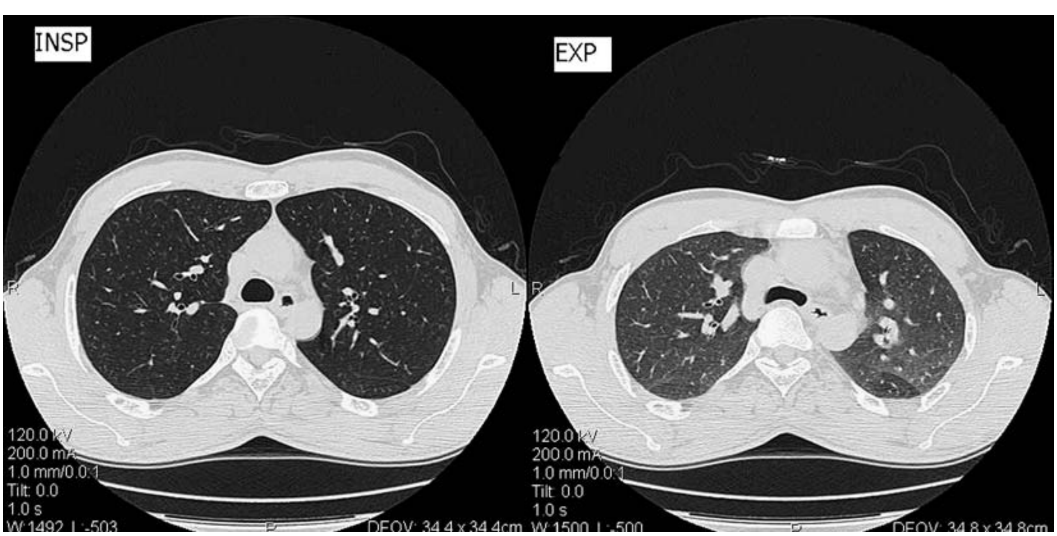

Figure 1. High-resolution computerized tomography (HRCT) from a 43-yr-old man (patient 9 in Table 1), exposed to mustard gas 15 yr earlier, presenting with typical tracheomalacia. The anteroposterior diameter of the trachea decreased more than 75% in this patient during expiration. EXP = expiratory; INSP = inspiratory.

TABLE 2. PULMONARY FUNCTION TEST RESULTS FOR ALL PATIENTS IN TRACHEOBRONCHOMALACIA GROUP

Patient No.	FVC (*% predicted*)	FEV_1 (*% predicted*)	FEV_1/FVC (%)	RV (*% predicted*)	TLC (*% predicted*)
1	93	88	78	129	102
2	—	—	—	—	—
3	85	78	77	133	101
4	74	67	75	129	99
5	87	80	62	134	101
6	57	61	70	136	100
7	70	67	87	125	100
8	84	77	57	133	101
9	99	95	81	123	102
10	91	83	75	133	101
11	89	93	84	128	101
12	84	69	80	123	101
13	71	57	78	123	102
Mean (SD)	82 (12)	76 (12)	75 (9)	129 (5)	100 (1)

Definitions of abbreviations: TLC = total lung capacity.
Patient numbers are the same as in Table 1.

The results show that 13 of 300 (4.3%) documented mustard-exposed cases are afflicted by TBM. This percentage is in agreement with several large-scale studies suggesting the incidence of TBM to be about 5% in patients presenting with pulmonary symptoms (19). Other studies reported an incidence of 1 to 4.5% in patients who underwent bronchoscopy for various pulmonary disorders (55). Among the 300 studied cases, 137 (45.6%) had various degrees of air trapping, with 45 cases (15%) having more than 25% air trapping in expiratory HRCT. In an earlier study (22), the percentage of mustard gas–exposed cases with air trapping has been shown to be 76%. This ostensible discrepancy originates from the fact that the previous study (22) was confined to symptomatic mustard-exposed cases, whereas in the current study, the documented mustard-exposed cases were enrolled regardless of symptoms. One should note that the majority of mustard-exposed cases will remain asymptomatic 15 yr after exposure (12).

The results also show that 11 of 137 patients with air trapping presented with TBM in their HRCT as well. As shown earlier by Zhang and colleagues (21), the severity of air trapping was higher in patients with TBM compared with the normal population. In the earlier studies (21), the remarkable severity of air trapping in TBM patients led the researchers to hypothesize that the etiology of air trapping in these patients is their underlying TBM. However, in light of the previous studies on our patient group, we can interpret this correlation differently as follows.

Radiologic studies show that air trapping is a common finding in the chest HRCT of mustard gas–exposed patients 15 yr after the exposure (22). It has been shown that air trapping, as detected on expiratory HRCT, is the most sensitive and accurate radiologic indicator of BO (56). Moreover, recent pathologic studies indicate that BO is the main pathologic change in patients with asymptomatic mustard gas–induced respiratory disorders (22, 50, 51). Given that air trapping is by far the more frequent finding than TBM in our patients, one can hypothesize that air trapping is not a consequence of TBM in this group. Rather, the same underlying pathologic mechanism that caused the small airway disease BO might also result in a disorder in the large airways such as TBM. In other words, mustard gas may have affected the epithelium in both small and large airways.

Interestingly, both BO and TBM have also been described as complications of lung transplantation (57–59). Although the role of the surgical interventions in the initiation of TBM in post–lung-transplant patients cannot be ruled out, based on

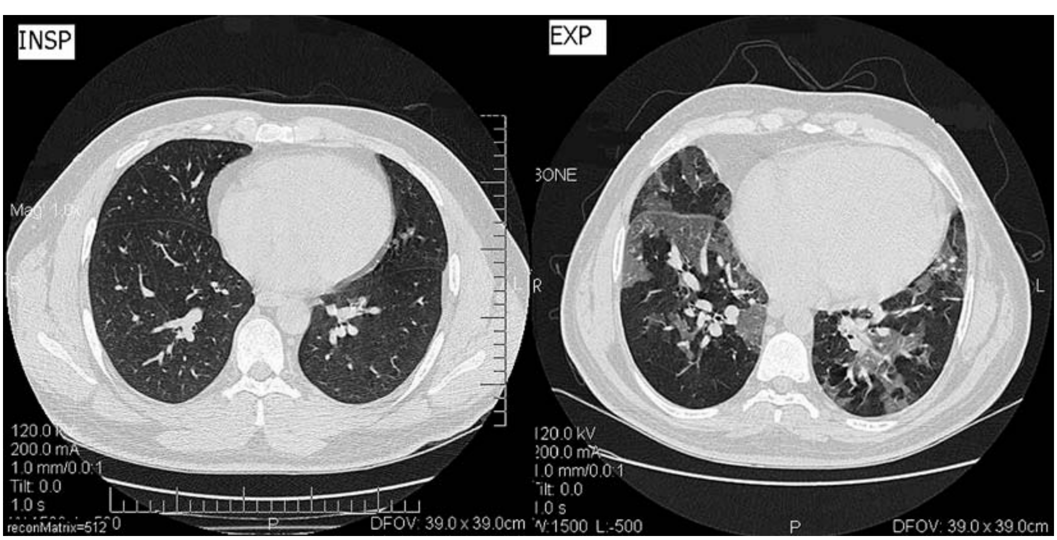

Figure 2. Inspiratory and expiratory HRCT scans from the patient in Figure 1, showing significant air trapping.

the findings of the present study one may speculate that as in mustard gas inhalation, in post–lung-transplant patients, TBM may be due to the same pathologic process that results in BO, that is, a single process causes disorders in both small and large airways.

***Conflict of Interest Statement*:** None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

***Acknowledgment*:** The authors thank Professor William S. Beckett for his invaluable scientific assistance.

References

1. United Nations Security Council. Report of the Specialists appointed by the Secretary-General to investigate allegations by the Islamic Republic of Iran concerning the use of chemical weapons. *Arch Belg* 1984;302–310.
2. Fidder A, Noort D, De Jong AL, Trap HC, De Jong LP, Benschop HP. Monitoring of in vitro and in vivo exposure to sulfur mustard by GC/MS determination of the N-terminal valine adduct in hemoglobin after a modified Edman degradation. *Chem Res Toxicol* 1996;9:788–792.
3. Noort D, Hulst AG, Trap HC, De Jong LP, Benschop HP. Synthesis and mass spectrometric identification of the major amino acid adducts formed between sulphur mustard and haemoglobin in human blood. *Arch Toxicol* 1997;71:171–178.
4. Langenberg JP, Van der Schans GP, Spruit HE, Kuijpers WC, Mars-Groenendijk RH. Van Dijk-Knijnenburg HC, Trap HC, Van Helden HP, Benschop HP. Toxicokinetics of sulfur mustard and its DNA-adducts in the hairless guinea pig. *Drug Chem Toxicol* 1998;21:131–147.
5. Matijasevic Z, Stering A, Niu TQ, Austin-Ritchie P, Ludlum DB. Release of sulfur mustard modified DNA bases by Escherichia coli 3-methyladenine DNA glycosylase II. *Carcinogenesis* 1996;17:2249–2252.
6. Niu T, Matijasevic Z, Austin-Ritchie P, Stering A, Ludlum DB. A 32P postlabeling method for the detection of adducts in the DNA of human fibroblasts exposed to sulfur mustard. *Chem Biol Interact* 1996;100: 77–84.
7. Watson AP, Griffin GD. Toxicity of vesicant agents scheduled for destruction by the Chemical Stockpile Disposal Program. *Environ Health Perspect* 1992;98:259–280.
8. Sohrabpour H. Observation and clinical manifestations of patients injured with mustard gas. *Med J Islam Repub Iran* 1987;1408:32–37.
9. Bismuth C, Borron SW, Baud FJ, Barriot P. Chemical weapons: documented use and compounds on the horizon. *Toxicol Lett* 2004;149: 11–18.
10. Rosemond ZA, Beblo DA, Amata R. Toxicological profile for sulphur mustard. Atlanta: Agency for Toxic Substances and Disease Registry, U.S. Dept of Health and Human Services, Public Health Service; September 2003. p.2.
11. Karimi Zarchi AA, Holakouie Naieni K. Long-term pulmonary complications in combatants exposed to mustard gas: a historical cohort study. *Int J Epidemiol* 2004;33:1–3.
12. Khateri S, Ghanei M, Keshavarz S, Soroush M, Haines D. Incidence of lung, eye, and skin lesions as late complications in 34,000 Iranians with wartime exposure to mustard agent. *J Occup Environ Med* 2003; 45:1136–1143.
13. Ghanei M., Hosseini AR, Arabbaferani Z, Shahkarami E. Evaluation of chronic cough in chemical chronic bronchitis patients. *Environ Toxicol Pharmacol* 2005;20:6–10.
14. Ghanei M, Mokhtari M, Mirmohammad M, Aslani J, Alaeddini F. High resolution computerized tomography of chest in patients exposed to sulfur mustard. *Iran J Radiol* 2003;1:1–6.
15. Ghanei M, Fathi H, Mohammad MM, Aslani J, Nematizadeh F. Long-term respiratory disorders of claimers with subclinical exposure to chemical warfare agents. *Inhal Toxicol* 2004;16:491–495.
16. Boiselle PM, Feller-Kopman D, Ashiku S, Week D, Ernst A. Tracheobronchomalacia: evolving role of dynamic multislice helical CT. *Radiol Clin North Am* 2003;41:627–636.
17. Palombini BC, Villanova CA, Araujo E, Gastal OL, Alt DC, Stolz DP, Palombini CO. A pathogenic triad in chronic cough: asthma, postnasal drip and gastroesophageal reflux disease. *Chest* 1999;116:279–284.
18. Johnson TH, Mikita JJ, Wilson RJ, Feist JH. Acquired tracheomalacia. *Radiology* 1973;109:577–580.
19. Carden KA, Boiselle PM, Waltz DA, Ernst A. Tracheomalacia and tracheobronchomalacia in children and adults: an in-depth review. *Chest* 2005;127:984–1005.
20. Ikeda S, Inuue Y, Fujino S, Fujioka S, Hamada H, Yokoyama A, Kohno N, Hiwada K. A case of diffuse panbronchiolitis associated with tracheobronchomalacia. *Nippon Ronen Igakkai Zasshi* 1993;30:974–977.
21. Zhang J, Hasegawa I, Hatabu H, Feller-Kopman D, Boiselle PM. Frequency and severity of air trapping at dynamic expiratory CT in patients with tracheobronchomalacia. *AJR Am J Roentgenol* 2004;182: 81–85.
22. Ghanei M, Mokhtari M, Mir Mohammad M, Aslani J. Bronchiolitis obliterans following exposure to sulfur mustard: chest high resolution computed tomography. *Eur J Radiol* 2004;52:164–169.
23. Stern EJ, Frank MS. Small-airway disease of the lungs: findings at expiratory CT. *AJR Am J Roentgenol* 1994;163:37–41.
24. Estenne M, Maurer JR, Boehler A, Egan JJ, Frost A, Hertz M, Mallory GB, Snell GI, Yousem S. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant* 2002;21:297–310.
25. Sweatman MC, Millar AB, Strickland B, Turner-Warwick M. Computed tomography in adult obliterative bronchiolitis. *Clin Radiol* 1990;41: 116–119.
26. Aquino SL, Webb WR, Golden J. Bronchiolitis obliterans associated with rheumatoid arthritis: findings on HRCT and dynamic expiratory CT. *J Comput Assist Tomogr* 1994;18:555–558.
27. Arakawa H, Webb WR. Air trapping on expiratory high-resolution CT scans in the absence of inspiratory scan abnormalities: correlation with pulmonary function tests and differential diagnosis. *AJR Am J Roentgenol* 1998;170:1349–1353.
28. Newman KB, Lynch DA, Newman LS, Ellegood D, Newell JD Jr. Quantitative computed tomography detects air trapping due to asthma. *Chest* 1994;106:105–109.
29. Lamers RJ, Thelissen GR, Kessels AG, Wouters EF, van Engelshoven JM. Chronic obstructive pulmonary disease: evaluation with spirometrically controlled CT lung densitometry. *Radiology* 1994;193:109–113.
30. Knudson RJ, Standen JR, Kaltenborn WT, Knudson DE, Rehm K, Habib MP, Newell JD. Expiratory computed tomography for assessment of suspected pulmonary emphysema. *Chest* 1991;99:1357–1366.
31. Lee KW, Chung SY, Yang I, Lee Y, Ko EY, Park MJ. Correlation of aging and smoking with air trapping at thin-section CT of the lung in asymptomatic subjects. *Radiology* 2000;214:831–836.
32. Chen D, Webb WR, Storto ML, Lee K. Assessment of air trapping using post expiratory high resolution computed tomography. *J Thorac Imaging* 1998;13:135–143.
33. Webb WR, Stern EJ, Kanth N, Gamsu G. Dynamic pulmonary CT: findings in healthy adult men. *Radiology* 1993;186:117–124.
34. Tanaka N, Matsumoto T, Miura G, Emoto T, Matsunaga N, Ueda K, Lynch DA. Air trapping at CT: high prevalence in asymptomatic subjects with normal pulmonary function. *Radiology* 2003;227:776–785.
35. Ghanei M, Akhlaghpoor Sh. Mir Mohammad M, Aslani J. Tracheobronchial stenosis following sulfur mustard inhalation. *Inhal Toxicol* 2004; 16:845–849.
36. Aquino SL, Shepard JA, Jinns LC, Moore RH, Halpern E, Grillo HC, McLoud TC. Acquired tracheomalacia: detection by expiratory CT scan. *J Comput Assist Tomogr* 2001;25:394–399.
37. Austin JH, Muller NL, Friedman PJ, Hansell DM, Naidich DP, Remy-Jardin M, Webb WR, Zerhouni EA. Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. *Radiology* 1996;200:327–333.
38. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152:1107–1136.
39. Quanjer PhH. Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows. Report working party. Standardization of lung function tests. European Coal and Steel Community. *Eur Respir J* 1993;6:5–40.
40. Altman DG. Practical statistics for medical research. New York: Chapman & Hall/CRC; 1990.
41. Morris JF. Spirometry in the evaluation of pulmonary function. *West J Med* 1976;25:110–111.
42. SensorMedics. Pulmonary utilities operator's manual: predicted normal equations. Yorba Linda, CA: SensorMedics; 1988.
43. Muller NL, Miller RR. Disease of the bronchioles: CT and histopathologic findings. *Radiology* 1995;196:3–11.
44. Muller NL, Fraser RS, Lee KS, Johkoh T. Diseases of the lung, radiologic and pathologic correlations. Philadelphia, PA: Lippincott, Williams & Wilkins; 2003.
45. Somani SM, Babu SR. Toxicodynamics of sulphur mustard. *Int J Clin Pharmacol Ther Toxicol* 1989;27:419–435.

46. Emad A, Rezaian GR. The diversity of the effects of sulfur mustard gas inhalation on respiratory system 10 years after a single, heavy exposure. *Chest* 1997;112:734–830.
47. Winternitz MC, Finney WP. The pathology of mustard poisoning. In: Winternitz MC, editor. Pathology of war gas poisoning., New Haven, CT: Yale University Press; 1920.
48. Freitag L, Firusian N, Stamatis G, Greschuchna D. The role of bronchoscopy in pulmonary complications due to mustard gas inhalation. *Chest* 1991;100:1436–1441.
49. Bagheri MH, Hosseini SK, Mostafavi SH, Alavi SA. High-resolution CT in chronic pulmonary changes after mustard gas exposure. *Acta Radiol* 2003;44:241–245.
50. Gilkeson RC, Ciancibello LM, Hejal RB, Montenegro HD, Lange P. Tracheobronchomalacia: dynamic airway evaluation with multidetector CT. *AJR Am J Roentgenol* 2001;176:205–210.
51. Thomason JW, Rice TW, Milstone AP. Bronchiolitis obliterans in a survivor of a chemical weapons attack. *JAMA* 2003;290:598–599.
52. Dompeling E, Jobsis Q, Vandevijver NM, Wesseling G, Hendriks H. Chronic bronchiolitis in a 5-yr-old child after exposure to sulphur mustard gas. *Eur Respir J* 2004;23:343–346.
53. Johnson JL, Kramer SS, Mahboubi S. Air trapping in children: evaluation with dynamic lung densitometry with spiral CT. *Radiology* 1998;206: 95–101.
54. Spaggiari E, Zompatori M, Verduri A, Chetta A, Bna C, Ormitti F, Sverzellati N, Rabaiotti E. Early smoking-induced lung lesions in asymptomatic subjects. Correlations between high resolution dynamic CT and pulmonary function testing. *Radiol Med (Torino)* 2005;109: 27–39.
55. Baxter JD, Dunbar JS. Tracheomalacia. *Ann Otol Rhinol Laryngol* 1963; 72:1013–1023.
56. Kraft M, Mortenson RL, Colby TV. Cryptogenic constrictive bronchiolitis, a clinicopathologic study. *Am Rev Respir Dis* 1993;148:1093–1101.
57. Egan JJ. Obliterative bronchiolitis after lung transplantation: a repetitive multiple injury airway disease. *Am J Respir Crit Care Med* 2004;170: 931–932.
58. Estenne M, Hertz MI. Bronchiolitis obliterans after human lung transplantation. *Am J Respir Crit Care Med* 2002;166:440–444.
59. Kaditis AG, Gondor M, Nixon PA, Webber S, Keenan RJ, Kaye R, Kurland G. Airway complications following pediatric lung and heart-lung transplantation. *Am J Respir Crit Care Med* 2000;162:301–309.