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Inhaled matters of the heart

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Abstract

Inhalations of atmospheric pollutants, especially particulate matters, are known to cause severe cardiac effects and to exacerbate preexisting heart disease. Heart failure is an important sequelae of gaseous inhalation such as that of carbon monoxide. Similarly, other gases such as sulphur dioxide are known to cause detrimental cardiovascular events. However, mechanisms of these cardiac toxicities are so far unknown. Increased susceptibility of the heart to oxidative stress may play a role. Low levels of antioxidants in the heart as compared to other organs and high levels of reactive oxygen species produced due to the high energetic demand and metabolic rate in cardiac muscle are important in rendering this susceptibility. Acute inhalation of high concentrations of halogen gases is often fatal. Severe respiratory injury and distress occurs upon inhalation of halogens gases, such as chlorine and bromine; however, studies on their cardiac effects are scant. We have demonstrated that inhalation of high concentrations of halogen gases cause significant cardiac injury, dysfunction, and failure that can be critical in causing mortalities following exposures. Our studies also demonstrated that cardiac dysfunction occurs as a result of a direct insult independent of coexisting hypoxia, since it is not fully reversed by oxygen supplementation. Therefore, studies on offsite organ effects of inhaled toxic gases can impact development of treatment strategies upon accidental or deliberate exposures to these agents. Here we summarize the knowledge of cardiovascular effects of common inhaled toxic gases with the intent to highlight the importance of consideration of cardiac symptoms while treating the victims.

Keywords

Inhaled gases; halogens; sulphur dioxide; cardiac dysfunction

Introduction

Many studies have been performed to investigate the cellular mechanisms of inhaled gas-induced injury to pulmonary tissues, however, very few have investigated the effect on cardiac tissue. Toxic gases such as halogens with a relatively higher water-solubility (e.g. Cl₂) are most readily dissolved in the upper airways and can lead to irritation of mouth and

airway mucosa. In contrast, agents with relatively lower water-solubility, such as bromine, can enter the deeper structures causing injury to the distal airways and the alveolar sac. In both cases the more stable secondary reactants can be absorbed into the circulation and reach other tissues and organs such as the heart [1]. The heart is the first recipient of the lung drainage. It is also a highly active pump that has a high metabolic rate to meet the high-energy demand. The excessive metabolic demand of the myocardium leads to increased rate of free radical production. The paucity of superoxide dismutase, catalase, and glutathione peroxidase in the heart makes it further susceptible to oxidative injury [2,3]. Circulating halogen reactants contribute to the additional burden on the heart by damaging important intracellular calcium (Ca^{2+}) regulators such as sarcoendoplasmic reticulum ATPase (SERCA) and causing cytosolic Ca^{2+} overload [1]. Excessive cytosolic Ca^{2+} cause mitochondrial production of reactive oxygen species [4, 5]. Mitochondrial ROS can itself perturb the cytosolic Ca^{2+} , cause cytoskeletal damage and lead to cardiac dysfunction [6, 7]. Chlorine exposure increases cytosolic Ca^{2+} in pulmonary smooth muscle cells suggesting a similar set of mitochondrial damage and events of ROS production precede in the lung [8]. Therefore, toxic inhalational injury is caused through a variety of mechanisms including direct injury of the respiratory tract mucosa, respiratory asphyxiation, oxidative stress and systemic absorption of the reactants [1,9]. Understanding the mechanisms of cardiac tissue injury by inhaled toxic gases is crucial for developing effective therapeutic countermeasures.

The aim of this manuscript is to review the experimentally or clinically described cardiovascular effects of common toxic gases such as chlorine, bromine, ozone, carbon monoxide and sulfur dioxide. Although they may not have a common mechanism of action, understanding the events (acute or chronic) leading to the cardiotoxicity is important. Environmental pollutants especially airborne particulates have already been widely investigated for their cardiopulmonary toxicity and will not be covered here.

Chlorine

Chlorine is a yellow-green gas classified as an inhalational toxin. Most common exposures to chlorine gas are accidental, including release of chlorine vapor at swimming pools, exposure to household cleaning products and transportation mishaps (Table 1) [1,10,11]. Use of chlorine as a chemical weapon was first proposed in World War I and continues as a chemical threat agent [1,12,13](April 2015: 100th anniversary).

Chlorine is a strong oxidizing agent and has high reactivity with water. Inhalational injury precipitated by chlorine in humans and experimentally have been reviewed extensively by White and Martin [14]. The primary site of action of chlorine gas is the epithelial cell surface of pulmonary tissue [15]. Pulmonary damage ranges from mild respiratory membrane irritation to non-cardiogenic pulmonary edema characteristic of acute respiratory distress syndrome (ARDS), and in some cases death [8,10,16–32]. The Majority of patients exposed to chlorine present with cough, dyspnea, and eye and throat irritation [10,21,33]. Because of the higher solubility of chlorine gas in water it can easily be dissolved in the epithelial lining fluid forming HOCl which may react with targets on cell surface directly with the cell membrane or matrix. Either Cl_2 or (HOCl) may react with reactive oxygen species (ROS) creating powerful oxygen free radicals that mix with a variety of biomolecules in the

epithelium including ascorbate, reduced glutathione, sulfur containing amino acids such as cysteine and methionine, histidine, and side chains of tryptophan, lysine, and tyrosine [34] [35] [1,12,15]. Other studies have shown that variations in inhaled concentrations of chlorine determine the site of action (upper airway epithelium versus alveolar epithelium), severity of injury, and reversibility of the damage [34] [36] [37]. Lower concentrations (less than 50 ppm) may affect the upper airway resulting in reversible bronchospasm, and higher concentrations (more than 50 ppm, mostly in industrial accidents or deliberate warfare attacks) may cause significant upper airway injury followed by alveolar damage [38].

Although chlorine gas respiratory toxicity has been extensively studied, reports of cardiac effects of chlorine inhalation are scarce and further studies are needed to explore cellular and molecular changes in the cardiac tissue, secondary to chlorine inhalation [39]. Known cardiac effects of chlorine exposure to the heart include arrhythmia (in the form of sinus tachycardia [10,11,40,41], sinus bradycardia [1,20], extra systoles [11]) myocardial infarction [42] and cardiac arrest [22,40]. Cardiomegaly was observed in autopsy of about 90% of victims that died due to chlorine inhalation [14]. Despite these reports it is still unclear whether cardiac complications after inhalation of chlorine gas result from a direct toxic effect of chlorine on cardiomyocytes or they are secondary to respiratory epithelial damage and elevated pulmonary vascular resistance and hypoxia [43]. Yet, chlorine gas inhalation results in injury to both respiratory and cardiovascular systems [1,15,30,44].

It has been shown that the harmful effects of inhaled toxic gases is not limited to the respiratory epithelium, but can also promote endothelial dysfunction in the systemic vasculature leading to cardiovascular diseases such as atherosclerosis and myocardial infarction [39], suggesting systemic release of deleterious factors from the lung injury. The pulmonary vascular bed has an extensive surface area and thus provides a large reservoir for release. The left heart is the first recipient of the pulmonary drainage and thus delivery into the coronary arteries. Environmental irritants such as chlorine can disturb the cardiovascular system by affecting nitric oxide (NO) signaling pathways resulting in endothelial disruption [39,45]. NO is an endogenous vasodilator derived from L-arginine [39]. Physiologic roles of NO are: regulating cellular respiration, maintaining an anti-inflammatory, antithrombotic (fibrinolysis), antioxidant, and anti-smooth muscle proliferation state [39]. Therefore, any disruption of this pathway can contribute to significant cardiovascular damage [39]. Daugherty *et al.*, 1994 [46] hypothesized for the first time that oxidation of low-density lipoproteins (LDL) catalyzed by myeloperoxidase (MPO) contributes to the vessel wall inflammation, promoting atherosclerosis [46,47]. Since then, many studies have confirmed that different oxidants such as reactive oxygen species, nitrogen species as well as HOCl can modify specific proteins on LDL and high-density lipoproteins (HDL) in human atheroma, and convert these proteins to pro-atherogenic molecules [39,47,48]. HOCl is a powerful oxidant with antibacterial properties that are important in host defense mechanisms [49]. MPO, which is released from activated leukocytes, catalyzes the reaction between H_2O_2 and Cl^- to generate HOCl [49]. However, excessive production of HOCl, such as during chlorine inhalation, can further add to vascular tissue damage [47,49]. Therefore NO and HOCl could play a role in mediating chlorine-induced cardiovascular toxicity.

Being the initiator of the heartbeat, intracellular calcium (Ca^{2+}) is the most important ion for cardiac function [50]. Ca^{2+} release from the sarcoplasmic reticulum (SR) is required for excitation-contraction coupling of cardiomyocytes that orchestrates cardiac contraction and relaxation. Optimal cytosolic Ca^{2+} content is critical for mitochondrial function, which is the source of cardiac energy required for contractility. However, excessive and unchecked cytosolic Ca^{2+} accumulation can result in mitochondrial production of reactive oxygen species severe enough to lead to heart failure [51–53]. The sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) plays a critical role in regulating cardiac intracellular Ca^{2+} homeostasis by mediating the transport of cytosolic Ca^{2+} into the sarco/endoplasmic reticulum at diastole and hence, lowering intracellular Ca^{2+} levels [1,54]. Activity of SERCA is susceptible to oxidants such as hypochlorous acid (HOCl), a product of chlorine and water [1, 54]. It was previously shown that exposure to HOCl decreases SERCA2 (the cardiac isoform) activity via irreversible oxidation of thiol groups on SERCA protein and increases cytosolic Ca^{2+} levels in endothelial cells of the coronary artery [54]. We have shown that acute exposure to high chlorine concentration in rats reduces cardiac SERCA activity via chlorination of tyrosines and oxidation of an important cysteine residue [1] (Figure 1). We demonstrated that markers of cardiac muscle injury and reactive chlorine intermediates (chloramines) were increased in the blood stream after chlorine exposure and that total cardiac ATP content was significantly reduced [1]. We believe that reduced SERCA activity was a primary effect of chlorine reactants on heart tissue and not secondary to tissue hypoxia (due to lung injury), because exposure of cardiomyocytes to hypoxia for the same duration of time did not lead to a reduction in SERCA activity. We also demonstrated that oxygen supplementation only partially reversed chlorine-induced cardiac dysfunction [1,44]. Using ex vivo perfused heart model we demonstrated loss of contractile function by chloramines, a potential chlorine reactant generated in circulation of chlorine-inhaling animals. Chlorine by-products can act in several ways including 1) direct modification of important enzymes; 2) causing increased oxidative stress by generating reactive oxygen species; 3) enhancing pro-inflammatory pathways; and 4) increasing activity of tissue damaging proteases such as calpains and chymases in heart. These and potentially other mechanisms may acutely impair cardiac function or chronically inhibit the cardiac injury repair process [55]. Further studies are needed to evaluate chronic effects of chlorine inhalation on cardiac function.

Bromine

Another common industrial halogen, bromine (Br_2), is a highly reactive ‘inhalational’ threat agent that can spread both as liquid and as fumes [56]. It causes extensive morbidity and mortality in exposed populations [56,57]. It is also one of the most common toxic gases that are incriminated in causing respiratory damage upon inhalation. Like Cl_2 , Br_2 inhalation causes skin and airway burns, severe respiratory symptoms and it’s ‘immediately dangerous to life and health’ concentrations are even lower than Cl_2 [56,58,59]. However, at similar concentrations and duration of exposure, Cl_2 -induced toxicity was greater than Br_2 in mice [60]. Br_2 also reacts with tissue components such as the respiratory epithelium to liberate reactive oxygen species and tissue damage. In addition, hydrobromic acid (HBr) and hypobromous acid (HOBr) formed on the moist surface contribute to tissue injury. At high concentrations Br_2 replaces atmospheric oxygen and its toxicity depends on confinement of

exposure area, concentration, length of exposure, age and preexisting medical condition of the victims. Along with respiratory, gastrointestinal and central nervous symptoms, severe cardiovascular morbidities resulting from hypoxemia, and cardiac arrhythmias severe enough to progress to cardiac arrest were observed in people with acute inhalational Br₂ exposure [56]. Chronic effects such as development of cardiomyopathy were also observed following Br₂ inhalation [56]. Although Br₂ ion and brominated compounds may persist in circulation for days following exposure in industrial workers and experimental animals, the mechanism of Br₂ gas cardiovascular toxicity are thus far unexplored [61,62].

Sulfur dioxide

Sulfur dioxide (SO₂) is one of the most toxic gases in air-polluted areas [63,64]. It is commonly released in the atmosphere from fossil fuel combustion [65]. Because of high solubility in water, SO₂ can be easily hydrated in respiratory mucosa to form sulfurous acid and its reactants such as bisulfite and sulfite ions [66–68]. These reactants may cause allergic reactions in the respiratory tract or can be reabsorbed into the blood and other body fluids and affect various organs in the body [67,68]. SO₂ is known to cause acute adverse effects on the human cardiovascular system [64,69–71] (Table 2). High concentrations of SO₂ inhalation cause mortality due to cardiopulmonary dysfunction [72]. Exposure to SO₂ is associated with an increased mortality people with underlying lung diseases such as chronic obstructive pulmonary disease (COPD) [69,73].

Little knowledge is available about the molecular mechanisms of SO₂ toxicity and its derivatives [67]. SO₂ causes oxidative damage to cells and tissues by increasing the content of lipid peroxides in the heart [67]. SO₂-dependent oxidative damage to several organs, including the heart in mice was also observed [74]. SO₂ and its derivatives also can cause DNA damage [75]. Protein oxidative damage and DNA–protein crosslinks induced by SO₂ have been demonstrated and protein carbonyl content and DNA–protein crosslinks coefficient were used as markers to determine the SO₂-induced damage in lungs, livers, and hearts from mice. Protein carbonyl content is the most general indicator of oxidative protein damage [76]. DNA–protein crosslinks are thought to be important genotoxic lesions induced by environmental agents and carcinogens and, unlike other DNA lesions that are readily repaired, are relatively persistent [76,77]. Thus SO₂ may further promote the progression of injury and disease in the cardiopulmonary system by crosslinking with DNA and proteins [67,74].

Carbon Monoxide

Carbon monoxide (CO) poisoning is a very common and crucial health concern with serious clinical effects and high morbidity and mortality [78]. CO is an odorless, colorless, non-irritating gas generated by incomplete combustion of carbon-containing fuels [79]. It binds to hemoglobin with high affinity (200–250 times greater than oxygen) to form carboxyhemoglobin and reduces the O₂-carrying capacity of the blood. The cardiovascular system and central nervous system are vulnerable to CO poisoning because of their high oxygen demand [80]. Severe myocardial injury occurs upon CO inhalation (Table 2) [81].

A population-based longitudinal cohort study was performed in Taiwan in 2015 to determine whether patients with CO poisoning are associated with higher risk of developing cardiovascular diseases [82]. They studied the incidence of arrhythmias, coronary artery diseases and congestive heart failure in CO-poisoned patients. Results of their study showed that CO poisoning was significantly associated with a higher risk of arrhythmias with only a trend for an association between CO exposure and coronary artery disease and congestive heart failure. The incidence of all three cardiovascular diseases was higher in patients with coexisting comorbidity or high poisoning severity [82].

Other studies show that CO poisoning can cause ischemia and myocardial injury (elevated troponin I, creatine kinase-MB fraction) and left ventricular dysfunction [83]. Heart-type fatty acid-binding protein (h-FABP) is a member of the fatty acid-binding protein family in serum with low molecular weight that is released from the injured myocardium [84]. It can be detected within 20 minutes after cardiac damage. It peaks at 3 to 4 hours and returns to reference range in 24 hours [85]. Recently, elevated serum hFABP levels were reported in CO-poisoned rats [86]. Studies show that it can be used as a novel biomarker of CO poisoning in humans as well translating into ST segment elevations and depressions on electrocardiogram (EKG) [70, 84]. CO poisoning also caused damage to the cardiac conduction system (dromotropic effects) manifested on the cardiac electrocardiogram (EKG) as T wave inversions and first degree atrioventricular block [87]. CO-induced cardiac toxicity was elegantly highlighted in a recent review by Cardiga *et al.*, [81].

Ozone

Ozone (O₃) is a major oxidative pollutant that causes respiratory damage, airway inflammation and exacerbation of pulmonary diseases such as asthma and cystic fibrosis [88]. O₃ can cause oxidation/peroxidation of biomolecules directly or via free radical reactions [89,90]. Cell injury/death can result from lipid peroxidation, free radical formation, loss of enzyme activity, and alteration of cell membrane permeability [89].

It has been shown that long-term exposure to ozone in highly polluted areas is associated with cardiovascular morbidity (coronary artery disease, myocardial infarction, atherosclerosis) and mortality [91,92] (Table 2). The combination of O₃ and ambient particulate matter in polluted areas can cause vasoconstriction and diastolic hypertension [93,94]. In animal models O₃ exposure results in increased atherosclerotic plaque size and enhanced susceptibility to ischemic injury [95] [96]. Farraj *et al.*, showed that O₃ results in autonomic modulation of cardiac function in rats [97]. This modulation of autonomic balance is concentration-dependent and includes bradycardia, PR interval prolongation, ST segment depression, substantial increases in premature atrial beats, sinoatrial block, and atrioventricular block, accompanied by concurrent increases in heart rate variability suggestive of increased parasympathetic tone [97]. Similarly, short term O₃ exposure of human subjects at environmentally relevant concentration may or may not demonstrate cardiac effects but do suggest that in vulnerable populations (e.g. those with preexisting cardiac disease) such exposures may cause fatal cardiovascular dysfunction [98,99].

In health, cardiopulmonary interaction is crucial in providing tissues with oxygenated blood. However, under toxic gas/halogen inhalation, these interactions may damage either and to other organs. Added to the challenge, each of cardiac and pulmonary dysfunction may present clinically similarly. Given the independent and potentially fatal cardiac toxicity of these halogens, it is therefore crucial to have a high index of suspicion of cardiac involvement with every halogen or toxic gas exposure.

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Figure 1. Schematic representation of mechanisms of halogen (Cl₂/Br₂) gas inhalation-induced cardiotoxicity

Inhaled gases react with the moist surface and form secondary reactants that are absorbed in circulation and travel to the heart. Modification and inactivation of important proteins such as SERCA cause pathologic events such as Ca²⁺ overload resulting in mitochondrial damage and loss of ATP contents and cardiac dysfunction. Blocking damage to SERCA may be a therapeutic strategy after such toxic exposures. Mito, mitochondria; ER, endoplasmic reticulum; SERCA, sarcoendoplasmic reticulum Ca²⁺ ATPase

Table 1

Cardiovascular effects of inhaled halogen gases (chlorine and bromine)

Halogen	Model	Type	Exposure Dose (ppm)	Duration (min)	Cardiac effect	Mechanism of toxicity	Ref.
Cl ₂	Rodent	Inhalation	500	30	↓ HR	↓ SERCA activity due to chlorination of cysteine	[1]
Cl ₂	Rodent	In vitro	100, 300	15	Loss of cell membrane integrity, apoptotic cell death	Non-physiologic-al PH	[15]
Cl ₂	Rodent	Inhalation	413	30	↓ HR	Stimulation of nociceptive reflexes	[20]
Cl ₂	Rodent	Inhalation	500 600	30 30	↓ HR, ↓ BP, hyperdynamic circulation, diastolic dysfunction ↓ HR, ↓ BP biventricular failure, severe tricuspid regurgitation ↓ Contractile force	↓ SERCA activity independent of hypoxia	[44]
Cl ₂	Rodent	Inhalation	0–400	30	↓ Vasodilation	↓ eNOS-mediated vasodilation	[30, 39]
Cl ₂	Swine	Inhalation	140	10	↓ CO, ↓BP, PAH, death	Inflammation of pulmonary vasculature	[43]
Cl ₂	Humans	Inhalation (accidental)	NR	NR	↑BP, cardiomegaly (on autopsy)	Hypoxia-mediated	[33]
Cl ₂	Humans	Infestation (accidental)	NR	NR	Acute coronary syndrome, heart block	Hypoxia-mediated	[100]
Cl ₂	Humans	Infestation (accidental)	6,12,18 g	NR	Cardiogenic shock	Hypoxia-mediated	[101]
Cl ₂	Humans	Inhalation (accidental)	NR	NR	Cardiomegaly	NR	[102]
Br ₂	Humans	Inhalation (accidental)	NR	NR	Myocarditis	Hypoxia-mediated	[103]
Br ₂	Humans	Inhalation (accidental)	NR	NR	Cardiac arrest & circulatory collapse, myocardial degeneration	NR	

Cl₂, chlorine; Br₂, bromine; ppm, parts per million; min, minutes; ref, references; NR, not reported; bp, blood pressure; HR, heart rate; SERCA, sarco-endoplasmic reticulum calcium adenosine triphosphatase; g, grams; eNOS, endothelial nitric oxide synthase; PAH, pulmonary artery hypertension; ↓, decreased; ↑, increased.

Table 2

Cardiac effects of inhaled toxic environmental gases

Toxin	Model	Type	Exposure Dose (ppm)	Duration (h/day)	Cardiac toxicity	Mechanism of toxicity	Ref.
O ₃	Rodent	Inhalation	1	6	↓ HR	Severe inflammation	[104]
O ₃	Rodent	Inhalation	0.5	8	↓ HR and BP	Diet-enhanced autonomic modulation	[105]
O ₃	Rodent	Inhalation	0.2/0.8	4	↓ HR, PR prolongation, ST depression, ↑ PACs, SAN, AVN block	↑parasympathetic tone	[97]
O ₃	Rodent	Inhalation	0.8	0.5	↓ LVDP, LVEDP, +/-dp/dt	↑ Sensitivity to ischemia-reperfusion injury (↑ myocardial TNF- α levels and lipid peroxidation and ↓ myocardial activities of superoxidase dismutase (SOD) and IL-10)	[96]
O ₃	Murine Primate	Inhalation	0.8	8	↑HR& BP, ↓ Vaso-relaxation	↓ vascular NO	[95]
O ₃	Humans	Inhalation	120 (ppb)	2	↑ brachial artery vasoconstriction	↑ sympathetic activity, ↑ vascular ET release	[93,106]
O ₃	Humans	Inhalation (accidental)	NR	NR	Acute coronary syndrome	Coronary vasospasm and thrombosis	[107,108]
CO	Humans	Inhalation (accidental)	NR	NR	Cardiac arrest Intramural hemorrhage and myocardial rupture (autopsy)	Hypoxia/direct effect	[109]
CO	Rodents	Inhalation	250,1000, & 3000	20, (minutes)	&40 ST segment elevation and depression, T-wave inversion and first-degree AV block	Hypoxia-mediated, erythropoietin reversed	[87]
CO	Humans	Inhalation (accidental)	NR	NR	Long term increased risk of arrhythmias, CAD, CHF	NR	[82]
CO	Humans	Inhalation (accidental)	NR	NR	Myocardial injury, ↑serum h-FABP & ↑natriuretic peptides,	NR	[70, 84,110,111]
CO	Humans	Inhalation (accidental)	NR	NR	Myocardial necrosis, & mitral valve dysfunctions	NR	[112]

Toxin	Model	Type	Exposure Dose (ppm)	Duration (h/day)	Cardiac toxicity	Mechanism of toxicity	Ref.
SO ₂	Rodent Murine	Inhalation	Variable	Variable	Dose-dependent organ damage	Ultra-structural damage	[6,68,76,113]
SO ₂	Humans	Inhalation	10 µg/m ³	24	↑ CVD mortality	NR	[64,114115]

O₃, ozone; CO, carbon monoxide; ppm, parts per million; h, hours; min, minutes; ref, references; NR, not reported; bp, blood pressure; HR, heart rate; CHF, congestive heart failure; CVD, cardiovascular disease; h-FABP, heart type fatty acid binding protein; AV, atrio-ventricular node; SN, sino-atrial node; g, grams; NO, nitric oxide; PACs, premature atrial contractions; CAD, coronary artery disease; ↓, decreased; ↑, increased