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Late Cardiac Complications of Sulfur Mustard Poisoning in 38 Iranian Veterans

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Abstract

It was aimed to investigate possible late cardiac effects of Sulfur mustard (SM) exposure in Iranian veterans. Thirty-eight veterans with late complications of SM exposure were investigated. Clinical history, physical examinations, 12 leads electrocardiography and transthoracic echocardiography were performed. Computed tomography coronary angiography (CTCA) was performed as clinically indicated for angiographic assessment and patients were stratified according to the CTCA findings. Incomplete right bundle branch block and right axis deviation were detected in 3 (7.9%) and 4 (10.5%) cases, respectively. Mean value of left ventricular ejection fraction was 55.7 ± 2.9%. Different degrees of right ventricular dilation was observed in seven (18.4%) patients. All the patients showed mild to moderate degrees of tricuspid regurgitation. Increased pulmonary artery pressure (PAP) was detected in 16 (42.1%) patients. Out of 18 patients who underwent CTCA, non-obstructive and obstructive coronary artery disease (CAD) were observed in three (16.66%) and eight (44.44%) patients, respectively. CAD was stratified to single vessel (5.5%), two vessels (27.8%) and three vessels disease (11.1%). Mean coronary artery calcium score was 50.91 ± 115.58. SM has cardiovascular toxicity, as a delayed complication of this chemical warfare poisoning.

Keywords Sulfur mustard · Poisoning · Electrocardiography · Transthoracic echocardiography · CT coronary angiography · Coronary artery disease

Introduction and Background

Sulfur mustard (SM) or bis (2-chloroethyl) sulfide ($C_4H_8Cl_2S$), is a potent toxic alkylating chemical warfare agent (CWA). Among wide ranges of CWAs, SM is known as "King of the Battle Gases". To date, it has remained the chemical weapon of choice in modern tactile warfare. SM was widely used in the World War one (WW1) and also during the Iran-Iraq battle in 1983–1988 [1].

Historically, it was synthesized in 1822 and modified in 1860 [2]. SM was first used at Ypres (a Belgian city) during the WWI and it is thus also called "Yperite". In World War II, SM usage was limited to bombing harbour of Bari in Italy by German troops, which caused more than 600 casualties [3]. Thereafter, SM was also applied by Italy against Ethiopia, Japan against China and by Poland against Germany [2–4]. Dramatic attacks of SM and other CWAs were performed in the Iran-Iraq war by Iraqi army which led to civil infrastructure damages of some border cities of Iran and Iraq such as Susangerd (Nov 1980), Hawizah Marsh (March 1985), Mehran (Oct 1987), Al-Faw (February 1986

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and April 1988), Halabja- a Kurdish town in Iraq- (March 1988), Oshnavie (July 1988) as well as many other bombardments which brought the number of chemical attacks to 30 during the war [3–5].

SM undergoes intramolecular cyclization to form an ethylene episulphonium ion intermediate which rapidly reacts with and alkylates a wide variety of electron-rich biological molecules, such as the sulphydryl (–SH) and amino ($–NH_2$) groups of proteins and nucleic acids, leading to chromatid aberration and inhibition of DNA, RNA and protein synthesis [4, 6, 7]. Although SM reacts with RNA, proteins and phospholipids, it is known as a DNA alkylating agent which plays an important role in delayed toxicity and healing [8].

Skin is the most route of SM absorption; however, it can be absorbed via inhalation, anterior surface of eyes or even via gastrointestinal tract after the consumption of contaminated water or food [1]. Comparing with other CWAs such as nerve agents, SM has relatively lower lethal activity and known as "incapacitating agent". Nevertheless, mortality rate of 3–4% in the Iran-Iraq battle and less than 2% during the WWI in SM exposed individuals was recorded [9]. Respiratory complications as well as skin lesions and eye disorders were observed in most of SM exposed veterans in acute phase of intoxication [10, 11].

The first report on delayed toxic effects of SM poisoning in 236 Iranian veterans, stated the respiratory tract (78%), CNS (45%), the skin (41%) and the eyes (36%) as the most involved organs [12]. More recently, Balali-Mood et al. described late toxic effect of SM in 40 Iranian veterans 16–20 years post exposure. Lungs (95%), peripheral nerves (77.5%), the skin (75%) and the eyes (65%) were the most affected organs [13].

Impaired immunity was also detected in SM survived veterans 20 years post exposure and assumed to be responsible for the increased risk of infections among the victims [14]. Late complication of neuromuscular system, reproductive system, gastrointestinal tract, bone marrow involvement, genotoxicity and mutagenicity were also evaluated and reported previously [1, 9, 14, 15].

There are limited reports on late cardiac complications of SM poisoning in the literature. Shabestari et al. has recently observed higher frequency of coronary artery ectasia in 40 veterans with late complications of SM poisoning compared with non-exposed controls by means of conventional angiographic study. The authors declared that it was the first proposed theory about coronary artery ectasia as a late effect of SM poisoning. It was also reported that the most involved artery in the veterans was left anterior descending artery with a prevalence of 22.5% within the case group [16].

In a retrospective case control study (2010), 50 Iranian SM veterans underwent exercise stress test and echocardiography and compared with a control group. Two patients were reported to have positive exercise stress test. Left ventricular diastolic abnormality was detected in 23% of the patients [17].

In a study conducted by Pishgoo and colleagues (2007), Iranian veterans with late complications of SM poisoning, underwent cardiac evaluation including Electrocardiography (ECG) (60 patients), Trans Thoracic Echocardiography (TTE) (58 patients) and conventional coronary angiography (7 patients), as clinically indicated, 18 years after initial exposure. Fifty-six subjects (96.5%) showed no significant coronary artery disease. In echocardiographic study, left ventricle diastolic abnormality was reported in 23% of the patients. No considerable valvular or conductive abnormality was reported in the patients. In conventional coronary angiography, one patient had non-obstructive coronary artery disease (CAD) and one patient suffered from single vessel disease [18].

In another case-control study of 22 consecutive SM intoxicated patients and 14 controls (2007), myocardial perfusion scan showed significantly higher prevalence of ischemia in SM exposed patients. Pattern of myocardial perfusion in the subject group was reported to be resembled to mild cardiomyopathic changes or coronary artery diseases [19].

As time passes, complications of SM poisoning may continue and more recognition shall lead to better medical care of the victims. On the other hand, a threat of chemical war or terrorism by SM in the future still exists. Since cardiovascular diseases are the main reason of CWA patients' death [20], and due to inadequate data on this topic in the literature, more investigations will help physicians for better cardiac management of SM patients. We thus aimed to investigate delayed cardiac complications of SM intoxication in Iranian veterans who were exposed to SM around three decades ago during the Iraq–Iran war in 1983–1988.

Materials and Methods

Participants and Sampling

This cross-sectional study was conducted in 2012–2014 on the veterans of Korasan Razavi with delayed complication of SM poisoning following obtaining the University medical research ethics committee and written informed consent from the patients. The veterans who had significant clinical complications of SM poisoning in one or more of the major target organs (respiratory system the skin and eyes) and obtained > 25% disability due to complications of SM poisoning according to the veteran's medical review committee criteria were selected. Out of 45 patients who recruited from the Veterans and Martyrs Affair Foundation (VMAF) of Khorasan Razavi province to Medical Toxicology Research Center, 38 completed the investigations. The study was conducted in a manner consistent with the Declaration of Helsinki.

Demographic data and SM exposure information as well as clinical history and general physical examination were performed by a clinician of the research team and recorded in a pre-designed questionnaire. History of cardiovascular particularly CAD risk factors was also obtained and inputted in pre-designed forms. The following cardiovascular risk factors were obtained: (1) Presence of hypertension: The criteria were systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg or current treatment with antihypertensive agents [21]. (2) Diabetes mellitus type II (defined as two fasting plasma glucose of more than 125 mg/dl, or current treatment with oral hypoglycemic agents or insulin) [22]. (3) Smoking and (4) positive family history of precocious CAD (defined as CAD in first-degree relatives younger than 55 years in men or 65 years old of age in women). The Morise risk score was calculated to stratify pretest cardiovascular risk [23]. Medical Research Council dyspnea scale was used to assess breathlessness severity in the patients, upon which the breathlessness was classified to functional classes of I–IV.

Patients with known cardiovascular diseases (such as significant mitral or aortic valve diseases and atrial fibrillation), known previous reaction to contrast medium and/or renal failure (creatinine clearance < 60 ml/min), inadequate image visualization, acute infection and disinclination to continue, were excluded from the study. Patients with confirmed nerve agent intoxication during the war were also excluded from the study.

Cardiac and Related Investigations

Each participant underwent complete cardiac examination by an experienced cardiologist of the research team. Twelve lead ECG and TTE was carried out for all the patients by a specialist and interpreted by a cardiologist who was blinded to history and examination results of the patients.

ECG was performed exactly after history taking by 12-lead placement and equipment (MAC 5500, GE Healthcare, Milwaukee, Wisconsin). We used "American Heart Association, Inc., American College of Cardiology Foundation, and the Heart Rhythm Society recommendations for the standardization and interpretation of the Electrocardiogram" for ECG interpretations [24].

TTE was carried out by Vivid 7 dimension edition (General Electric Medical Systems), 2 dimensional, M mode Doppler and colour Doppler study was performed. Basic measurements were performed according to the "American College of Cardiology, Inc., American Heart Association and American Society of Echocardiography 2003 guidelines update for the clinical application of echocardiography" [25].

Computed Tomography Coronary Angiography (CTCA) was performed with a single source 64-slice CT system (Somatom Sensation 64 Cardiac, Siemens, Forchheim, Germany). Images for assessment of coronary artery calcium score (CACS) were acquired by a non-contrast enhanced sequential scan just prior to CTCA and analyzed by an experienced radiologist with a commercially available software package (Siemens Calcium Score, Siemens, Erlangen, Germany). CACS were calculated according to the method of Agatston et al. [26]. Based on CACS, patients were divided to four groups: group 1, CACS of 0–10; group 2, CACS of 11–100; group 3, CACS of 101–400; group 4, CACS of more than 400. CTCA was performed after intravenous administration of 115 ml bolus of Visipaque 320 mg, at a flow rate of 4–6 ml/s depending on patient status. Contrast material was administered by power injector via an antecubital vein and was followed by 50 ml of saline bolus chaser at the same flow rate. Nitroglycerin was administered sublingually by dose of 0.3 mg to the patients had no contraindications (severe aortic stenosis, systolic blood pressure < 100 mmHg) [27]. Moreover, if the patients' heart rate was > 65 bpm, beta-blocker (atenolol 5–10 mg) was administered IV, if there was no contraindications (asthma or bronchospasm, systolic blood pressure < 100 mmHg) [27].

Details of scan protocol is described elsewhere [28]. In order to image analysis, the coronary artery tree was segmented according to the modified 15 segment American Heart Association classification [29]. Each segment was evaluated by one cardiologist blinded to the patients' names and one radiologist blinded to the patients' names and underlying SM poisoning. Any disagreement was settled by consensus. The degree of stenosis in coronary arteries was measured using electronic calipers at the level of the largest stenosis and comparing it to a normal segment just proximal and distal to the lesion. Coronary stenosis was categorized as follows: none, mild, ≤ 50% stenosis; moderate, 50–70% stenosis; severe, ≥ 70% stenosis; except in the left main artery where a stenosis of more than 50% was considered as severe stenosis. Segments of coronary arteries that were poorly visualized because of small size, were excluded from the analysis.

Data Analysis

The obtained data were analyzed by an independent statistician using Statistical Package for Social Sciences computer software (SPSS version 16, Chicago, IL, USA) and Prism software version 3.02 (Graph Pad Software, San Diego, CA, USA). Quantitative data were presented as mean ± standard deviation (SD). Qualitative data were shown as numbers and percentage values. Comparison of electrocardiographic and echocardiographic values with maximum standard levels were performed using one-sample Student *t*-test and

Wilcoxon's test, and the test of significance was one-tailed at the significance level of $p = 0.05$.

Results

Subjects

Thirty-eight patients with late complications of SM exposure during Iran-Iraq war with mean chemical disability percentage of 49.73 ± 16.53 were studied. The patients were exposed to SM 25.5 ± 1.7 years before this investigation. All the veterans were male and married with mean age of 51.95 ± 9.7 (range 42–75 years old). Their body mass index (BMI) was 27.89 ± 4.52 (normal < 25). Demographic data and clinical history of the patients are shown in Table 1.

Clinical Findings

Typical chest pain was recorded in 7 patients (18.42%), while 11 patients (28.94%) reported atypical chest pain. Dyspnea was reported in 24 veterans (63.15%), among which functional classes of one to three were reported as 42.10%, 15.79% and 5.26%, respectively.

Electrocardiographic Results

All the patients had normal sinus rhythm. Mean heart rate was 79.21 ± 9.78 (range 65–100). Six patients (15.79%) had normal ECG pattern. QRS durations and voltages and PR intervals was in normal range according to Ref. [24]. Right Axis Deviation (RAD) and Left Axis Deviation (LAD) were recorded in 4 (10.52%) and 2 (5.27%) of the veterans, respectively. ST segment depression was observed in 8

Table 1 Demographic and clinical data, general findings and CAD risk factors in 38 male veterans with delayed cardiac complications of sulfur mustard poisoning in Mashhad, Iran

Demographic characteristics		Histories	
Age (years)	51.95 ± 9.72	Years past from exposure time	25.5 ±1.72
Height (cm)	168.84 ± 6.67	Chemical disability percentage (%)	49.73 ± 16.53
Weight (kg)	79.22 ± 11.43	Symptoms	
BMI (kg/cm^2)	27.86 ± 4.52	Typical chest pain	7 (18.42%)
		Atypical chest pain	11 (28.94%)
Job status:		Dyspnea	24 (63.15%)
Employed	8 (21.05%)		
Retired & unemployed	22 (57.89%)	FC I	16 (42.10%)
Disabled	8 (21.05%)	FC II	6 (15.79%)
		FC III	2 (5.26%)
Educational status:		Pretest likelihood of CAD[a]	
		Low	10 (26.31%)
		Intermediate	16 (42.10%)
More than 11 years	11 (28.94%)	High	12 (31.57%)
Less than 11 years	27 (71.05%)		
Risk factors		Medication	
Hypertension	14 (36.84%)	Acetylic salicylic acid	19 (50%)
		Beta blockers	18 (47.36%)
		ACE/AT1 inhibitors	14 (36.84%)
Hypercholesterolemia	29 (68.42%)	Statins	17 (44.73%)
Diabetes mellitus type II:			
Insulin dependent	2 (5.26%)		
Not insulin dependent	3 (7.89%)		
Obesity (BM≥27 kg/m^2)	21 (55.26%)		
Smoking:			
Former	9 (23.68%)		
Current < 1 pack/day	3 (7.89%)		
Current ≥ 1 pack/day	7 (18.42%)		
Family history of CAD	4 (10.52%)		

Data given as occurrence (percentage) or mean ± standard deviation, otherwise, it is noted in the table

BMI body mass index, *CAD* coronary artery disease, *FC* functional class

[a]According to the Morise scoring method

veterans (21.05%). Pathologic Q wave and T wave inversion was not detected in any of the veterans. Premature Ventricular Contraction (PVC) and Premature Atrial Contraction (PAC) was observed in 6 (15.79%) and 8 (21.05%) of the patients, respectively. Detailed ECG data are presented in Tables 2 and 3.

Echocardiographic Results

Mean value of LVEF (according to Simpson formula) was 55.66 ± 2.93%. Mean measured value of left ventricular end diastolic dimension (LVED) was 44.11 ± 4.99 mm. LV diastolic dysfunction (LV impaired relaxation) was not detected in any of the patients. In fact, all the cases had normal left ventricular filling pressure by echocardiographic study. Mean value of mitral E wave deceleration time was recorded as 223.53 ± 41.89 ms. Mean ratio of early to late ventricular filling velocities (E:A ratio) was 0.71 ± 0.38 in the patients. Right ventricular dilation dysfunction (including all degrees) was detected in 7 (10.54%) patients.

Mild mitral, pulmonary and aortic regurgitations were observed in 36 (94.73%), 18 (47.37%) and 8(21.05%) of the patients, respectively. All the veterans showed at least mild tricuspid regurgitation. None of the patients had any indication for valvuloplasty. Mild degrees of pericardial effusion was observed in 4 (10.52%) patients. Sixteen patients (42.10%) showed increased PAP in echocardiographic studies, however; average value did not show any significant

Table 3 Prevalence of electrocardiographic and echocardiographic abnormalities in 38 male veterans with long-term cardiac complications due to sulfur mustard poisoning in Mashhad, Iran

Variable	Number of patients (%)
Electrocardiographic values	
Right axis deviation (RAD)	4 (10.52%)
Left axis deviation (LAD)	2 (5.27%)
ST segment depression	8 (21.05%)
Incomplete right bundle branch block (incomplete RBBB)	3 (7.89%)
Premature ventricular contraction (PVC)	6 (15.79%)
Premature atrial contraction (PAC)	8 (21.05%)
Echocardiographic values	
Mild mitral regurgitation	36 (94.73%)
Mild tricuspid regurgitation	34 (89.47%)
Severe tricuspid regurgitation	4 (10.52%)
Mild pulmonary regurgitation	18 (47.37%)
Mild aortic regurgitation	8 (21.05%)
Mild right ventricular dilation	2 (5.27%)
Severe right ventricular dilation	5 (13.16%)
Pericardial effusion	4 (10.52%)
Increased pulmonary artery pressure (PAP)	16 (42.10%)

Table 2 Quantitative variables of electrocardiographic and echocardiographic findings in 38 male veterans with long-term sulfur mustard poisoning complications in Mashhad, Iran

Variable (unit)	Results (mean ± SD)	Normal values[a]	*p* Values
Electrocardiographic values			
Heart rate	79.21 ± 9.78	60–100/min	0.999
QRS duration	62.69 ± 13.63	Less than 60 msec	0.490
PR interval	81.53 ± 12.81	Less than 120 msec	0.999
Echocardiographic values			
Left ventricular ejection fraction (%)	55.66 ± 2.93	55–70	0.999
Left ventricular end diastolic dimension (mm)	44.11 ± 4.99	40–55	0.999
Left ventricle out flow tract velocity time integral (cm)	21.44 ± 5.28	> 15	0.999
Early diastolic wave (mitral) (cm/s)	72.44 ± 23.11	< 80	0.999
Accelerated diastolic wave (mitral) (cm/s)	76.83 ± 19.84	< 85	0.901
Early diastolic wave (mitral) deceleration time (msec)	223.53 ± 41.89	150–200	0.047
Early diastolic wave (mitral) tissue Doppler velocity (cm/s)	7 ± 2.99	> 7	0.999
Accelerated diastolic wave (mitral) tissue Doppler velocity (cm/s)	10.55 ± 3.36	> 8	0.995
Tricuspid annular plan systolic excursion (mm)	22.61 ± 4.70	> 18	0.999
Velocity of tricuspid annular velocity by tissue Doppler study (cm/s)	12.38 ± 1.85	> 8	0.999
Tricuspid regurgitation peak velocity (mmHg)	21.64 ± 4.24	< 20	0.200
Pulmonary artery pressure (systolic) (mmHg)	22.64 ± 10.62	< 30	0.999

[a]Normal values are according to the American Heart Association recommendations for standardization of electrocardiogram and echocardiogram (Refs. [24, 25])

increase comparing with normal values. Complete echocardiographic details are shown in Tables 2 and 3.

Computed Tomography Coronary Angiographic Findings

Eighteen patients underwent CTCA according to clinical and echocardiographic assessment (Fig. 1). Out of eighteen SM patients who underwent CTCA, eleven patients (61.11%) had abnormal findings in their coronary arteries. Three patients (16.66%) had non-obstructive CAD and eight patients (44.44%) had obstructive CAD. One patient (5.55%) had occlusion or stenosis in a single vessel, while the occurrence of two vessels and three vessels were 27.77% (5 patients) and 11.11% (2 patients), respectively. Mean CACS was 50.91 ± 115.58. The results of CTCA are summarized in Table 4.

Discussion

Long-term cardiac complications have been observed around 25 years after SM exposure in Iranian veterans of Khorasan-Razavi. Delayed cardiac complications of SM have previously not been investigated in details. Long-term CT- coronary angiographic effects in particular have already not been reported. Both acute and late effects of SM on different organs vary according to different confounding factors such as ambient gas concentration, duration of exposure, route of exposure, gas mask protection, wind direction, activity level of the soldier, humidity and high temperature [9, 10, 30–32]. In our study, according to the document of VMAF, SM exposure was recorded in all the veterans; however, the exposed dose could not be measured during the chemical war, especially when the gas spreads through the area and the combatants remain in the field for several hours/days.

Table 4 CT-coronary angiographic parameters in 18 patients with late cardiac complications of sulfur mustard poisoning during Iran-Iraq war

	Stenosis grade		
	Mild	Moderate	Severe
Coronary artery			
Left main	2 (11.11%)	1 (5.55%)	1 (5.55%)
LAD	2 (11.11%)	4 (22.22%)	3 (16.66%)
LCX	1 (5.55%)	2 (11.11%)	1 (5.55%)
RCA	0 (0%)	3 (16.66%)	1 (5.55%)
Dominancy			
Right dominant	15 (83.33%)		
Left dominant	3 (16.66%)		
Number of vessels affected			
1 vessel disease	1 (5.55%)		
2 vessel disease	5 (27.77%)		
3 vessel disease	2 (11.11%)		
Absence of CAD	7 (38.88%)		
Non-obstructive CAD	3 (16.66%)		
Obstructive CAD	8 (44.44%)		
Obstructive CAD in			
Left main	2 (11.11%)		
LAD	8 (44.44%)		
LCX	4 (22.22%)		
RCA	4 (22.22%)		
Total Agatston CACS	50.91 ± 115.58		
Agatston CACS			
0	10 (55.55%)		
1–100	7 (38.33%)		
101–400	1 (5.55%)		
> 400	0 (0%)		

Data are given as occurrence (percentages) or mean ± standard deviation

RCA right coronary artery, *LAD* left anterior descending artery, *LCX* left circumflex artery, *CAD* coronary artery disease, *CACS* coronary artery calcium score

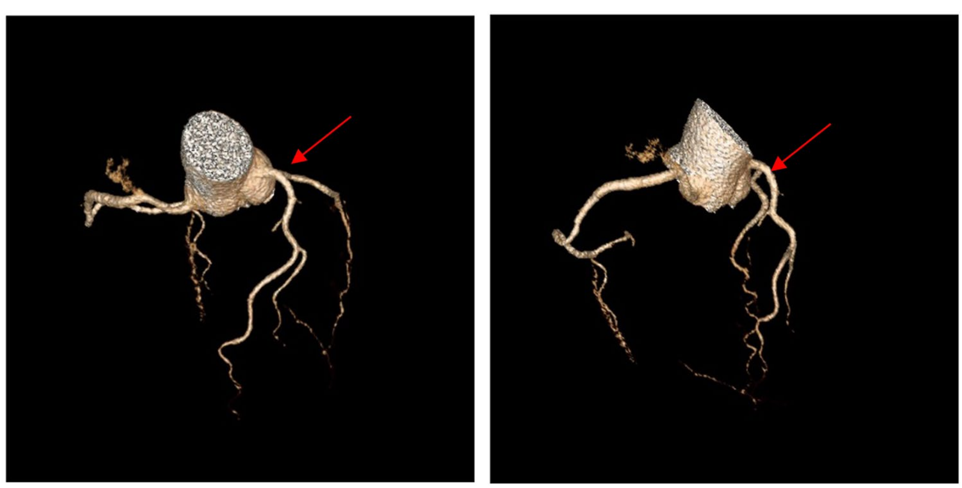

Fig. 1 Coronary CT angiography (CTCA) in a patient with delayed SM intoxication, 3D volume rendering with demonstration of main and side branches. The red arrows show proximal Left Anterior Descending (LAD) stenosis. (Color figure online)

Since all the veterans were poisoned via inhalation, influence of the other routes of entry was negligible [33].

The patients in this study were intoxicated by SM exposure just once during the Iran-Iraq conflict 25.5 ± 1.72 years before the study and they are still suffering from long-term complications. Typical and atypical chest pain was recorded in 18.42% and 28.94% of the patients, respectively. Regarding several pulmonary problems in the veterans associated with chronic cough and dyspnea, and also due to symptoms exaggeration among the veterans for gaining, it does not seem to be a definite cardiac evidence in veterans. In a 24 months cohort study conducted by Iyriboz et al. on 247 SM exposed victims and control group, no cardiac chest pain was reported in the patients [34].

We recorded dyspnea in 63.15% of our patients. Triad of dyspnea, cough and expectoration, as the most common respiratory symptoms, has been reported in most of SM exposed veterans in a previous study [35]. It could be due to the heart involvements such as ventricular impairments and different stages of heart failure as well as lung involvements such as chronic bronchitis, asthma and airway narrowing due to granulation tissues [9, 13, 35–39]. High BMI (27.89 ± 4.52) is certainly a deteriorating factor. However, we believe that RV enlargement and dysfunction can play a role in patients' discomfort. Early diagnosis and management of RV dysfunction can even alleviate respiratory symptoms in the patients.

Ventricular diastolic abnormalities have been previously reported as late cardiac complications and were much more frequent than the ventricular systolic abnormalities in the literature [17–19]. RV diastolic abnormalities were detected in 10.54% of our patients, unlike progressed LV diastolic dysfunction (or impaired relaxation of LV filling) which was not reported in any of the patients. According to the respiratory disorders in the veterans, as one of the most common long-term SM complications, such as bronchiectasis, bronchiolitis obliterans and lung fibrosis, which can lead to the well-known cor pulmonale phenomenon [38, 39], role of cardiac performance in occurrence of this phenomenon remains to be clear. Moreover, respiratory disorders in SM exposed veterans tend to increase the restrictive patterns over the time leading to increased RV pressure and subsequent cardiac effects in these patients [13, 40]. Increased RV size in these patients corroborates the hypothesis of potential effect of SM in developing some degrees of dilated cardiomyopathy with predominant effect on right ventricle, though, the hypothesis needs further investigations to be proven.

In our study, Mean value of PAP was in normal range, however, mild increased PAP was recorded in 42.10% of the patients. Gholamrezanezhad et al., in scintigraphic myocardial perfusion scans in 22 Iranian veterans with late complications of SM and 14 controls, have declared that patterns of myocardial perfusions in case group was significantly different from the control group and was resembled to either coronary artery disease or cardiomyopathic changes. The authors also noted that both dilated RV chambers and ischemia were significantly more prevalent among SM patients [19].

It seems that right ventricular dilation and diastolic dysfunction are the most striking long-term echocardiographic findings among SM veterans. It might be due to respiratory complications of SM poisoning, as the most common finding in previous reports, or cardiac and other non-cardiac etiologies of diastolic dysfunction.

The current study was the first study on delayed CT-angiographic changes of coronary arteries due to SM, worldwide. Previously, Shabestari et al. in a case-control study on 40 mustard-poisoned patients, reported coronary artery ectasia as the most finding of conventional angiography with a prevalence of 22.5% versus 2.2% in the control group. They concluded that coronary ectasia occurs approximately 11 times more frequently in SM poisoned veterans [16]. Contrary to that result, in the current study, we did not detect coronary ectasia in CTCA study in any of the patients. The discrepancy could be due to both differences in severity of injuries and prevalence of CAD risk factors, as known CAD patients had not been excluded from the former study. However, it has been stablished that chronic inflammation may cause ectasia formation in coronary arteries [41], therefore, it seems that further studies with large samples are required in this case.

More recently, Karbasi-Afshar et al. compared conventional angiography findings of SM exposed patients with unexposed ones, after two decades of SM exposure during Iran-Iraq war and reported significantly higher incidence of atherosclerotic lesions among SM patients, compared to control group. Single vessel, two vessel and three vessel diseases in the study group were reported as 12%, 38% and 42%, respectively, which were significantly higher than the control group [42].

Our results are in contrast with Shabestari el al. [16] findings, as we have observed different degrees of coronary artery stenosis but no coronary artery ectasia; but, is in agreement with Pishgoo et al. [18] and Karbasi-Afshar et al. [42] studies. With regard to sparse data in the literature, delayed SM cardiac complications should be more evaluated in the future.

Conclusion

Regarding to our findings and also previous studies focused on cardiac effects of SM, we conclude that strong correlation between SM and heart diseases exists. Knowledge about long-term mustard-induced cardiotoxic effects can provide us with new preventive and screening routes to alleviate patients' complications. Considering that late toxic effects of SM are more serious than the acute effects [43], and with Regard to cardiovascular diseases as the main reason of CWA patients' death [20, 44], we recommend yearly cardiac checkup and echocardiography follow up for SM intoxicated patients. Early detection and management of right ventricular dysfunction should be considered in long-term SM exposed victims to prevent right ventricular heart failure and aggravated functional capacity. Additionally, extensive preoperative cardiac evaluation should be considered in cardiac or non-cardiac surgeries in patients with long-term complications of SM exposure [45].

In this study, findings of quantitative variables from ECG and TTE, was compared with maximum standard levels. We should emphasize that one limitation of our study was absence of a control arm beside the study group. Thus, SM cannot be specified as the only cause of cardiac complications among the victims. It cannot even be concluded whether SM has direct effects on cardiac dysfunction- particularly on right ventricular diastolic dysfunction- or play its role through respiratory complications, as the most long-term SM complications. In the current study, long-term cardiac complications of SM were revealed and the need for early detection and management of mentioned disorders was emphasized. Long-term cardiac effects of SM could be more evaluated in the presence of adjusted control group in future studies. Also, the study findings should be addressed in a larger series of patients to reduce confounding cardiovascular risk factors contributing to the overall risk to the patients.

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Compliance with Ethical Standards

Conflict of interest All authors state that there is no potential conflict of interest with respect to the research, authorship and/or publication of this article.

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