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Air Pollution and Cardiac Diseases: A Review of Experimental Studies

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Abstract

Air pollution is associated with around 6.5 million premature deaths annually, which are directly related to cardiovascular diseases, and the most dangerous atmospheric pollutants to health are as follows: NO_2, SO_2, CO, and PM. The mechanisms underlying the observed effects have not yet been clearly defined. This work aims to conduct a narrative review of experimental studies to provide a more comprehensive and multiperspective assessment of how the effect of atmospheric pollutants on cardiac activity can result in the development of cardiac diseases. For this purpose, a review was carried out in databases of experimental studies, excluding clinical trials, and epidemiological and simulation studies. After analyzing the available information, the existence of pathophysiological effects of the different pollutants on cardiac activity from exposure during both short-term and long-term is evident. This narrative review based on experimental studies is a basis for the development of recommendations for public health.

Keywords

air pollution, cardiac arrhythmias, experimental studies, heart diseases

Introduction

Air pollution is defined as the presence of one or more substances in adequate amounts and time in the atmosphere to produce health alterations. This is presented in the form of aerosols and gaseous components, altering the quality of life and the degradation of ecosystems.[1] The United States Environmental Protection Agency (EPA) has designated six specific air pollutants as "criteria" air pollutants. This classification is due to the regulation of them through the development of human health-based and environmentally-based criteria for setting permissible levels. These six pollutants are carbon monoxide (CO), lead (Pb), nitrogen oxides (NO_x), ground-level ozone (O_3), particle matter (PM), and sulfur dioxide (SO_2),[2] which have become a concern for health systems around the world, due to the existing evidence of their toxic effects on human health.

The lower levels of air pollution in a city (in short- and long-term), the better the cardiovascular and pulmonary health of its population. Globally, the primary cause of death is cardiovascular disease, taking an estimated 17.9 million lives annually.[3] Data from the Global Burden of Disease study in 2019, identified air pollution as a leading cause of morbidity, in particular in low- and middle-income nations,[4] been associated with more than 6.5 million deaths each year worldwide.[5] Health impacts related to exposure to air pollution are estimated at an annual economic cost of $8.1 trillion.[6] According to The Organization for Economic Co-operation and Development (OECD), global air pollution–related healthcare expenses are expected to increase to USD 176 billion in 2060,[7] becoming a major public health problem.

More than 90% of the world population has been exposed to air quality levels that do not adhere to World Health

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Organization (WHO) guidelines on acceptable levels of air pollutants.[8] As a result, the risks of stroke, heart disease, and other health problems have increased significantly. In recent years, studies on the impacts of exposure to air pollutants on human health have found a strong relationship between exposure and adverse respiratory and cardiac effects[9]). Short-term effects involve headaches, dizziness, nausea, and infections like pneumonia or bronchitis, in addition to irritation to the nose, throat, eyes, or skin. Long-term effects involve heart diseases, lung cancer, and respiratory diseases such as emphysema. Likewise, damage to nerves, brain, kidneys, liver, and other organs can also result from long-term air pollution exposure.[10] Particularly, air pollution raises the risk of cardiovascular disease death by 76%,[11] mainly related to ischemia, myocardial infarction, arrhythmias, and heart failure.[12-14] Epidemiological studies have associated an increased probability of cardiac arrhythmia generation in the population after air pollutants exposure,[15,16] even at low concentration levels,[16] concluding that these arrhythmias are acutely triggered by air pollution.[15] Hospital admissions increased for cardiovascular diseases because of exposure to high pollutant levels have also been reported.[17,18]

PM is a mixture of mainly sulfates, nitrates, ammonia, sodium chloride, soot, minerals, and water[8] and is classified according to its size. PM pollution includes total suspended particulate matter (TSP), particles with a diameter of 10 micrometers and smaller (PM_{10}), and those up to 2.5 micrometers ($PM_{2.5}$). A significant portion of PM sources is produced by human activity.[19] PM is considered one of the most severe air pollutants, generating a public health problem related to decreased life expectancy,[20,21] especially in people with heart and lung diseases.[22] Elderly, children, people with heart and lung diseases, and asthmatics groups are more likely to have health problems by exposure to PM.[23] Epidemiological and cohort studies published by the Institute for Health Effects[24,25] showed a correspondence between increased death rates and increased PM and sulfates in the air. Fine PM air pollution is the most important environmental risk factor contributing to global cardiovascular mortality and disability.[26] In the long-term, PM exposure is mainly related to increased cardiovascular disease,[27-29] bradycardia, premature contraction[30] and with the occurrence of atrial arrhythmias as atrial fibrillation[31,32] and ventricular arrhythmias as ventricular tachycardia, and ventricular fibrillation.[33] In general, long-term PM exposure is associated with premature mortality due to heart failure, stroke, and ischemic heart disease.[34] In the short term, exposure to PM can impact subclinical markers of cardiovascular health[35] and cause myocardial infarction.[36] Likewise, PM from anthropogenic sources had demonstrated a high oxidative potential per mass unit[37] and a high risk of arrhythmia events.[38] It is remarkable the link between PM and inflammation-related cardiovascular diseases, including ischemic heart disease, congestive heart failure, cerebrovascular disorders, cardiac dysrhythmias, and stroke.[39] Lead (Pb) as a PM component is a highly polluting chemical element. It is as toxic as mercury or arsenic. It is one of the four metals with the greatest harmful effect on human health.[2]

SO_2 is one of the sulfur compounds most frequently present in the air. It is a sulfur-derived gas and comes largely from fossil fuel combustion and less from the exhaust gases from diesel and gasoline engines. It irritates the eyes and respiratory tract and aggravates respiratory diseases. A relationship has also been found between sulfur oxides presence in the atmosphere and a higher number of chronic cardiovascular diseases[2] such as heart failure, atrial fibrillation, and coronary heart disease,[40] and a risk of ischemic heart disease and non-accidental mortality, which is greater in elderly populations.[41,42]

CO is a flavorless, odorless, flammable, and highly toxic gas. It is produced whenever there is incomplete combustion. CO breathing eventually leads to tissue hypoxia and carbon dioxide retention, resulting in symptoms of poisoning.[43] A cohort study indicates that CO poisoning, in particular, is responsible for developing cardiovascular diseases.[44] CO pollution increases risk factors for heart failure[45] and decreases heart rate variability.[46] Higher exhale CO levels (over 3 ppm) are linked to a higher risk of ischemic stroke[47] and deaths due to ischemic heart disease for each 10 $\mu g/m^3$ increase in CO.[48] Outdoor CO exposure is strongly correlated with cardiac mortality and hospital admissions for cardiovascular illness, even at low concentrations like those found in metropolitan environments.[49]

NO_x are part of a group of highly reactive gases, emitted mainly in the combustion processes related to the automotive fleet and thermoelectric power plants.[50] Of all the nitrogen oxides indoors, the most abundant is nitric oxide (NO) and, to a lesser proportion, nitrogen dioxide (NO_2). The highest NO_x levels are found in large urban agglomerations, metropolitan areas, and around roads with the heaviest traffic. Likewise, it can also aggravate existing heart disease, leading to increased hospital admissions and premature death.[2] Epidemiological studies suggested linked high outdoor NO_2 levels to enhanced morbidity and mortality by ischemic heart disease and cardiovascular disease[51,52] and has been found to increase the risk of heart failure and adverse cardiac remodeling in patients with dilated cardiomyopathy that include higher indexed left ventricular mass and lower left ventricular ejection fraction.[53] Although these findings show an association between ambient NO_2 concentrations and cardiovascular disease, they cannot establish causality of NO_2 effects. Many of the observed health effects likely occur because of exposure to secondary pollutants including ozone, acid aerosols, and particles. Adverse biological effects have been reported for some pollutants like NO_2 and PM below the current legal limits of annual average exposure.[21,53–55]

O_3 is a trace gas in the lowest level of the atmosphere, and it is created by chemical reactions between NO_x and volatile organic compounds in the presence of sunlight. It is considered a greenhouse gas that contributes to global warming. Although tropospheric ozone is less concentrated than

stratospheric ozone, it is of concern due to its effects on health. Epidemiological studies[56,57] and clinical trials[58,59] have suggested that O_3 exposure has impacts on the cardiovascular system as well.

Despite there being several epidemiological studies and clinical trials in the literature that have associated these six air pollutants with cardiovascular morbidity and early mortality worldwide, only a few experimental studies have demonstrated causality and pathogenesis of acute and chronic exposure to the air pollutants PM, Pb, CO, and SO_2. To our knowledge, there are no reports in the literature of experimental studies to evaluate the underlying causes of O_3 impacts on cardiovascular health. Therefore, the biological mechanisms underlying the link between air pollution and cardiovascular disease remain largely unknown. Further research is imperative to discern the role of individual pollutants in distinct facets of cardiovascular diseases, establish causal relationships, and clarify the fundamental physiological mechanisms involved.[60]

Experimental studies are indispensable to understanding the underlying mechanisms of heart diseases, offering controlled conditions for isolating and examining individual components, allowing access to biophysical properties to manipulate specific variables and observe the effects from the cellular to organ level. A better understanding of the underlying mechanisms by which air pollutants generate and aggravate heart disease allows the proposal of mitigation strategies, interventions in public health policies, and changes in lifestyles of the people to promote the prevention of these pathologies. Furthermore, it allows suggesting approaches to address research challenges more effectively in future studies. Therefore, this work presents a narrative review of experimental studies related to the effects of air pollutants on the heart, for a deeper understanding of the pathophysiological mechanisms that contribute to heart diseases.

Methods

This work is a review of experimental studies of the air pollutants effects on the cardiac system. In this review, three filters were applied to collect (search procedure), select (through inclusion and exclusion criteria), and extract (by data extraction) relevant information from the literature. The sources of information used were secondary and were obtained from the following databases: ScienceDirect, Pubmed, Scielo, Researchgate, and Scopus. The search for information in the databases was carried out using the combination of terms with logical operators (Boolean) AND, OR was used to perform an advanced search and limit the amount of information according to the needs of the study, by the following search strategy: (*air pollutant* OR *air pollution* OR *sulfur dioxide* OR *carbon monoxide* OR *nitrogen oxides* OR *particulate matter*) AND (*cardiac disease* OR *cardiac remodeling* OR *cardiac arrhythmia)* AND *(experimental studies,* OR *cardiomyocytes).* Further studies were identified by searching the bibliographic reference lists of eligible studies and relevant reviews.

Inclusion and exclusion criteria

Relevance was evaluated on titles and abstracts of publications found in the bibliographic search. The bibliographical selection included experimental studies, with in vitro or animal models, with relevant information on the effect of air pollutants on cardiomyocytes, cardiac activity, and/or heart diseases. The studies in English that have been published in the last 30 years were retrieved and subsequently assessed about the eligibility criteria described above.

As exclusion criteria were not considered for this review publications with reported effects on physiological systems other than the heart, such as the respiratory system. Epidemiological studies and clinical trials were also excluded, as these do not provide clarity on the underlying mechanisms linking atmospheric pollutants to cardiac system effects. Although the United States Environmental Protection Agency (EPA) considers O_3 as one of the six most common air pollutants,[2] to our knowledge, there are no reports in the literature of experimental studies to evaluate the underlying causes of O_3 impacts on cardiovascular health, therefore, was excluded it from the study.

The chosen studies were classified by author, year, studied air pollutant, harmful cardiac effect, and by additional specific information (if applicable), such as affected ionic channel, tested cell type, and obtained values of the half-maximal inhibitory concentration (IC_{50}) or half-maximal effective concentration (EC_{50}).

Results

A total of 57 full papers were identified for inclusion in the methodological review. Of these, 21 were characterized as PM effects studies, 9 NO_x effects studies, 11 SO_2 effects studies, and 17 CO effects studies. The following section contains a table and a quantitative representation (Table 1 and Figure 1), which shows a summary of the effects and quantity of air pollutants. Then, the effect of atmospheric pollutants on cardiac disease by each pollutant PM, SO_2, CO, and NO_x is described.

Particulate matter

Different studies have reported that both the acute cardiovascular risk and the sensitivity to triggering cardiac arrhythmias can increase by exposure to PM. Watkinson et al[103] in a study with 32 rats, 16 healthy and 16 cardiopulmonary-compromised, showed that exposure to fugitive residual oil fly ash (ROFA) PM during 96 h caused the incidence and duration of severe arrhythmic events linked to impaired atrioventricular conduction and myocardial hypoxia in a dose-dependent manner, and the frequency and severity of arrhythmias

Table 1. Harmful Effects of Major Air Pollutants on Cardiac Health.

Effect	PM	SO_2	CO	NO_x
Electrical remodeling	61-64	65-72	73	74–76
Structural remodeling	77-93	71,94	95,96	97-101
Cardiac arrhythmia	87,102-104	94	105-108	
Reduced myocardial contractility	62,64,87		109,110	
Myocardial infarction	87		111	
Myocardial hypoxia	103	67	45	
Ischemia	112	67	111,113,114	
Heart rate variations	78,79,84	71,94		
Cardiac injury	84	65	45,111,113	98
Cardiac dysfunction	77,79,80,84,88			

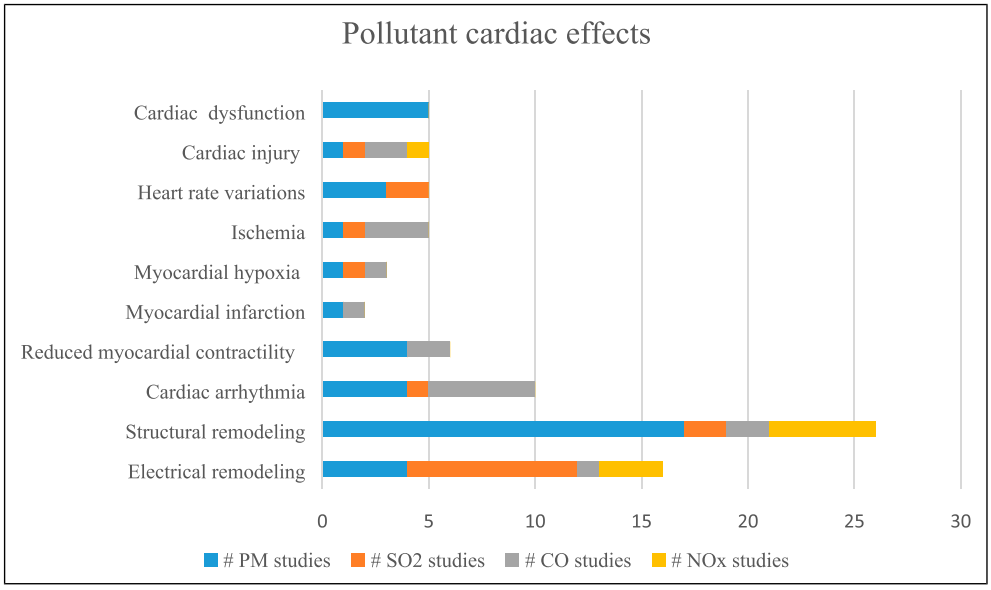

Figure 1. The number of effects reported by PM, SO_2, CO, and NO_x.

were significantly worsened in the treated animals and were accompanied by six deaths. Different studies have reported that exposure to PM can increase the acute cardiovascular risk and the sensitivity to triggering of cardiac arrhythmias. Hazari et al[104] exposed hypertensive rats implanted with radio-telemeters to monitor electrocardiogram, to either 500 μg/m^3 (high) or 150 μg/m^3 (low) whole diesel exhaust or filtered diesel exhaust, or to filtered air, for 4 hr. Individual chemical compounds that have been found in diesel exhaust (PM, O_2, CO, NO_x, and SO_2) have also been found in filtered air or diesel exhaust mixed with filtered air, at lesser concentrations. They showed increased susceptibility to cardiac arrhythmias monitored via electrocardiogram recording mediated by activation of sensory nerves bearing transient receptor potential channels member A1 (TRPA1) and subsequent sympathetic modulation. Likewise, Calderón-Garcidueñas et al[115] studied the cardiac tissue of 152 healthy dogs from different cities in Mexico, of which 109 belonged to the most polluted cities in Mexico and 43 to less polluted cities. The histological analysis exhibited little or no cardiac abnormalities in dogs living in cities with lower levels of pollution, while the other dogs exhibited substantial vascular abnormalities and myocardial changes, such as apoptotic myocytes. Godleski et al[112] conducted a study where they exposed dogs to concentrated ambient particles from Boston air, using a device that could increase particle concentration up to 30 times. The study involved 14 tracheostomized dogs, exposed in pairs for six hours over three days, and induced coronary occlusion in 6 dogs to mimic human coronary artery disease. In dogs with induced coronary occlusion, exposure to particles affected the ST segment, which is the main ECG sign of myocardial ischemia, heart rate variability, and a slight decrease in heart rate were observed. Kim et al[102] in a group of 5 male Sprague–Dawley rats exposed to PM (diesel exhaust particles) by

endotracheal intubation with 100, 200, and 400 μg/mL concentrations and 12 rats by infusion with 12.5 μg/mL for 20 min, demonstrated a close association with cardiovascular disease, observing after endotracheal exposure premature ventricular contractions in all 5 rats, ventricular tachycardia only in one and increased PR and QT interval in 4 rats and induced a dose-dependent APD prolongation. In 12 Langendorff-perfused rat hearts, diesel exhaust particles infusion induced APD prolongation, and spontaneous early afterdepolarization in 8 hearts (67%) and ventricular tachycardia in 6 hearts (50%) were observed, vs no spontaneous triggered activity in any hearts before infusion. Kim et al also evaluated diesel exhaust particles effect on neonatal rat ventricular isolated cardiomyocytes, highlighting dose-related increases in the reactive oxygen species (ROS) generation.

Individual PM components have also been evaluated in isolated cells. Bernal et al[61] evaluated the cardiotoxicity in either *Xenopus laevis* oocytes or human embryonic kidney cells (HEK 293), the effect of different concentrations (1 and 10 mM) of Pb. Through the data obtained experimentally and fitted to the Hill equation, in oocytes the IC_{50} value was 152 nM, and in HEK 293 cells, it was 169 nM with a Hill coefficient (*h*) of .5, reporting as a result the cardiotoxicity of Pb modulated by voltage-dependent blockade of the L-type calcium channel currents (I_{CaL}). Similarly, in an experimental study on isolated guinea pig hearts,[62] evaluated the effect of exposure to inorganic Pb ($PbCl_2$) added to Tyrode solution at different concentrations (1-200 μM), where increasing concentrations decreased the papillary muscle contractile force measurements. The parameters of the Hill equation were experimentally determined, obtaining an IC_{50} value of 18 μM and an *h* coefficient of −1.28. They also reported the effects of acute exposure to inorganic Pb (0-100 μM) and demonstrated a negative inotropic effect on isolated guinea pig hearts, including a gradual increase in diastolic pressure and irregular cardiac rhythms. Pb in the same concentration range blocks L-type Cav1.2 channels and increases its rapid inactivation. Also was found a reduction in cardiac contractility, an early afterdepolarization, and a reduction of the action potential plateau whose effect was accentuated as the concentration increased, leading to an increased vulnerability of the heart to arrhythmias. Vasallo et al,[64] in right ventricular strips isometrically contracted in 45 male Wistar rats, studied the acute Pb administration effects and showed a reduction in sarcolemma calcium influx and the myosin ATPase activity that results in decreased myocardial contractility. The mechanism of the association between arrhythmia and PM exposure continues unclear. Among the reasons reported to explain this possible association are systemic inflammatory processes, including oxidative stress. In human cardiomyocytes exposed to $PM_{2.5}$ for 24 h, measured cytotoxicity indicated that $PM_{2.5}$ may exacerbate cardiac dysfunction by apoptosis pathway.[91] Indeed, Miller et al[92] in an animal study, where healthy male nonsmoking volunteers (18-35 years) were exposed to gold nanoparticles for 2 h via inhalation, and male mice were exposed to 2, 5, 10, 30, or 200 nm concentrations by instillation while engaging in intermittent exercise, observed that nanoparticles could reach the circulation in both, mice and humans, and accumulate at sites of vascular inflammation.[92] Titanium dioxide nanoparticles were introduced directly in the isolated adult healthy rat which induces ventricular cardiomyocytes, leading to a shortened action potential duration (APD) and effective refractory period (ERP). In vivo, intratracheal administration enhanced cardiac conduction velocity and tissue excitability, which increases the likelihood of inducible arrhythmias.[63]

Recent research using animal models has revealed insight into the physiological, cellular, and molecular pathways underlying adverse cardiac remodeling. PM exposure may contribute to adverse ventricular remodeling and exacerbate myocardial fibrosis.[86] Kodavanti et al[84] in an experimental study with male Sprague-Dawley, Wistar Kyoto, and spontaneously hypertensive rats observed that exposure through the nose to fugitive PM emissions from oil combustion (2, 5, or 10 mg/m^3, 6 hours per day for 4 consecutive days, 10 mg/m^3 for 6 hours per day, and 1 day each week for 4 or 16 consecutive weeks) resulted in duration- and dose-dependent myocardial injury in vulnerable Wistar Kyoto rats, where exposure to PM for 16 weeks in 5 of 6 rats leading to the multifocal, inflammatory, degenerative, and fibrotic myocardial lesions and none of these lesions were present in Wistar Kyoto exposed to clean air. In a study with 75 rats,[82] were divided into 5 groups: a control group; a control exposed to $PM_{2.5}$ pollution; a myocardial infarction group; a group with infarction immediately exposed to pollution; and an infarcted group that had been polluted before and kept exposed after infarction. The main findings showed that groups exposed to PM concerning the control group had a greater deposition of interstitial collagen (fibrosis), and greater collagen deposition, in the left and right ventricle, respectively, and modulated the inflammatory response and oxidative stress in the control groups exposed to $PM_{2.5}$ pollution than control groups. However, these increases were not observed because of $PM_{2.5}$ in myocardial infarcted groups. Furthermore, in a study conducted by Wold et al[93] in C57BL/6 mice exposed to $PM_{2.5}$ or filtered air, 6 hours per day, 5 days each week, for 9 months, long-term effects resulted in an increase in heart rate, systolic and diastolic blood pressure, mean arterial blood pressure, and hypertrophic markers leading to structural remodeling characterized by fibrosis, compared with filter air-exposed mice. Likewise, in mice exposed to $PM_{2.5}$, in vitro results showed cardiac dysfunction, increased transforming growth factor (TGF)-β and collagen I, and marked decreased levels of SERCA-2a, indicating a profibrotic phenotype and reduced mechanisms to stimulate Ca reuptake into the sarcoplasmic reticulum. This agrees with Su et al[77] where 48 C57BL/6 mice were randomly divided into 3 groups: exposed to filtered air for 8 or 16 weeks, exposed to unfiltered air for 6 hours per day, and exposed to $PM_{2.5}$ for 7 days each week. Since the eighth week after $PM_{2.5}$ exposure,

manifestations of the cardiac structure were significantly increased compared with filtered and unfiltered air mice, with the presence of cardiac hypertrophy and fibrosis in a dose- and time-dependent manner, leading to decreased cardiac systolic function. Exposure of rats to other sources of air pollution, such as dilute motorcycle exhaust by inhalation, 2 hours per day for 8 weeks led to increased cardiac weight and wall thickness, besides focal cardiac degeneration and necrosis, mononuclear cell infiltration, and fibrosis seen on histological evidence.[81] In addition, Jiang et al[83] studied the effect of individual and combined exposure to $PM_{2.5}$ and a high-fat diet on cardiac fibrosis, in 40 male C57BL/6J mice, randomly divided into four groups, including control conditions with mice on standard diet and mice treated with saline. Mice in the groups treated with $PM_{2.5}$ received 10 mg per kg body weight suspended in saline solution, via intratracheal instillation for 30 days once every other two days. The findings of this study indicate a marked increase in the area of fibrosis in the groups treated with $PM_{2.5}$, with a percentage of fibrotic regions in the hearts between 1.0 and 3.0%, effects that contribute to the deterioration of cardiac function. These findings are similar to results of recent studies in C57BL/6J mice that attributed an elevated inflammatory response, an increasing thickness of the right ventricular free wall (36.3%-46.5%), and increased average heart rate, to the PM exposure in chambers at 3, 6 and 12 weeks in a time-dependent manner.[78] Likewise exposure to $PM_{2.5}$ in female C57BL/6 mice at different ages (4 weeks old, and 10 months old) to each alternate day for 4 weeks, and then exposed for 4 weeks, induced heart rate and blood pressure increase, and cardiac systolic dysfunction in the 10-month-old mice, and triggered fibrosis in mice aged 4 weeks and 10 months.[79] Another study[88] with C57BL/6J mice exposed to PM (diesel exhaust) for 6 hours per day, 5 days each week, throughout pregnancy and until offspring were 3 weeks of age reported that exposure to diesel exhaust air pollution promoted a higher vulnerability to cardiac hypertrophy as well as systolic failure and myocardial fibrosis in exposed mice compared to filtered air control mice. Exposure to PM is also linked to cell death in human cardiomyocytes, by lactate dehydrogenase increase in a dose-dependent, as a protein involved in mitochondria-mediated apoptosis pathway, which suggests that PM may conduce to cardiac dysfunction.[80]

Sulfur dioxide

Literature has revealed that long-term and short-term exposure to SO_2 is linked to cardiovascular diseases by damage to cardiac tissue cells. In vitro studies with rats exposed to SO_2 and SO_2 derivatives had observed abnormal histopathological changes, including edema, interstitial myocardial infarction, myocardial fiber atrophy, and necrosis. Zhang et al[71] in a population of isolated rat hearts perfused with SO_2 and SO_2 derivatives adding concentrations of 10, 300, and 1000 micromolar (μM) to the perfused fluid for 10 min found at high concentrations, potential damage effects on heart functions, that could be associated with increased reactive oxygen species content and a marked decrease in the ATPase activity, showing a reduction in left ventricular pressure and heart rate, and increased coronary flow. The combination of aerobic exercise and SO_2 exposure also has been studied. Findings from Hu et al[94] point to the worsening of negative effects of a combination of aerobic exercise and SO_2 exposure for 1 hour per day for 4 weeks, in 4 groups of Sprague-Dawley rats randomly divided into rest group, exercise group, SO_2 pollution group, and SO_2 pollution + exercise group. The main findings indicated that the adverse effects of SO_2 inhalation on cardiovascular function can be exacerbated by aerobic exercise and SO_2 exposure together. For rats of the SO_2 group increased left ventricular end-diastolic pressure, angiotensin II concentration, angiotensin-converting enzyme concentration, and activity decreased. For rats of the SO_2 pollution + exercise group, the systolic blood pressure, pulse pressure, and left ventricular systolic pressure decreased significantly, and the heart rate, left ventricular end-diastolic pressure, angiotensin II concentration, angiotensin-converting enzyme concentration, and activity increased significantly. In twenty-four healthy male rats were randomly divided into 4 groups under the same conditions of the study by Hu et al, myocardial collagen concentration, myocardial collagen volume fraction, perivascular collagen area, and the expression of angiotensin II type 1 receptor and connective tissue growth factor expression in SO_2 + exercise group increased significantly.[116] Consequently, in rats exercising in environments with SO_2 pollution, an increased angiotensin II and connective tissue growth factor expression in the myocardium may lead to myocardial fibrosis and reduced cardiac function.[94]

Predisposition to cardiac arrhythmias mechanism could involve the SO_2 effects on multiple ion channels in cardiac myocytes. The effects of SO_2 derivatives exposure (5–1000 μM), in isolated rat ventricular cardiomyocytes showed a blocking effect on L-type calcium channels, where SO_2 derivatives at high concentrations (50, 100, 500, and 1000 μM) depressed the peak amplitudes of calcium current within 6 min, and the I_{CaL} peak was attenuated by 13.19%, 16.59%, 21.23%, and 24.72%, respectively, compared to the corresponding controls.[72] Zhang et al[69,70] also showed that SO_2 played an important role in the generation of cardiovascular disease in the isolated rat aortas in vitro. The vasorelaxant effect of SO_2 on rat aorta can activate adenosine triphosphate-sensitive potassium channel (K_{ATP}), and large conductance calcium-activated potassium channels (BK_{ca}), which positively regulate the expression of subunits Kir6.1, Kir6.2, sulfonylurea receptor 2B (SUR2B), BK_{ca} α and BK_{ca} β1, whereas it blocks the L-type calcium current (I_{CaL}) channels by negatively regulating the expression of $Ca_v1.2$ and $Ca_v1.3$. Nie et al[67] in single-cell rat ventricular cardiomyocytes, evaluated the effect of SO_2 derivatives, prepared in a neutral solution by 3:1 M/M mixing of sodium bisulfite and sodium sulfite, where SO_2 derivatives increase the peak amplitude of I_{CaL}, in a dose-dependent manner. SO_2 derivatives at 2 μM and

100 μM increased the peak amplitude of calcium current by 14.8 ± .74% and 81.9 ± 4.10%, respectively, and an EC_{50} of 10.64 ± 1.33 μM, where imbalanced ionic homeostasis might explain for tissue damage during ischemia/reperfusion and hypoxia/reoxygenation. In addition to I_{CaL}, Nie, and Meng presented a series of experiments about the effects of SO_2 derivations on ion channels in rat cardiac myocytes. In potassium channels, Nie et al[65] used single concentrations of 10 μM and reported an increase in the peak currents amplitude of I_{to} and I_{k1} by 37.4% and 26.2%, respectively, corresponding to the maximum effect on the current. These findings suggested that SO_2 inhalation could damage cardiac myocytes by elevating intracellular calcium and extracellular potassium levels, through voltage-gated calcium channels and voltage-gated potassium channels, respectively. In another study, in isolated adult rat ventricular myocytes, they studied the effects of SO_2 concentrations (1–200 μM) setting to an exposure chamber on voltage-dependent sodium channel,[66] finding an increase in the peak amplitude of I_{Na} by 8.3 ± 1.1% and 84.1 ± 5.3% at 1 μM and 200 μM, respectively; where the EC_{50} of SO_2 derivatives on I_{Na} was 10.97 ± .61 μM, with h of 1.07 ± .05. Further, Wei et al[68] on ventricular myocytes of rats, SO_2 derivatives exposure (1–100 mM), reported an increase in I_{Na} current in a concentration-dependent manner, with a maximum sodium current amplitude of 76.24% ± 3.52, with an EC_{50} of 19.85 ± .9 mM, and h of 3.12 ± .34.

Carbon monoxide

Experimental studies have shown the CO effects on cardiovascular health. When breathing, CO binds to hemoglobin, with an affinity of 200-250 times higher than the affinity of oxygen,[114] to form carboxyhemoglobin, then, delivery of oxygen to the tissues is reduced. In different studies about case reports, CO poisoning was marked as one of the suspected risk factors for ischemic stroke developed[114] and ventricular and atrial arrhythmias,[117] as atrial fibrillation. In experimental studies, Meyer et al[111,113] in isolated rat hearts exposed to CO for 4 weeks, observed that prolonged exposure to CO worsens myocardial ischemia-reperfusion injury, resulting in decreased myocardial function and increased infarct size. Different studies have shown the effect of CO on electrical and contractile activity. In isolated rats, atrial and ventricular myocardium results highlight a marked decrease in APD_{50} and APD_{90}, and of the cycle length by higher CO concentrations (100, 300, and 500 y 1000 μM), and suppress contractile activity (all tested concentrations) as well as significant acceleration of sinus rhythm in isolated atrial and ventricular preparations.[109] Reboul et al[110] showed that daily (4 weeks) peaks of CO mimicking urban exposure worsen cardiac alterations, with the presence of hypertrophy characterized by contractile dysfunction. Moreover, heart failure rats exposed to CO developed more frequent ventricular extrasystoles and sustained ventricular tachycardia, than rats exposed to standard filtered air, where Ca handling disruptions within the cardiomyocytes may explain this additional effect of CO exposure both on contractile and rhythmic functions.

The aggravating CO effects can be explained by intracellular changes. Additionally, CO aggravates lactic acidosis and apoptosis by hindering mitochondrial ATP formation, forcing myocytes to switch to anaerobic metabolism.[118] Besides, CO has been involved in calcium handling, inducing a cellular diastolic calcium overload, and a reduction in calcium-transient amplitude, which might contribute to the reduced contractile function and arrhythmic events observed in vivo.[110] In addition to these mechanisms, CO affects multiple ionic channels. In a study performed on rat embryonic cardiomyocyte-derived H9c2 cells,[119] the ischemic medium was bubbled with hypoxic-CO gas ($CO/O_2/N_2/CO_2$, 1,0/2,0/92/5%) at concentrations of 1 mM for 30 minutes, observing a blocking effect on the I_{CaL} current of 44.5% ± 8.3. Guinea pig and rat single isolated ventricular myocytes exposed to CO 3 μM or 10 μM for currents and action potentials recording, respectively, showed a decrease in the maximal I_{CaL} peak and could decrease the conduction velocity of electrical propagation, action potential duration increased in both rat and guinea pig myocytes, and generated early after-depolarizations in guinea pig myocytes.[120] Andre et al[95] exposed Wistar rats to filtered air or air enhanced with CO concentrations consistent with urban pollution (30 ppm with five peaks of 100 ppm per 24-h period) for 4 weeks, showing in an excitation-contraction coupling analysis that chronic CO pollution alters the Ca dynamics of rats ventricular myocytes after exposure to CO concentrations of 150–200 ppm for 12 hours daily for 4 weeks, by reduction of sarcoplasmic reticulum Ca load by 27% ± 2, which could contribute to transient Ca depletion, increased diastolic intracellular Ca after decreased SERCA-2a expression and impaired Ca reuptake. Likewise, CO exposure in rats increased basal heart rate, decreased heart rate variability, and doubled the number of premature ventricular beats. Dallas et al[73] exposed isolated male Wistar rats ventricular myocytes to filtered air or CO at 500 ppm for 1 hour, and reported decreases in the Na current peak amplitude by 53.4 ± 7.7% and 58 ± 5.6%, with CO applied as the CO-releasing molecule, CORM-2, and dissolved CO, respectively, resulting in prolongation of the action potential and reactivation of I_{CaL} in approximately 50% of cells. In addition to calcium currents and sodium (I_{Na}), potassium channels including the rapidly activating delayed rectifier potassium current (I_{Kr})[105] and the inwardly rectifying potassium channel current (I_{k1})[108] also be affected by CO. Al-Owais et al[105] in guinea pig cardiac myocytes and HEK293 cells, after the first 3 minutes of exposure (10 μM) to CORM-2, action potential duration gradually increased, indeed, before 5 minutes, in all 11 myocytes early after-depolarizations arrhythmias were observed in guinea pig myocytes. On the other hand, in both, guinea pig and HEK293 cells CO reduced I_{kr} outward current, suggesting

that CO induces arrhythmias through the formation of peroxynitrite and mitochondrial ROS mediated inhibition of ether-a-go-go related gene (ERG) K+ channel (Kv11.1).

In addition to the reported electrical remodeling effects, structural remodeling was also found in the literature as an effect of CO exposure. In a study,[45] 11 adult male Wistar rats were exposed to CO in a Plexiglas chamber to 1000 ppm for 20 minutes, then 3000 ppm for an additional 80 minutes which showed higher left ventricle internal dimension in diastole and systole, lower left ventricular ejection fraction and left ventricle fractional shortening immediately after CO poisoning, moreover, were increased the myocardium damage scores, and fibrosis area after deposited collagen on the left ventricular myocardial tissue where, it could be involved as mechanisms of hypoxic injury, free radical generation, mitochondrial inhibition, and inflammation. In the same study,[95] Andre et al showed the effects of CO on cardiac morphology and function, where rats exposed to the CO group exhibited hypertrophic characteristics, including increased heart weight/body weight and left ventricular/body weight ratios, promoting pathological cardiac phenotype by the presence of interstitial fibrosis (3.72% of the total area in exposed rats) and perivascular fibrosis of the left ventricle, where fibrous tissue was nearly doubled, and posterior wall hypertrophy linked to significant global contractile dysfunction. Both structural and electrical remodeling modulated mainly by intracellular calcium overload would increase the risk of arrhythmias.[95,121]

Nitrogen oxides

Experimental studies have reported effects generated by NOx on cardiac ionic currents. Kirstein et al[76] studied the NO effects at three different concentrations (100 PM, 1 nM, and 10 nM) of a peroxynitrite generator, a nitric oxide donor (SIN-1) in human right atrial appendage cells, finding an increase in I_{CaL} current. The equation based on the Michaelis-Menten formula was used, with an EC_{50} of 7 PM and emax of 59% for SIN-1. Bae et al[74] in human cardiac fibroblasts evaluated the effect of NO donor, S-nitroso-N-acetylpenicillamine (SNAP), on voltage-gated K_v channels, and showed fast activation and slow inactivation in I_{Kr}, instead of a fast activation and inactivation kinetics in I_{to}. No affected I_{kr} in a concentration-dependent manner with an EC_{50} value of 26.4 μM but did not affect $I_{to.}$

The effect of NO_2 exposure on the generation of pulmonary fibrosis can trigger lung and heart disease.[122] NO_2 has been implicated in the etiology of oxidative damage.[99] A study in rats[98] showed that inhalation exposure to NO_2 diluted with fresh air resulted in cardiac injury and reduced cardiac output, associated with oxidative stress, endothelial dysfunction, and inflammatory response. Pollutants such as NO_2, which induce a positive inotropic effect, can cause an increase in oxygen consumption and trigger oxidative stress due to an increase in mitochondrial metabolic activity, which, consequently can trigger to excessive production of superoxides involved in peroxynitrite formation, which finally contribute to the occurrence of fibrosis.[99] Reactive oxygen species preferentially react with specific atoms to modulate functions ranging from cellular homeostasis to cell death.

The effects of NO_2 have also been studied in Wistar rats,[97] in ROS production and its impacts on mitochondrial, coronary endothelial, and cardiac functions after acute (single exposure) and repeated (3 h/day, 5 days/week for 3 weeks) exposures. Production of mitochondrial ROS (oxidative stress) induced by acute exposure to NO_2 was accelerated but reversible, and with respect to the control group which induced a significant increase in left ventricular diastolic from 10% and systolic diameters from 38%.

Combined pollutants

A study carried out in Northern California in rats exposed to traffic-related air pollution or filtered air for 24 hours per day, 7 days/week, for a total of 14 months in a freeway tunnel system conducted via real-time showed higher expression of genes related to fibrosis, aging, oxidative stress, and inflammation in the rat heart. These genes included significantly higher expression of cytokines interferon-gamma (IFN-c), IL-6, and tumor necrosis factor-alpha (TNF-a). Enhanced collagen accumulation was found only in exposed female hearts. In contrast, inflammatory macrophages were higher only in traffic-related air pollution–exposed male spleens. Findings suggest that female rats may be more susceptible to traffic-related air pollution–induced cardiac fibrosis than male rats.[100]

Tables 2 and 3 exhibit the ion channel changes experimentally reported for each pollutant.

In summary, in this review, the relevant information has been presented focused on the hazardous air pollutants, PM, Pb, SO_2, CO, and NO_x, finding mechanisms that partly explain the conditions underlying the occurrence, aggravation, or death from cardiovascular disease following exposure to these pollutants, even at low concentrations; other review studies have also evaluated the effect of pollutants, including ozone and hydrogen sulfide based also on epidemiological studies.[120,125] Other studies evaluated specific effects, such as inflammatory health effects[39] or just an individual pollutant as well CO[126] and PM.[127] Indeed, studies related to the pollutant effects from the cell to the organ level remain limited. In this narrative review, we focus on literature with an experimental scientific basis and examine several pollutants effects on mechanisms inducing the generation or aggravation of heart disease and/or fibrosis. The information reviewed in this article could be used as a scientific resource for the future planning of public policies focused on mitigating the impact of atmospheric pollutants on cardiac health. Likewise, a future line might focus on computational modeling, which plays a key role in supplying a powerful means for integrating multiscale models with

Table 2. Blockage of Ion Channels Caused by Pb, CO, NO and SO_2.

Air Pollutant	Ion Channel	Type of Cell Tested	IC_{50}	Reference
Pb	I_{CaL}	HEK293	169 nM	61
		Xenopus laevis oocytes	152 nM	
		Isolated cardiomyocytes	18 ± 8 μM	62
			55 μM	
NO	I_{Na}	Mice and guinea pig ventricular myocytes	523 nM	123
SO_2	I_{CaL}	Rat myocytes	35.99 μM	72
CO	I_{CaL}	Rat myocytes	Not measured ↓44.5 ± 8.3% (1 nM)	119
		Rat myocytes	14.8 ± .9 μM	124
		Rat myocytes	Not measured ↓12.5% (1.8 mM)	120
	I_{Na}	Rat myocytes	Not measured ↓53.4 ± 7.7% (30 μM CORM-2) and 58 ± 5.6% (30 μM dissolved CO)	73
	I_{kr}	HEK293	1.6 μM	105
		Guinea pig myocytes	Not measured ↓43.5 ± 2.3% (10 μM)	
	I_{k1}	Rat myocytes	Not measured ↓34.43 ± 4.27% (10 μM)	108

Table 3. Increase of Ion Channels Caused by Pb, CO, NO, and SO_2.

Air Pollutant	Ion Channel	Type of Cell Tested	Emax	EC_{50}	Reference
NO	I_{CaL}	Human atrial myocytes	.59	.007 nM	76
SO_2	I_{to}	Rat myocytes	.374	Not measured ↑ 37.3% (10 μM)	65
	I_{K1}		.262	Not measured ↑ 26.2% (10 μM)	65
	I_{Na}		.841	10.97 ± .61 μM	68
	I_{CaL}		.819	10.64 ± 1.33	67

experimental data to evaluate electrophysiological mechanisms involved in cardiac disease dynamics by individuals or combined pollutants exposure.

Conclusions

Sufficient evidence had been reviewed to conclude that a slight exposure to high levels of air pollution could reduce quality of life. The experimental studies reported in this review present a consensus on the proarrhythmic effect of exposure to PM, lead, and the gaseous pollutants CO, SO_2, and NO_x. Most studies have reported cardiovascular diseases such as heart failure, ischemia, and atrial and ventricular arrhythmias, as the main effects of air pollution causing morbidity, which in turn, are generated by electrical, contractile, and structural remodeling underlying exposure to these pollutants. In this review, it was also found that exposure to atmospheric pollutants generates a harmful effect not only in healthy patients but also in sick patients, where the alterations caused by the pollutants and the mechanisms involved in the pathology act in a synchronized manner leading to a worsening of the initial pathological conditions. Although the association between short- and long-term exposure to air pollution and cardiac diseases is recognized, further research, such as in vitro and in silico studies, would be useful to more precisely determine the underlying electrophysiological mechanisms of heart diseases.

Limitations

A meta-analysis was not performed due to the heterogeneity in the design and content of the included studies. We evaluated the studies using qualitative narrative synthesis and supported the understanding of the review by including tables and a graph, which resume the effects of air pollutants studied on ionic channels and cardiac health.

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