Original Article

Coronary angiography findings in lung injured patients with sulfur mustard compared to a control group

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ABSTRACT

Aims and Objectives: We evaluated the incidence of coronary artery disease (CAD) in Sulfur mustard (SM) exposed veterans. We also evaluated the relationship between exposure to SM and angiography findings and compared angiography findings of SM exposed individuals with unexposed ones after two decades from the time of exposure to SM. **Materials and Methods:** A case-control study was conducted on 200 consecutive patients (100 SM exposed vs. 100 unexposed) undergoing angiographic assessments due to CAD. **Results:** The coronary angiography findings between two groups were significantly different ($P < 0.001$). Ninety two (92%) patients in SM exposed group and 82 (82%) in unexposed group had abnormal findings in their coronary arteries ($P = 0.031$). **Conclusions:** The incidence of CAD and angiographic changes were significantly increased with exposure to SM. Further studies on cardiovascular effects of SM are needed.

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INTRODUCTION

Coronary artery disease (CAD) is one of the most important causes of acute cardiovascular event, which is characterized by coronary arterial stenosis and atherosclerotic plaques on angiographic study. These patients are often referred to the medical care centers with typical and atypical chest pain, and/or dyspnea on exertion. Many intrinsic and extrinsic factors have been identified which can injure endothelium of arteries. One of the well-recognized pathogenesis of atherosclerosis is endothelial injuries (EI) and the ability of the endothelium to repair it.[1-4] Hyperlipidemia, especially hypercholesterolemia, aging, male gender, and hypertension are well-identified factors, which predispose patients for atherosclerosis and CAD.[4,5] Nicotine inhaled during smoking, medications, bacterial endotoxins, venom, synthetic toxins, and other chemical substances are recently identified toxins, which can induce atherosclerosis via EI.[6-9] Sulfur mustard (SM), an alkylating chemical agent, was used during Iraq-Iran conflict (1980-1988). SM can induce cell injuries in various organs even with a single exposure.[10] Some of the long-term complications of SM exposure are explained, but cardiovascular changes has not been studied well.[11-13] In this study, we evaluated CAD prevalence and its characteristics by angiography among patients with a history of SM exposure and compared to un-exposed peers as a control group.

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MATERIALS AND METHODS

A case-control study was conducted on patients who were selected from cases undergoing coronary angiography in the Baqiyatallah University Hospital, Tehran, Iran between May 2009 and June 2010. We included all patients who have suffered CAD symptoms like acute chest pain and have experienced stable angina at least once. These subjects had positive tests for inducible angina including: Dobutamine

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stress echocardiography, Exercise stress test, or Thallium single photon emission computed tomography. Patients who had a previous history of coronary artery bypass grafting or coronary angioplasty and/or were treated with medication which can potentially affect the cardiovascular system were excluded.

Thus, 100 subjects with above criteria and a history of SM inhalation (low dose and single exposure) and mild respiratory symptoms and mild air trapping in high resolution computed tomography (HRCT) were selected as SM exposed group (case group) and compared with another 100 patients with above criteria but without history of SM exposure (unexposed group; control group). These participants were matched for age, sex, military service, tobacco use, and socio-economic status using the block randomization method. Furthermore, exposure to SM was confirmed by using the medical records in the Veterans and Martyrs Affair Foundation. This study was performed as per the rules outlined in the Declaration of Helsinki. All patients were negative for Hepatitis B surface antigen; anti-Hepatitis C virus and anti-human immunodeficiency virus antibody; these tests were routinely checked before coronary angiography in this medical center. Coronary angiography was performed and analyzed by a cardiologist who was blinded to the study. Analysis of the angiograms was carried out offline by the same cardiologist. A more than 50% decrease in diameter of the coronary artery was considered significant CAD.[14] The C type lesion was defined based on American College of Cardiology/American Heart Association criteria as a lesion with following characteristics: Diffuse (> 2 cm length) lesion, excessive tortuosity of proximal segment, extremely angulated segments (> 90°), and inability to protect major side branches.[15] Baseline and laboratory characteristics such as body mass index, systolic, and diastolic arterial blood pressures, fasting lipid profile including serum total cholesterol, and total triglycerides were also measured and recorded.

The SPSS 17 was used for statistical analysis. Mean ± standard deviation (SD) and the percentage were used for description of continuous and categorical variables, respectively. Normality of continuous variables was checked by Kolmogorov-Smirnov criterion. Student's *t*-test and Mann-Whitney U-test were used for comparison of continuous variables between two groups; categorical data (e.g., coronary angiography findings) were compared using χ^2 and ANOVA tests. A $P < 0.05$ was considered statistically significant.

RESULTS

The mean age (± SD) of the SM exposed and the non-exposed patients was 52.7 ± 4.5 and 53.3 ± 7.1 years, respectively. Twenty three and 22 cases were smoker in the exposed and unexposed groups, respectively; and 14 and 12 cases in these groups had a previous history of myocardial infarction. All subjects were male and there was no significant difference in demographic findings between the two groups ($P > 0.05$). The demographic characteristics of patients are shown in Table 1. All the cases in SM exposure group had mild pulmonary injuries (based on HRCT findings; mild air trapping).

The incidence of angiographic abnormality between the two groups was significantly different ($P < 0.001$). Ninety two (92%) patients in SM exposed group and 82 (82%) in non-exposed group had abnormal findings in their coronary arteries ($P = 0.031$). Twelve patients (12%) in the study group had occlusion or stenosis in a single vessel against 52 patients (52%) in the control group ($P = 0.004$). The occurrence of stenosis in two vessels and three vessels were 38% and 42% in the study group and 17% and 13% in the control group, these differences were statistically significant (0.025 and 0.009, respectively). There was no significant difference in incidence rate of C type lesion between two groups (21% vs. 19%, $P = 0.197$) [Figure 1].

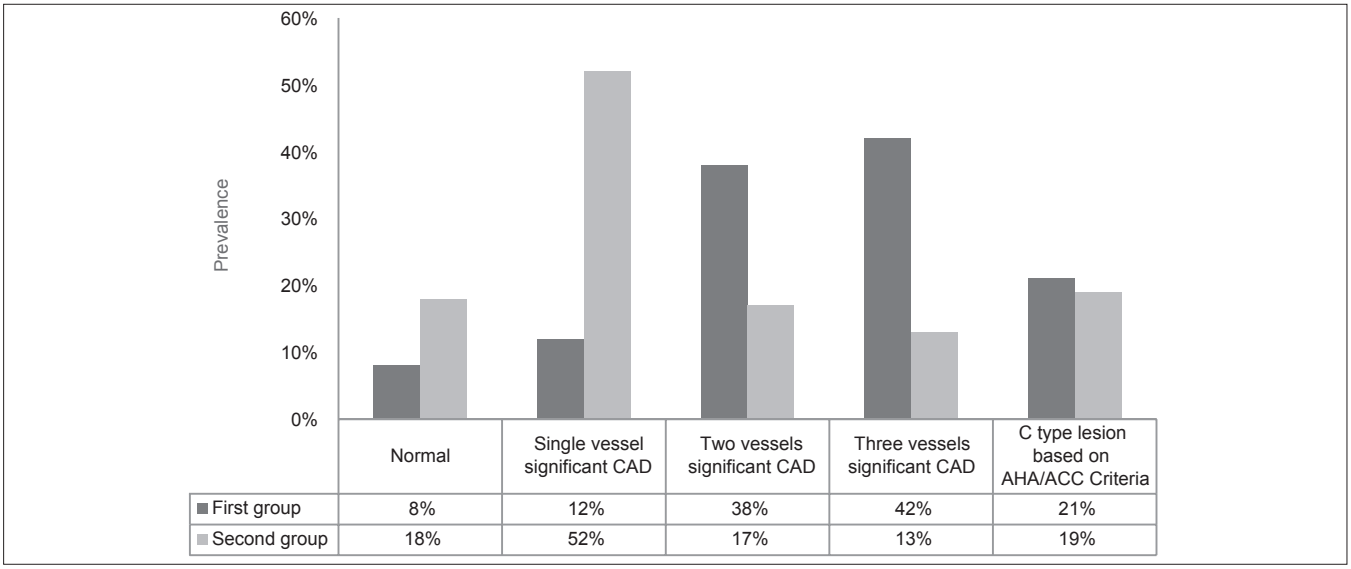
DISCUSSION

The incidence of coronary atherosclerotic lesions among SM exposed patients was significantly higher compared with the control group; however, the type of lesions was not different between them. This study is one of the preliminary studies on the coronary angiography

Table 1: Demographic characteristics in SM exposed group (case group) and unexposed group (control group)

Variable	Case group	Control group	*P* value
Mean age ± SD	52.7 ± 4.8	53.3 ± 7.1	NS
Patients (male ratio) (%)	100	100	-
Systolic blood pressure (mmHg)	133.4 ± 9.1	132.1 ± 10.2	NS
Diastolic blood pressure (mmHg)	84.4 ± 3.4	85.3 ± 2.4	NS
Smoker (%)	23	22	NS
BMI (kg/m^2)	28.1 ± 2.3	27.7 ± 2.6	NS
Diabetes mellitus (%)	12	13	NS
Previous MI (%)	14	12	NS
Serum total cholesterol	230.1 ± 40.7	229.6 ± 36.4	NS
Serum total triglyceride	290.3 ± 40.5	281.2 ± 38.9	NS

SD: Standard deviation, SM: Sulfur mustard, BMI: Body mass index, NS: Not significant, MI: Myocardial infarction



	Normal	Single vessel significant CAD	Two vessels significant CAD	Three vessels significant CAD	C type lesion based on AHA/ACC Criteria
First group	8%	12%	38%	42%	21%
Second group	18%	52%	17%	13%	19%

Figure 1: Coronary angiography findings in sulfur mustard exposed group (case group) and un-exposed group (control group)

findings in chemically injured patients, although, pulmonary, ocular, and cutaneous consequences of SM exposure were described previously.[10] In a similar study, Rohani *et al*., investigated 50 SM injured patients by exercise test and echocardiography.[13] They found 4 patients with abnormal exercise test and they also had CAD. They also found that the prevalence of diastolic dysfunction was significantly higher among SM injured patients compared with the control group. However, they did not perform coronary angiography for all cases; therefore, the incidence of CAD in their study is not available. Shabestari *et al*., demonstrated that ectasia of coronary artery was more frequent in SM injured patients than unexposed ones (OR: 11). In the present study we did not evaluate cases for coronary artery ectasia, which is a limitations of this study.[16] It is established that chronic inflammation can predispose coronary artery for ectasia formation.[17] Gholamrezanezhad, *et al*., assessed myocardial perfusion by scintigraphic patterns in 22 subjects who were exposed to blistering gases.[11] They found that the prevalence of ischemia in the injured cases was higher than controls and the pattern of myocardial perfusion in exposed patients was significantly different from controls. They proposed that these changes in myocardial perfusion may be due to CAD or mild cardiomyopathy changes in exposed patients; however, they did not evaluate these patients by angiography, therefore, their findings cannot be compared with our findings. We, additionally, found that coronary atherosclerotic plaques in exposed cases were more extensive and frequent than controls. Regarding our findings and some surveys focused on cardiac effects of SM, it seems that there is a strong correlation between SM exposure and heart diseases; it further appears that time from exposure, duration of exposure and severity of lung diseases are confounding factors and can affect beginning and progression of heart disorders in these exposed cases.

Lung injuries are the most lethal and disabling consequences of SM, which are described as bronchiolitis obliterans. It seems that late toxic effects of SM are more important and more serious than the acute effects.[18] There are cellular and molecular changes, which help to understand the late systemic effects of SM. Two important pathways were introduced for pathogenesis of SM injuries; inflammatory pathway and oxidative-anti-oxidative pathway. According to the first theory there is an increase in serum and tissue levels of inflammatory markers. Attaran, *et al*., demonstrated that the serum levels of highly sensitive C-reactive protein (CRP) was raised in patients exposed to SM and may have a direct correlation with severity of disease.[19] Earlier, CRP was shown as an inflammatory marker and has a direct correlation with the presence of coronary atherosclerotic disease.[20] However, higher levels of other inflammatory markers such as tumor necrosis factor-α, interleukin 1, 6, 8, and transforming growth factor beta (TGF-β) have been shown in SM injured patients in previous investigations.[10,18,21] These markers can be a significant risk factor for CAD as well.[22-24] Further, it was shown that TGF-β has a significant role in progression and development of both coronary atherosclerosis and SM lung injury.[18,25]

Recently, the oxidant-antioxidant imbalance has been implicated in the SM toxicity and pathogenesis of

CAD. Lower level of serum antioxidants have been confirmed in SM exposed subjects.[10,18] Shohrati, *et al.*, demonstrated that SM injured patients with higher severity of injures had a decreased level of glutathione than those with mild injuries.[26] Furthermore, it was shown that glutathione peroxidase is associated with CAD.[27] Likewise, the role of antioxidants on protecting and modulating endothelial cell dysfunction especially in patients, who were exposed to reactive oxygen species and free radicals has been established.[2,28] The medications, which enhance the antioxidant supply such as N-acetyl-cysteine and curcumin can be effective on the cardiovascular system health[29,30] and late complications of SM.[31,32]

Other long-term complications of SM can confound mentioned association. For example, pulmonary fibrosis, pulmonary hypertension or bronchiectasis, a consequence of SM injuries, can affect cardiovascular health.[33] Further, it has been shown that cardiovascular health can be affected by psychological factors such as anxiety disorders,[34] which is more frequent among SM injured patients than the normal population although all cases (exposed and unexposed subjects) had a similar risk profile including psychological distress.[35] Other limitations of this investigation were lack of echocardiographic study and scintigraphic myocardial perfusion scan, which could have helped assessing heart function. Apparently, in patients exposed to SM, extensive preoperative cardiac evaluation should be considered before cardiac or non-cardiac surgeries.[36]

In conclusion, SM as a chemical warfare agent can injure several organs in the short or long term. Although the majority of previous studies explained pulmonary, ocular and cutaneous consequences of SM, we found evidences of a relationship between SM exposure and cardiovascular toxicity in long-term. However, those exposed to SM need to be counseled on this issues and probably screened routinely. Further studies are needed for assessment of the cardiovascular status in SM injured patients.

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