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MiniReview

Investigating Prevalence and Pattern of Long-term Cardiovascular Disorders in Sulphur Mustard-exposed Victims and Determining Proper Biomarkers for Early Defining, Monitoring and Analysis of Patients' Feedback on Therapy

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Abstract: Among the most readily existing chemical warfare agents, sulphur mustard (SM), also known as mustard gas, is the most commonly used agent owing to its ease of synthesis and stockpiling. Unprotected exposure mostly results in debilitation rather than lethal injuries, leaving an exposed victim incapacitated for days to even months. Although acute toxicity of sulphur mustard has been fairly established, the long-term post-exposure effects either chronic or short-term but significant are still evolving. A total of 30,000 Iranian victims of the Iran–Iraq imposed war have now – after 30 years – formed the key population demonstrating long-term effects from sulphur mustard exposure. Recent studies have shown that the prevalence of several long-term cardiovascular disorders (CVDs) has significantly increased among SM-exposed victims including coronary artery disorders (CAD), coronary artery ectasia (CAE), congestive heart failure (CHF) and myocardium abnormalities. The more important point is the lack of a determinant biomarker for early screening, recognizing, treating, monitoring and estimating exposed victims' response to applied therapy. Additionally, unidentified risk factors significantly decrease the chance of a successful therapy and result in undesired failure of a comprehensive therapeutic strategy. In this MiniReview, we examined the literature in detail to evaluate relevant reports considering long-term cardiovascular complications of SM, detecting possible risk factors and determining possible preventing events.

Being classified as a powerful vesicating agent with potent alkylating capability, sulphur mustard, 'KING OF THE WAR GASES', is one of the most frequently used chemical warfare agents, owing to its simplicity of synthesis and stocking up on large quantities. Acute complications of SM exposure and underlying mechanisms have been immensely studied, and several acute complications have been identified [1]. However, little information is available regarding long-term complications and the mechanisms involved. Heterogeneity of study population and different criteria of eligibility for proper selection of volunteers make the condition more complex [2]. Enrolled patients in studies mostly consist of those who were exposed during the Iran–Iraq war (1980–1988) or World War I (1914–1918) [3]. Encountering multiple poisoning agents other than SM during World War I and overageing plus many other confounding factors including smoking and different lifestyles make victims of World War I improper for study enrolment [4]. Conversely, victims of the Iran–Iraq war, especially those exposed during 1984–1988 in Sardasht and Halabja, consisting of more than 100,000 veterans and civilians receiving primary medication for controlling acute symptoms and being under observation for further possible abnormalities, now, about 30 years post-exposure, have formed an eligible population for examination and evaluation of long-term complications [5].

Owing to the late manifestation of symptoms, intricate nature of disease, very high incidence rate and absence of a specific biomarker for screening, diagnosing, evaluating treatment efficacy and planning proper preventive strategies, cardiovascular disorders (CVDs) are now ranked as the leading cause of death in both developing and developed countries. Since early screening, diagnosing and treatment can mostly alleviate delayed development of CVDs, many efforts have been dedicated for developing a comprehensive protocol, covering every aspect of therapy from initial preventive interventions up to end-stage drug therapies [6,7]. Reviewing results of population-based studies clearly depicts that Iranians are developing several CVDs risk factors including diabetes, hypertension, abnormalities in lipid profile and obesity together with chronic inflammation and oxidative stress at an alarmingly increasing rate [8–11]. This becomes more significant in military employees, due to their work overload,

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responsibilities and specific lifestyle [12]. Many of these military employees and innocent civilians of Sardasht and Halabja who were exposed to SM are now encountering several incapacitations and deal with several dreadful and in some cases undiscovered long-term complications. Due to the importance of delayed development of CVDs and high probability of interconnection between SM exposure and increasing rate of delayed occurrence of CVDs, we carefully reviewed the literature for enumeration of any probable long-term CVDs becoming more prevalent due to SM exposure, in order to identify proper biomarkers for screening, diagnosis and follow-up on patients' response to applied medication and then propose current possible preventive medications for prohibiting SM-encountered patients from development of further incapacitation or even life-threatening complications.

Comparison of Long-Term Prevalence of CVDs Among SM-Exposed and Non-Exposed Individuals

Review of the literature has brought about precise information about several cardiovascular abnormalities that are more prevalent in SM-exposed patients; these are summarized in table 1. On examination of 100 cadavers of SM-exposed victims, Taghaddosinejad and colleagues reported 22 cases of direct death from cardiac complications. Further review of pathological findings from these victims attributed atherosclerosis, pericardial fibrosis and myocardial infarction as the main causes of death [13]. Comparison of primary cardiac signs and symptoms of SM-exposed patients with non-exposed ones with the same mean age, smoking habits, marriage state, body mass index (BMI) and diabetes history did not demonstrate any significant differences in heart sounds including S_3, S_4 and murmurs, heart rate, systolic and diastolic blood pressure, chest pain, fatigue and weakness between the two groups [14].

Based on Karbasi-afshar *et al.* studies, comparison of the coronary artery atherosclerosis (CAA) prevalence rate, the main cause of CAD, between SM-exposed and non-exposed individuals demonstrated a significant increase, however, with a similar pattern in the prevalence rate among SM-exposed individuals ($p > 0.01$). Coronary artery ectasia (CAE) was also more prevalent in the SM-exposed group ($p > 0.01$). [15] Angiographic abnormalities consisting of two- and three-vessel stenosis were other findings in the SM-exposed individuals reported by Shabestari *et al.* which was not observed in the control group. The incidence of C type lesions was similar between the two groups [16]. Interestingly, in a recent study on 30 SM-exposed non-obese males with average age of 47 years and no previous history of familial cardiac abnormalities, Rohani *et al.* did not report any significant increase in occurrence rate of CAD between the two groups. In their study, two patients demonstrated a highly positive exercise test, and further investigations demonstrated three- and two-vessel disease. This study also showed a significant increase in left ventricle diastolic abnormality (relaxation impairment) occurrence rate in the SM-exposed group ($p = 0.001$). [17]. Pishgoo and coworkers investigated cardiovascular healthfulness of 58 SM-exposed male patients. Similar to a previous study, no significant increase in prevalence rate of CAD was observed. Additionally, vascular and heart conductivity was similar between both study groups [18]. Nevertheless, a significant increase in left ventricular diastolic abnormality in the SM-exposed individuals was reported.

Comparing angiography results of 22 exposed patients with 10-year cardiovascular risk of 2.45 (determined according to the Framingham criteria), Gholamrezanezhad *et al.* demonstrated a significant increase in prevalence of non-homogeneity of radiotracer uptake throughout the myocardium in visual interpretation in SM-exposed individuals ($p = 0.01$). Also the mean capacity of left ventricular cavity in SM-exposed individuals was significantly lower than in the control group ($p = 0.001$). These abnormalities are mainly a result of either CAD or mild cardiomyopathy. The prevalence rate of reversible perfusion defects was also higher in the SM-exposed group compared with the control group. Ischaemia incidence rate was also significantly more prevalent in the SM-exposed group compared with the control group ($p = 0.01$(. Dilated right ventricular chamber was another prevalent cardiac abnormality which was only observed in the SM-exposed group. Quantitative assessments both in stress and in rest conditions confirmed visual interpretations as well [19].

Serum profile of SM-exposed victims 20 years after SM exposure has been almost completely investigated in studies performed by Riahi-zanjani *et al.* [20], Yaraee *et al.* [21], Pourfarzam *et al.* [22] and Ghasemi *et al.* [23]. Measured factors consist of inflammatory and pro-inflammatory mediators plus lipid profile and levels of antioxidant enzymes and reservoirs. Almost all important pro-inflammatory mediators including IL-1α, IL-1β, IL-6, IL-8, TNF-α and MCP-1 were significantly decreased. However, interestingly, inflammatory mediators including RF, CRP, MMP-1, MMP-2, MMP-9, E-selectin, vICAM and sICAM were significantly increased compared with the non-exposed healthy group [21–25]. The haematological parameters of SM-exposed patients and control individuals were almost similar [20]. Total protein and albumin levels were also significantly lower in the SM-exposed patients. Additionally, serum triglyceride (TG), cholesterol (CT) and gamma-glutamyl transferase (GGT) activity of the patients were either disturbed or increased ($p < 0.05$) [26].

Possible Biomarkers for Early Detection and Risk Factors of Long-Term CVDs from SM Exposure

Numerous comprehensive studies have been performed to introduce a complete model describing the aetiology of CVDs. However, the complexity of involved signalling pathways and their interconnection have made it almost unreachable. Inflammatory and oxidative stress are two well-defined pathways in pathogenesis of CVDs, both of which are significantly affected by SM exposure. Identification of a specific biomarker for early detection, determination of specific therapeutic regimen and monitoring of therapeutic regimen outcomes can mostly help physicians in prescribing proper therapeutic regimens and planning future interventions for optimizing administered therapeutic regimen outcomes. As none of the identified

Table 1.
Prevalent cardiovascular abnormalities observed in SM-exposed patients

Cardiovascular disorder	Incidence rate: SM-exposed Group	Incidence rate: SM non-exposed group	*p* Value	Criteria of eligibility	References
Abnormal Coronary Artery findings	92/100	82/100	0.031	• Demonstrating CAD Symptoms (acute chest pain) • Experienced stable angina at least once. • Positive tests for inducible angina	[16]
Coronary Artery Ectasia (CAE)	15/40	2/40	0.001	• Documented exposure to mustard gas • Demonstrating significant clinical complications of mustard poisoning in the major target Organs • Similar Cardiovascular disease risk factors	[17]
Coronary Artery Disease (CAD)	2/58	–	–	• Cardiologic evaluations adequate to meet the requirements of the study • No history of rheumatic or congenital heart disease • No major risk factors of CAD such as hyperlipidemia, diabetes, heavy smoking and family history of CAD	[18]
Ischemia	5/44	0/14	0.01	• No known cardiac disorders or positive family history of any cardiac diseases. • Presence of other confirmed complications	[19]
Single vessel stenosis	12/100	52/100	0.004	–	[16]
Two-vessel stenosis	38/100	17/100	0.025	–	[16]
Three-vessel stenosis	42/100	13/100	0.009	–	[16]
Left Ventricle Diastolic Abnormality	23/100	10/100	0.02	–	[17]
(relaxation impairment)	23/100	–	–	–	[18]
Non-homogeneity of Radiotracer uptake by Myocardium	9/22	1/14	<0.05	–	[19]
Mean Capacity of Left Ventricular Cavity (ml)	2.43 ± 0.92	1.56 ± 0.73	0.001	–	[19]
Reversible perfusion defects	21/100	19/100	0.197	–	[16]
Dilated right ventricular Chamber	13/44	0/14	0.001	–	[19]

biomarkers possess all these properties together, application of a single biomarker may cause misinterpretation of results, designing suboptimal therapeutic regimen or even failure of therapeutic interventions. Consequently, physicians usually consider multiple biomarkers simultaneously to minimize these errors and misinterpretations as much as possible. In addition, application of multiple specific biomarkers can help make further evaluations more simple and at the same time more accurate. In this part, we briefly introduce some of the potent biomarkers in relation to prognosis of CVDs (table 2).

Inflammatory biomarkers.

As a specific 'surrogate marker', E-selectin reflects activation of vascular endothelial cells and acceleration of underlying inflammatory pathway [27]. In contrary to other members of cellular adhesion molecules (CAMs) family (L-selectin and P-selectin), E-selectin only becomes overexpressed on vascular endothelial cells [27,28] and is a potent promoter of leucocyte interaction and adhesion on the surface of endothelial cells [29], an important stage in the pathology of atherosclerosis [27]. Increased levels of E-selectin have been shown to accompany several CVDs including acute coronary syndrome (ACS) [26], CAD [30,31] and unstable angina (UA) [32,33]. Elevation in levels of heat-shock proteins (HSPs) is now considered a poor prognosis for CVDs. Studies have demonstrated that HSP60 specifically accumulates in atherosclerotic legions and triggers autoreactive T-cell response. Elevation of this biomarker is an important risk factor in progression of atherosclerosis, especially in patients with hypertension [34]. Anti-HSP65 antibodies can predict CVDs progress, independent from other classic biomarkers and inflammatory markers [35]. Matrix metalloproteinases (MMPs) are mostly secreted from macrophages, vascular smooth muscle cells, lymphocytes and endothelial cells playing an important role in vascular remodelling, aneurysm formation, atherosclerosis progression, post-angioplasty stenosis and plaque destabilization [36]. In addition, MMPs can restrain inflammation by activating TGF-β. It has been shown that MMPs are also elevated after MI, unstable angina and sudden cardiac death [37–39]. MMPs can also weaken coronary plaques by extracellular matrix degradation [40]. VCAMs are inflammatory biomarkers, secreted from both large and/or small vessels after activation of corresponding cells under control of pro-inflammatory cytokines [41]. The most important role of these molecules includes facilitation of rolling, adhesion and migration of leucocytes across endothelial barriers. The most important note which must be considered is that soluble VCAM (sVCAM) is only considered as a biomarker in patients with established disorder, demonstrating stage of atherosclerosis progression and is not

Table 2.
Pro-inflammatory, inflammatory and anti-oxidant biomarkers for cardiovascular disorders

Cardiovascular disorder	Biomarkers		
	Pro-inflammatory	Inflammalory	Anti-oxidant
Cardiovascular Disease (CVD)	MCP-1 [85]	AGE [85–87]	CoQ10 [88,89], Isoprostans [90] Nitrotyrosine [91], oxLDL [92]
Coronary Artery Disease (CAD) (consisting of CAE, CAA. Single, two-, three vessel stenosis)	CRP [93], INF-γ [94], IL-1 [95], IL-6 [96], IL-8 [97], MCP-1 [30], TNF-α [95]	E-selectin [98], HSP [99], 1CAM-1 [100,101], VCAM-1 [93]	Lp-PLA_2 [102], SOD [103]
Chronic Heart Failure (CHF) (consisting of Left Ventricle Diastolic Abnormality (relaxation impairment), Dilated right ventricular Chamber, Mcan Capacity of Left Ventricular Cavity, Non-homogeneity of Radiotracer uptake by Myocardium)	CRP [104], INF-γ [105], IL-6 [106], IL-8 [107], TNF-α [106]	–	CoQ10 [88], GSH [108], oxLDL [43]
Myocardial Infarction (MI) (Consisting of Reversible perfusion defects)	CRP [109], INF-γ [110], IL-1 [37], IL-6 [111], IL-8 [112], MCP-1 [31],TNF-α [31]	E-selectin [34], HSP [113]	GSH [114], Isoprostanes [115], oxLDL [116], SOD [117]
Unstable Angina (UA) (Ischemia)	CRP [118], IL-1 [119], IL-6 [111], IL-8 [120], MCP-1 [32]	E-selectin [31], ICAM-1 [121], MMPs [76], VCAM-1 [34,111]	SOD [122], oxLDL [123]

applicable in healthy cases [42,43]. In CAD patients, E-selectin, VCAM-1, MMPs and HSPs are all increased; however, VCAM-1 demonstrates more significant relation with CAD prognosis, and in the case of COX regression, it can independently predict future cardiovascular events. It can also be an important biomarker in estimation of UA and type II diabetes development [33,44–47].

Pro-inflammatory biomarkers.

Cytokines are group of glycoproteins, responsible for intracellular communication and regulation of several fundamental biological processes such as adiposity, lactation and haematopoiesis [48,49]. However, their most important role appears to be the control of innate and adaptive immunities. The main role of cytokines in development of atherosclerosis consists of a complex interplay with adhesion molecules (discussed above), leading in infiltration of monocyte within the arterial wall [50,51]. These molecules are mostly trapped by neighbouring cells through their high affine and sensitive receptors. Consequently, measuring levels of circulatory cytokines is not a proper surrogate marker and is only used for risk stratification and selection of patients which can be benefited from targeted therapy. However, it has been proposed that cytokines can play a role in plaque stability determination, too [48]. The list of most important pro- and anti-inflammatory cytokines is depicted in table 3. Specific mediators including CRPs, rheumatoid factor (RF), IL-6, IL-8, IL-10, IL-17, IL-18, TNF-α and INF-γ are valuable biomarkers for determining progression in CVDs stage (table 3). The most important inducer of CRP synthesis in liver is IL-6. Consequently, increase in amounts of IL-6 appears to be another proper biomarker. From other side, the direct relation between the number of circulating cells and the ones presented at the site of inflammation with severity of coronary syndrome has been well stablished [52]. INF-γ, even in the absence of immune-involved cells, can affect vascular smooth muscle cells and accelerate mutagenesis induced by growth factors [51]. This makes INF-γ an independent biomarker for CVDs detection. In the case of unstable CAD, the most important and independent biomarker associated with increased mortality is IL-6. Thus, it has been proposed that by increasing the levels of IL-6, application of invasive therapy becomes applicable [53]. The level of IL-18 is the most important independent biomarker in prediction of death from CAD regardless of the clinical status at admission [54]. Increase in amounts of specific cytokines including TNF-α, IL-1β, IL-6, IL-6Ra, and IL-17 is also linked with development of aged vessels or abnormal ones. IL-10 as a biomarker has been proposed to increase in the case of more favourable prognosis in patients suffering from acute coronary syndromes [55]. IL-1, IL-6 and TNF-α are the most important biomarkers related with negative inotropic effects and cardiac contractility [56].

Oxidative stress biomarkers.

As mentioned above, oxidative stress pathway is also another important factor in induction of CVDs and is mostly formed during free radicals formation and when there is imbalance between free radicals and antioxidants reservoirs [57]. As free radicals are extensively reactive, they bind with their extra single electron to the other proper targets and oxidize them.

Table 3.
Biomarkers for Identifying vulnerability, progression stage of disease and type of assay for monitoring response of treatment in SM-Exposed victims

Identification of Vulnerability and initiation of therapy	Determining stage of CVD	Cardiovascular risk assessment
• Serological biomarkers of arterial vulnerability (Abnormal lipid profile [124], Apo B [125] and Lp(a) [126]) • Inflammatory risk factors (CRP [127]. sICAM [45], IL-6 [53], IL-18 [128]) Homocysteine [129], Natriuretic peptides [130] • Structural markers of arterial vulnerability (Coronary artery calcium [131]) • Functional markers of arterial vulnerability (Blood pressure [132], Urine albumin excretion [132]) • Serological markers of blood vulnerability (Fibrinogen [133]) • Structural markers of myocardial vulnerability (LVH, LV dysfunction [134,135]) • Functional markers of myocardial vulnerability (Exercise stress test/stress echo [136]) • Serological markers of myocardial vulnerability (troponin [137])	• Plaque formation (Total cholesterol, LDL/HDL, LDL particle size, Lp(a), Homocysteine) • Plaque instability/rupture (Matrix metalloproteinase-9, Myeloperoxidase, RANTES, C-reactive Protein/hsCRP, ICAM/VCAM, Ischemia modified albumin, Fibrinogen) • Myocardial necrosis (Myoglobin, Cardiac troponin T, Cardiac troponin I. Creatine kinase MB isoenzyme) • Myocardial dysfunction (BNP, NT-pro-BNP)	• Inflammation (IL-6 [138], IL-18 [139], S-albumin [140], WBC [141], fibrinogen [142], hyaluronan [143], MPO [144], CRP [145], PTX3 [146]) • Oxidative stress (MPO [144], plasmalogens [147], oxLDL [148], AOPP [149]) • Endothelial dysfunetion (Endothelial dysfunction) • Protein-energy wasting (S-albumin [140], S-creatinine [140], prealbumin [150]) • Coagulalion/fibrinolysis disorders (Fibrinogen [142]) • Genetics/epigenetics (SNPs [151], telomere attrition [152], DNA-methylation [153]

These targets in cell mostly consist of DNA, mitochondrial malfunction cell membrane damage and finally cell death in apoptosis form. As measurement of antioxidant reservoir is easier, the biomarkers mostly consist of antioxidant enzymes or reservoirs in cells. Coenzyme Q-10, glutathione (GSH) and superoxide dismutase (SOD) are the most important members of this group of biomarkers, and their increase is mostly associated with better prognosis. Among oxidative stress markers, oxidized LDL, F_2 isoprostane and LP-PLA 1 and nitrotyrosines are the most important biomarkers [58].

Any factor interrupting the balance between cytokines and oxidoreductase enzymes as mentioned above can be considered as important risk factors. As the levels of free radicals and inflammatory cytokines are mostly related to lifestyle [59], pollution and inhalation of heavy metals suspending in inhaled air [60] and food nutrients [61] can be considered as important predisposing factors. On the other hand, obesity [62] and its underlying disorders including diabetes are other important factors [63]. Finally smoking and excessive consumption of alcohol can also take part as important risk factors in induction of latent CVDs [64].

Justifying Long-Term CVDs from Sulphur Mustard Exposure Based on Developed Biomarkers

As discussed above, several complex cellular and molecular reactions, signalling pathways and crosstalks take part in development of CVDs (briefly depicted in fig. 1). Inflammatory and oxidative stress reactions have shown to be significantly evolved in the pathology of several cardiac abnormalities [65]. As Pourfarzam *et al.* demonstrated, RF and CRP, both of which are significantly raised through CVDs, were significantly elevated in the SM-exposed group [22]. IL-1Ra concentration was reported to be significantly increased in SM-exposed patients, too [21]. Today, it has been understood that IL-1Ra is a more significant marker for assessing prognosis of CVDs in comparison with IL-1 itself [66]. Interestingly, this pro-inflammatory mediator significantly increases in SM-exposed patients, particularly at the site of inflammation, resulting in exacerbation of several acute and chronic CVDs [22]. However, before any data interpretation or making decisions, two points must be considered: the site of sample collection and the studied population's heterogeneity. Obviously, at the site of inflammation, the concentration and pattern of inflammatory mediators' negotiation may significantly differ compared to what we see or predict in serum profile, even when being tightly interconnected [67]. No significant differences were reported among case and control groups considering GM-CSF production levels, which is in agreement with blood analysis tests [68]. This may happen partly due to the high proliferation rate of bone marrow cells and possibility of occurrence of genetic and epigenetic mutations and subsequent development of alteration, resulting in formation of new immune-involved cells with decreased capacity of cytokine production [69]. As most of the SM-exposed victims suffer from severe pulmonary complications and corticosteroid therapy is part of their routine and maintenance treatments, encountering a mild decrease in levels of cytokines serum profile is not astounding [70]. Additionally, pro-inflammatory cytokines present in very low concentrations in serum (from nanograms to picograms) and their measurement requires very sensitive and meticulous devices, because small errors in measurement can result in misinterpretation. In addition, although extremely low levels of cytokines in serum is enough for their action, based on the accuracy and validity of used method (ELISA), few picogram variation may not be considered as a significant difference. Additionally, down-regulation of cytokines receptors can also take part and result in lowering of their serum levels [71].

Coronary artery disorders (CAD) has shown to be significantly inter-related with IL-6 and TNF-α plasma levels, and as

these mediators are decreased in SM-exposed patients, one can claim that risk of CAD occurrence must be less in the exposed groups. This conclusion can be considered both right and wrong. Like Attaran *et al.* and Keramati *et al.* reported, although cytokines were slightly lower in concentration compared to the control group, other important inducers of CAD including disturbed levels of triglycerides (TGs) still remains untouched [26,72]. In addition, oxidative stress induced by SM and activation of poly (ADP ribose) polymerase (PARP) makes the situation more complex and accelerate development of CAD [73]. Consequently, it is not surprising to observe more atherosclerosis or CAD in SM-exposed patients even with decreased serum profile of cytokines. Increased incidence of stenosis and ectasia as reported by Shabestari *et al.* can be explained in the same manner. On the other hand, considering the lifestyle and age of the patients, the results of Rouhani *et al.* become logical. Their studied population had a mean of 45 years of age, no familial history of cardiac disorders and obesity, thereby ignoring main risk factors of CAD development. In other words, remodelling in vascular structures appears not to have happened yet and as pro-inflammatory cytokines are presented in low levels, the risk of CAD occurrence in this population remains low. However, the most important point presented in the Karbasi-afashar *et al.* study is that both groups demonstrated a significant number of patients with diabetes and/or MI history, and this may be the result of controversy between reported results by Karbasi-afshar *et al.* and Rouhani *et al.*

Induction of cardiomyopathy, reduction in left ventricular ejection fraction and loosening of right ventricle appear to be the most important latent complications of sulphur mustard exposure. Discounting the initiating stimuli, in the case of compromised cardiac pump function, several compensatory pathways and mechanisms including activation of neurohormones, elevation in circulatory catecholamine concentrations and an increase in sympathetic activity take place. Response of myocardium to the stress condition consists of several biological processes including apoptosis of cardiomyocytes or necrosis. The extracellular collagen deposit becomes significantly increased, and concurrently, extracellular proteins become degraded, ending in enhancement of matrix turnover. Oxidative stress and inflammatory pathways also facilitate this process in several steps. The final result of these altered pathways is left ventricular remodelling [74]. Remodelling results in hypertrophy of left ventricle and decline in ejection fraction which is similar to the findings reported by Gholamrezanezhad *et al.* In addition, induction of oxidative stress and overexpression of PARP enzyme have shown to induce myocyte death [75]. The inflammatory biomarkers mentioned above can also result in vasoconstriction and thrombosis, both of which result

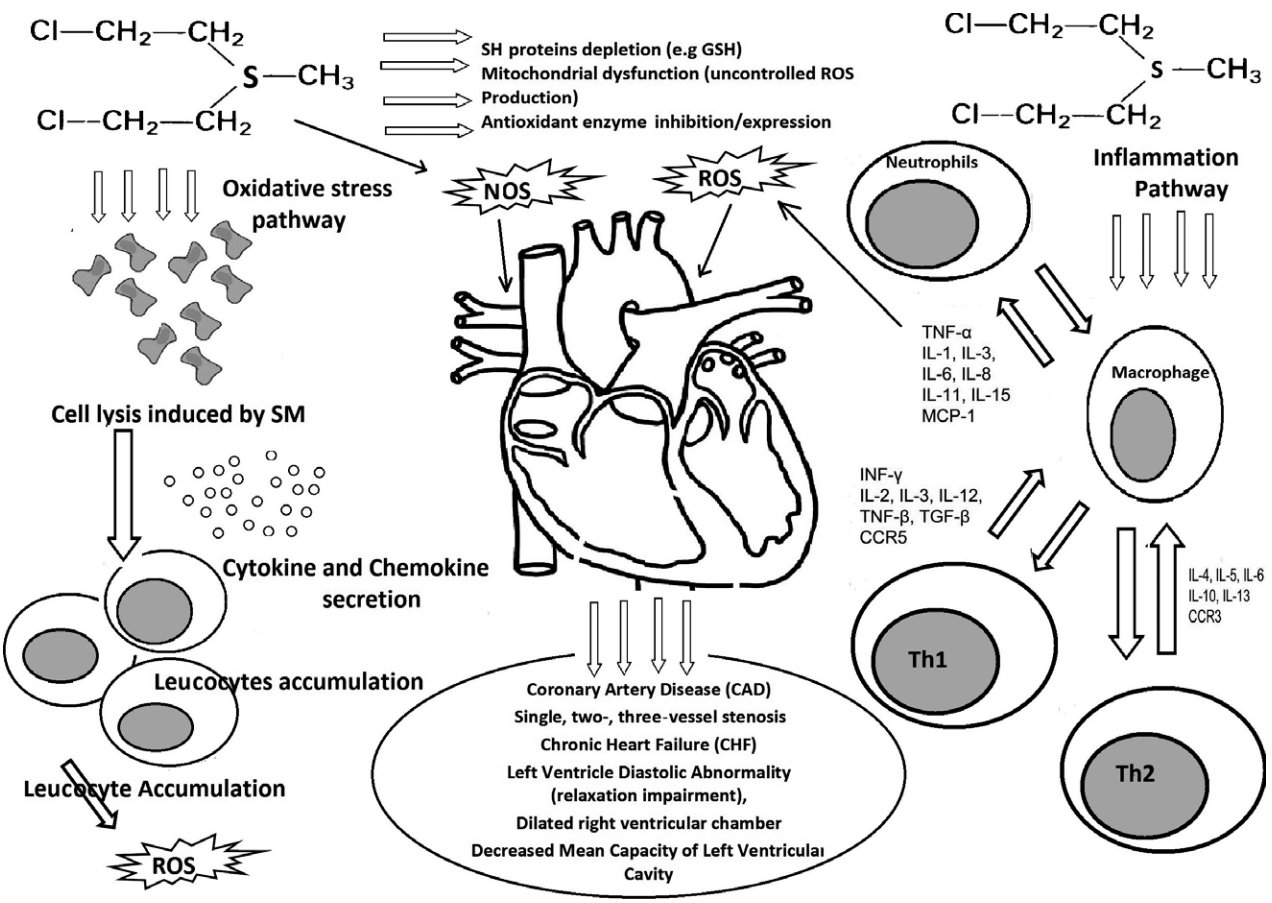

Fig. 1. Cellular and molecular pathways taking part in CVDs.

in vascular dysfunction and remodelling [76]. This process continues with depletion of O_2 and glucose reaching to the myocytes, induction of hypoxic and malnutrition state and increasing the risk of CHF induction [77].

Possible Preventing Agents

As endothelial cells are the most important targets of immune-mediated injuries, vasculoprotective therapies including angiotensin-converting enzymes inhibitors (ACEIs) and angiotensin II type I receptor blockers (ARBs) are the most important preventing agents from induction of CVDs. On the other hand, HMG-COA reductase inhibitory agents can take part in prevention of these side effects by correcting TG profile [78]. Other important preventing drugs include aspirin, which neutralizes negative remodelling effects of cytokines on endothelial cells and down-regulation of IL-1 synthesis [79]. Blocking TNF-α with their proper antibodies such as infliximab has shown to significantly decline the prevalence of cardiovascular disorders. [80–82]. In addition, several studies have shown that naturally occurring compounds including curcumin and epigallocatechin gallate (EGCG) by suppressing inflammatory and oxidative stress pathways can significantly decrease risk of CVDs [83]. Reviewing recent studies focusing on SM-induced dermotoxicity, categorized six classes of new promising therapeutic agents including intracellular scavengers (N-acetyl cysteine), cell cycle inhibitors (mimosin), PARP inhibitors (niacinamide), calcium modulators (EBSF a calcium chelators), protease inhibitors (AEBSF, a sulfonyl fluoride) and anti-inflammatory agents (capsaicin, hydrocortisone and indomethacin) against sulphur mustards toxic complications [84]. However, the limiting point of these agents is their effectiveness only in the acute toxic phase. In addition, it has not been stablished yet whether these agents are effective against induced CVDs or not. Consequently, further studies are required to find out whether these agents are effective in prevention from CVD development or not.

Conclusion and Future Perspective

As discussed in this MiniReview, although the mechanism of acute sulphur mustard exposure toxicity has been fairly well-established, the gap of interrelation between basic cellular and molecular mechanisms and long-term induced clinical complications still remains deprived, and further comprehensive and rigorous studies appear to be essential. Furthermore, highly non-uniform nature of study individuals – due to differences in lifestyle patterns and habitual activities – makes comparison and achieving certain conclusions too difficult. Possibly, determination of an independent and concurrently selective biomarker for assortment of individuals and design of study appears to be the key solution for determining trends and mechanisms associated with long-term complications of SM exposure especially in the case of CVDs. Although the mechanism of long-term CVD associated with SM exposure is not yet completely understood, the obvious thing is that SM can significantly result in increasing the risk of CVDs and worsening of developed disease prognosis. Based on the literature, the most probable mechanism of long-term CVD occurrence is the cardiovascular remodelling induced by different pro-inflammatory, inflammatory and oxidative stress-inducing agents. Finally, development of a standard treatment protocol from the beginning of exposure, development of critical caregiving interventions early after exposure and design of long-term preventive interventions seem to be the most effective way of lowering the risk of long-term exposure complications.

Conflicts of Interest

Authors declare no conflict of interest.

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