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Sulfur Mustard Exposure and Cardiovascular Effects: A Review

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Abstract

Sulfur mustard (SM) has been used as a chemical weapon in some conflicts, and many veterans and civilians have been injured thereby. Pulmonary, cutaneous, and ocular effects of SM have been frequently reported, although it seems that other organs such as the cardiovascular system are probably also affected. There are a number of studies evaluating the cardiovascular impacts of SM. However, these are dispersed and unfocused. In this paper, these studies have been reviewed to draw conclusions about the cardiovascular effects of SM. It seems that there is a probable relationship between SM exposure and cardiovascular toxicity in the long term. It appears that coronary artery diseases especially coronary ectasia and diastolic dysfunction are among the significant cardiovascular abnormalities frequently seen in these patients. Abnormal coronary arteries may occur due to direct endothelial injury by SM, sustained inflammatory status in patients with chronic lung disease, and abnormal mediators of tissue injury and repair or oxidative stressors.

Keywords: Cardiovascular System, Heart, Sulfur Mustard, Chemical Warfare Weapons

1. Introduction

Many toxins are known to injure the heart and cardiovascular system. Some other toxins, such as alkylating agents and cancer chemotherapeutic treatments that affect the cardiovascular system, have been identified as well (1). Among these toxins are potential chemical weapons that humans rarely encounter, which can have an impact on the cardiovascular system. Sulfur mustard (SM) was used by Iraqi forces against veterans and civilians in the Iraq-Iran conflict (1980-1988). SM is an alkylating agent that can induce cell injury in various organs, even after one exposure (2). Some of the long-term complications of SM exposure such as pulmonary (mainly bronchiolitis obliterans (BO), ocular, and cutaneous consequences have been well explained; however, the probable cardiovascular impact of SM exposure has not yet been fully studied or elaborated upon (2-5). Specific defects of all mentioned organs have been defined, and their pathogenesis has been studied, although the findings have not revealed an accurate or definite mechanism of injury. There are some shared cellular and molecular characteristics between mechanisms of injury in the cardiovascular system and the injury caused by SM.

SM exhibits rapid distribution from the lung capillary bed to the blood circulation, with a long terminal half-life ($t1/2\alpha$ = 5.56 minutes; $t1/2\beta$ = 3.59 hours). Eight hours after administration, unchanged SM is still detectable in the systemic blood circulation (6). Given this, we can postulate a potential relationship between SM exposure and cardiovascular disorders. Some studies have evaluated the cardiovascular impacts of SM, but they seem to be dispersed and unfocused. In this study, we have evaluated the cardiovascular impacts of SM among published articles dealing with patients with a history of SM exposure. The Medline database was reviewed to interpret and present the data in separate sections according to the assessment tools and procedures.

1.1. Angiographic Findings

Coronary artery ectasia in SM injured patients is more frequent than in non-injured patients. In a rare study on this issue, a case-control investigation on 40 SM injured patients and a non-exposed control group who underwent coronary artery angiography due to typical chest pain was conducted.

Shabestari et al. demonstrated that ectasia in the coronary arteries is more prevalent in SM injured patients than in non-exposed cases. They found that 15 (37.5%) cases in the case group and two (5%) individuals in control group had coronary artery ectasia. The main artery that was affected by ectasia was the left anterior descending artery. The odds ratio in their study was estimated at 11.4, and it was also estimated that the prevalence of coronary artery ectasia is 6.2 times higher in SM exposed cases than in non-exposed

cases with similar symptoms and indications for angiography. This difference may be due to the occupation of the patient, which in our case was military (either exposed or non-exposed subjects); these patients also had other risk factors, such as psychological distress (7).

The first study to suggest a significant correlation between SM exposure and coronary artery ectasia was a recently published study by Karbasi-Afshar et al., which was conducted as a case-control study on 200 consecutive patients (100 SM lung injured patients vs. 100 matched non-injured patients). In this study, it was discovered that severity and distribution of atherosclerotic lesions were significantly higher in exposed patients than in non-exposed ones. In this regard, the researchers found that the frequency of occlusion or stenosis in two vessels and in three vessels was 38% and 42%, respectively in the exposed group and 17% and 13%, respectively in the non-exposed group (8). In addition, Pishgoo et al. described coronary angiographic findings of seven SM injured patients, and they reported one case with abnormal findings (4).

There is some evidence linking the pathogenesis of coronary artery disease and SM injury. Many intrinsic and extrinsic factors have been identified that can injure the endothelium of arteries. One of the well-recognized pathogenesis pathways of atherosclerosis is endothelial injury (EI) and reduction in the ability of the endothelium to repair itself (9-12). It has been established that chronic inflammation, similar to that found in SM injury, can predispose the coronary artery to ectasia formation (13). This association has not been found in certain animal studies; however, all human studies have reported that ectasia in the coronary artery occurs in the long-term and after high-dose exposure to SM.

1.2. Echocardiographic Findings

Rohani et al. investigated 50 SM exposed cases with a mean age of 45.6 $\pm$ 6.2 years by echocardiography and they found that the prevalence of left ventricular (LV) diastolic dysfunction was significantly higher in SM injured patients (23%) than in the control group (5%) ($P = 0.02$) (5). They concluded that LV dysfunction was the most common cardiovascular abnormality in the echocardiographs of SM exposed patients. They also demonstrated that the mean ejection fraction in SM injured patients was significantly lower than in controls. The right ventricular (RV) diastolic dimension was significantly higher in SM exposed cases than in controls. They did not report a significant valvular abnormality in these two groups (LV and RV). Although it seems that their case and the control groups were not carefully matched, their study can be useful in the echocardiographic assessment of these patients.

Pishgoo et al. (4) reported 13.7% mitral valve prolapse among 58 SM injured patients (a mean age of 46.3 + 9.18 years), and, similar to the results of Rohani et al. (5), they reported LV diastolic abnormalities at 24.13%. They stated that this LV dysfunction can be due to "increase in diastolic filling pressure responsible for occurrence of dyspnea that is revealed in Doppler echocardiography of mitral valve flow with decreased E wave (early left ventricular filling velocity) and increased A wave (velocity of LV filling contributed to axial contraction)" (14). Echocardiographic findings have shown that diastolic dysfunction is the most common abnormality in SM exposure.

1.3. Exercise Test

In 2008, Rezaian et al. assessed exercise intolerance and chronotropic impairment in 51 patients with SM exposure (a mean age of 30.7 $\pm$ 5 years) in a paired-comparative study using a spirometric and exercise tolerance test that covers parameters such as FEV1/FVC, heart rate (beats/min), diastolic/systolic blood pressure (mm-Hg), and resting HR. They compared the results of the two groups of patients with chronic bronchitis with/without exposure to SM (15). In addition to these two groups, findings on a group of healthy veterans with no SM exposure were compared with each other. The outcome of the study revealed that exercise capacity was similar in exposed and non-exposed patients, whereas it was significantly lower than in non-exposed, healthy individuals ($P < 0.001$).

They also reported that the mean resting heart rate was remarkably higher in exposed veterans than in non-exposed individuals with bronchitis, whereas the mean peak exercise heart rate of these veterans was significantly lower than that of chronic obstructive pulmonary disease (COPD) patients ($P = 0.01$). Significantly lower peak exercise heart rates were observed in exposed and non-exposed patients with bronchitis compared than in the healthy veterans. The metabolic equivalents and the total duration of exercise were not significantly different in exposed cases in comparison with non-exposed patients, whereas the difference was noticeable in healthy individuals. They concluded that "SM exposure can restrict the exercise capacity and abolish the normally expected chronotropic response to exercise" (15).

Rohani et al. investigated 50 SM injured patients using echocardiography and the exercise test (5). They also found that two (4%) cases with abnormal exercise test results had coronary artery disease (CAD). They found that the prevalence of diastolic dysfunction was significantly higher among SM injured patients than in the control group.

In a recently published study, Aliannejad et al. assessed SM exposed patients and compared them with controls us-

ing the cardiopulmonary exercise test. They found that only exercise capacity index (WR max), peak VO2/kg, VO2 predicted, and peak respiratory rate were statistically different between the two groups. Moreover, peak VO2 and predicted VO2 in the case group were significantly lower than in the control group (16).

Normal exercise stress tests and exercise tolerance tests in these cases were reported at 90.6% by Pishgoo et al. (4), although they did not compare their results with those of controls. Consequently, their results were not constant. Additionally, in an observational study, Tavakolipour et al. reported findings of six minutes to complete a walking test among 19 cases with a history of SM exposure (17). They stated that these patients could walk 263 ± 82 m, whereas a recent report estimated a normal amount as 571 ± 90 m, which is higher than that of SM exposed patients (18).

Abnormal cardio-pulmonary response to exercise can be caused by impaired sympathetic response in addition to post-synaptic β-adrenergic desensitization, baroreceptor abnormalities, or attenuated sinus nodes, none of which have been assessed in patients with SM injuries (19). Although an impaired cardiopulmonary exercise test was observed in these patients, it was declared that the severity of impairment of this test does not depend on the severity of lung injury (20).

The long-term cardiovascular consequences of mustard gas-exposure are quite limited; however, it is clear that it can limit exercise capacity and abolish the normally expected chronotropic response during exercise.

1.4. Heart Perfusion Scan

Gholamrezanezhad et al. assessed myocardial perfusion by scintigraphy (a one-day stress and rest protocol using 99mTc-MIBI) in 22 subjects (21 males and one female, all < 44 years) who were previously exposed to SM and compared the results with those of 14 controls (3). They concluded that the prevalence of myocardial ischemia in the injured cases was outstandingly higher than in controls; to be precise, it was exactly 3.2 times higher than in non-exposed controls ($P < 0.05$). It is worth mentioning that based on the Framingham criteria, all cases had a cardiovascular risk of less than 5%. The researchers reported that "the prevalence of non-homogeneity of uptake and left and right ventricular enlargement in both visual and quantitative analyses in the SM exposed patients were higher than in unexposed controls" (3).

An affected ejection fraction in the exposed patients has also been reported in comparison to the controls by measuring the size of the myocardium cavity. They reached the final conclusion that the pattern of myocardial perfusion in exposed patients is dramatically different from that of normal controls. They also proposed that these changes in myocardial perfusion may be due to CAD or mild cardiomyopathic changes in these cases; however, they did not evaluate patients by angiography. Therefore, their findings were not interpretable for CAD. Moreover, Pishgoo et al. demonstrated their findings about stress myocardial imaging in these patients, and they found that 24% of them have shown abnormal results, including decreased tracer uptake in a surface and reversible or fixed abnormal segments (4). Therefore, that pattern of myocardial perfusion in these patients is significantly different from that of normal controls, which could resemble either coronary artery disease or mild cardiomyopathic changes.

1.5. Pulmonary Hypertension

Pulmonary hypertension (PHT) is one of the challenging issues in SM exposure. Some studies have confirmed that PHT was not observed in these patients (4); however, it seems that the presence of PHT hinges upon the severity of pulmonary injury and the type of long-term pulmonary consequences. The frequency of lung disease among SM exposed patients, except BO, was reported as follows: bronchiectasis (32.5%), hyper-reactivity of airway (25%), large airway narrowing (15%), pulmonary fibrosis (7.5%), and simple chronic bronchitis (5%) (21). Pulmonary fibrosis, emphysema, or bronchiectasis as a consequence of SM injuries can affect pulmonary arterial pressure (21-24).

Abnormal angiogenesis (due to vascular endothelial growth factor (VEGF) over production due to impaired tissue repair) can provide a widespread vascular bed in the injured lung (25). Other clinical evidence that has confirmed excess angiogenesis in these patients results hemoptysis and bronchoscopic findings (26). Pishgoo et al.'s findings confirmed this hypothesis; they demonstrated that out of 58 SM injured patients, only one case had abnormal pulmonary arterial pressure (PAP = 28) and tricuspid valve regurgitation (4). Conversely, Tavakolipour et al. reported 20 SM exposed cases with PHT (pulmonary arterial pressure in Doppler echocardiography) who were treated by Sildenafile; however, the type of pulmonary consequence of the exposure has not been specified (17).

Unpublished studies conducted at our center have shown that pulmonary hypertension can be increased by increased expression of inflammation factors such as IL-8 and TNF-α and oxidative stress. Changes in the expression pattern of these factors can be achieved with epigenetic drugs, resulting in a return to their normal state.

1.6. Electrocardiologic Findings

It seems that results of electrocardiography (ECG) depend on the time of the follow-up process after the exposure. No heart abnormalities were observed among 65 SM

exposed victims of the Iran-Iraq conflict treated in European hospitals in the acute phase after the exposure (27). In addition, it was reported that mild tachycardia can be seen in the acute phase of the exposure (i.e., 18 - 24 hours following the exposure, among children and young adults, due to post-stress anxiety disorder (28).

In a study on 60 SM injured patients after at least 18 years of exposure, only 1% of the abnormalities including 0.5% hemi-block and 0.5% ST segments changes in the conductive system of the heart were observed. For many cases being and also lack of a control group are the main limitations of this report. In another study, Rohani et al. did not report an abnormal conductive disorder in 50 SM exposed veterans compared to the non-exposed controls (5).

In an observational study on 247 SM exposed workers conducted by Yuruk Iyriboz during the first four days after the exposure, sinus arrhythmia (95%) was the most common conductive disorder (95%), which was followed by first- and second-degree blocks (35%), premature ventricular contractions and premature atrial contractions (10%), and nonspecific ST-T segment changes (36%); however, after six months, the ECG abnormalities returned to normal (29).

1.7. Cardio-Metabolic Evidence

Obesity, hyperlipidemia (especially hypercholesterolemia), aging, male gender, and hypertension are well-identified intrinsic factors that predispose patients towards atherosclerosis and cardiovascular disease (12, 30). Accordingly, SM injured patients, due to their limitations in physical activity, are susceptible to these factors, such as obesity. In a cross-sectional study conducted by Ghoddousi et al. on 434 SM induced cases of BO, it was demonstrated that 47.2% and 17.5% of patients were overweight and obese, respectively (31). A significant relationship between body mass index and disease severity indicated by clinical and HRCT assessment has not been found in the above-mentioned study (P = 0.02). In addition, Aliannejad et al. in a study on 159 SM exposed cases, with low dose SM in comparison with normal individuals, found that the possible cause of the differences in cardiopulmonary exercise test results can be due to a defect in cellular O_2 metabolism (16).

On the other hand, sleep disorders are likely to be observed in patients with chronic pulmonary disorders and can predispose these patients to heart diseases, such as CAD (32, 33). In the same vein, Vahedi et al. assessed potential correlations between chronic obstructive airway disease (COPD) and sleep disorders (obstructive sleep apnea) in 30 male SM injured patients, and they eventually concluded that patients with less severe COPD had a significantly higher rate of apnea-hypopnea index (34). It is possible that lung injury via periodic intermittent apnea-hypopnea provides a situation conducive to the production of free radical and endothelial injury and finally the development of CAD (35, 36).

1.8. Biochemical and Laboratory Findings

Lung injuries are the most lethal and disabling consequences of SM, which have been mostly indicated as BO. It seems that late toxic effects of SM are more important and more serious than the acute effects (37). There are cellular and molecular evidences that support the late systemic impacts of SM. Two important pathways have been introduced for the pathogenesis of SM injuries: the inflammatory pathway and the oxidative-antioxidative pathway.

Increases in serum and tissue levels of inflammatory markers support the first theory. Attaran et al. demonstrated that the serum level of hs-CRP (highly sensitive C-reactive protein) had risen in patients exposed to SM and may have had a direct correlation with severity of disease (14). On the other hand, it was established that CRP, as a remarkable inflammatory marker, has direct correlation with the presence of coronary atherosclerotic disease (38). Higher levels of other inflammatory markers such as TNF-α, interleukin 1, 6 and 8, and transforming growth factor beta (TGF-β) in SM injured patients have been shown by previous investigation (2, 37); this can be a significant risk factor for CAD as well (39-41). It has also been documented that COPD, as a form of local airway inflammation, releases inflammatory mediators into the systemic circulation and may contribute to an increase in cardiovascular disorders in these patients (42). Furthermore, it was recommended that TGF-β plays a significant role in the progression and development of both coronary atherosclerosis (43) and SM lung injury (37).

In addition, oxidative-antioxidant imbalance has recently been suggested as a mechanism for SM toxicity and pathogenesis. Lower levels of serum antioxidants in patients suffering from SM injuries supports the oxidative-antioxidant imbalance hypothesis (2, 37). Shohrati et al. demonstrated that SM injured patients with higher severity of injuries had lower levels of glutathione than those with mild injuries (44). In addition, it was shown that glutathione peroxidase can be associated with CAD (45).

Likewise, the role of the antioxidant system in protecting and modulating endothelial cell dysfunction, especially in patients who were treated by reactive oxygen species and free radical molecules, was established (10, 46). Moreover, mediations that enhance the antioxidant supply, such as N-acetylcysteine and Curcumin, can be effective in both improving cardiovascular system health (47, 48) and treating the late complications of SM (49, 50). How-

ever, there are no studies on the therapeutic effects of antioxidants on cardiovascular systems in these patients.

In addition to oxidative stress-antioxidant imbalance, the roles of increased nitric oxide (iNOS), nitro-oxidative stress, peroxynitrite (ONOO-) production, activated nuclear factor-kappaB (NF-kappaB), activator protein-1 (AP-1), and depleted nicotinamide adenine dinucleotide (NAD^+) in the pathogenesis of SM injury have been partially identified (51, 52). In addition, the mentioned molecules and mediators play a remarkable role in cardiovascular disorders, such as endothelial injuries secondary to reactive oxygen species and toxins (9, 45, 53). Although the inflammatory process is carried out in airway leaking, even small amounts of these mediators within the systemic circulation can affect other organs.

For example, when vast amounts of the body's supply of coenzyme NAD(P)H, which plays an important role in the cellular energy crisis, are consumed to repair damaged DNA by SM due to over-activation of the PARP system, injuries of other tissues that have routinely occurred may remain without effective repair in addition to the defect in mitochondrial cells, resulting in energy crisis (45). Moreover, the defect in mitochondrial oxygen metabolism in SM exposure can explain the impairment in the cardiopulmonary exercise test while O_2 saturation is normal (54).

Attaran et al. reported that "the serum hs-CRP level is increased in SM patients with bronchitis and may have a direct correlation with disease severity"(14). They have also recommended this inflammatory biomarker to estimate the severity of lung injury in patients with SM exposure. On the other hand, the relationship between the increased level of CRP and cardiovascular diseases, especially CAD, was clarified (55). The increased level of inflammatory biomolecules due to sustained inflammation can predispose cardiovascular systems to CAD or other disorders.

In a study on pulmonary injured patients with SM compared with controls, Jafari and Ghanei demonstrated that "SM may induce an oxidative stress response by depleting the antioxidant defense systems and increasing lipid peroxidation" (56). On the other hand, oxidative stress is one of the most important agents affecting the cardiovascular system, especially coronary artery endothelial health, and it is worth mentioning that human natural antioxidants, such as glutathione and NADH, neutralize them (10, 46, 47).

When antioxidant supply is not sufficient (such as in SM injured patients, in whom the oxidative stress-antioxidants balance is disturbed), the oxidative stress can damage the cardiovascular tissue more freely and effectively than in normal people (37). Therefore, although a definite heart toxicity of SM has not yet been explained, these patients have more predisposing factors (in terms of genomics, proteomics and metabolomics) to cardiovascular diseases, especially CAD.

1.9. Potential Confounding Factors

It has been shown that cardiovascular health can be affected by psychological disorders, such as anxiety disorders (e.g., post-traumatic stress disorders) (57), which are more common among SM injured patients than among the normal population (58, 59).

Some medications, such as corticosteroids, are routinely used by these patients and potentially affect the cardiovascular system; therefore, researchers should evaluate the effect of these medications on the cardiovascular system when designing further studies. Physical activity in patients with SM injured lungs, due to decrease in ventilation capacity and respiration problems (e.g., extensional dyspnea), is restricted. Restricted physical activity and excessive weight are important potential risk factors for cardiovascular diseases, especially CAD. Moreover, many studies conducted on SM exposed patients were designed based on periodic assessments for screening of these patients. Therefore, their findings on these patients were not comparable with findings of patients referred to a medical center symptomatically.

Recently, molecular and cellular studies on asthma and COPD for reduction of inflammation and oxidative stress have indicated the important role of epigenetic and histone modifications (59). The recognition that epigenetic modifications of DNA and histones regulate inflammatory gene expression and play a role in diverse functions such as DNA repair, proliferation, and RNA interference indicates the global importance of these effects in several diseases (60, 61). For example, studies have shown that levels of histone deacetylases (HDACs) and acetyltransferase (HATs) are important biomarkers for regulating inflammation and oxidative stress (62). Therefore, the expression of inflammatory cytokines and oxidative stress in cardiac muscle impels us to investigate histone modifications in cardiac muscle and immune cells of SM exposed patients. A prospect for epigenetic therapeutic studies goes toward increasing the stability and activity of HDACs enzymes (particularly HDAC-2). We expect in the near future to reduce cardiovascular disorders in SM exposure to move in this direction.

Arrhythmias, CAD, PHT, and ventricular dysfunction are some of the coexisting cardiovascular disorders of COPD (60, 61). Therefore, COPD, regardless of the etiology, can affect cardiovascular system health, and the pure effects of SM on the heart should be examined more closely experimentally. Besides this, patients with SM exposure have other complications that can affect their general health, such as neurological disorders. These complications can affect the quality of life of these patients and

cause these patients to pay less attention to their general health (62).

2. Conclusion

Although SM as a chemical warfare agent can injure several organs in the short or long term, the majority of previous studies have explained the pulmonary, ocular, and cutaneous consequences of SM. It seems that there is a probable relationship between SM exposure and cardiovascular toxicity in the long term.

There is some evidence of the pure cardiovascular impact of SM, whereas the pulmonary system has been involved in some of these cases. Abnormal coronary arteries can be due to direct endothelial injury by SM, sustained inflammatory status in patients with chronic lung disease, and abnormal mediators of tissue injury and repair or oxidative stressors (63). It seems that coronary artery diseases, especially coronary ectasia, and diastolic dysfunction can cause significant cardiovascular abnormalities, which were seen more frequently in these patients. Prolonged inflammatory status, defects in adhering molecules such as laminine and fibronectin and impaired repair processes can predispose injured vessels to dilation and ectasia. This defect in the repair process of connective tissue is notable after exposure with alkylating agents, such as SM (64, 65).

Systemic HTN as a significant risk factor of cardiovascular disease was not observed more in the SM group than in the control group, although medications (such as corticosteroids) and limited physical activity can predispose these patients to it (66).

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