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 REVIEW

Cardiovascular Diseases Induced by Air Pollution

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Abstract
Air pollution is a major global issue associated with human health and represents severe threats for public health. The sources of air pollution include particulate matter, PM2.5 defined by size range < 2.5 μm, and nanoparticles, NPs with size < 100 nm. This review focuses on cardiovascular diseases induced by air pollution as demonstrated by epidemiological and toxicological studies. A strong association is demonstrated between increases in airborne PM2.5 and NPs concentrations and premature mortality, cardiopulmonary diseases, asthma, and lung cancer. The mechanisms (direct and indirect) of toxicological effects induced by PM2.5 and NPs are related to their size, chemical compositions, lung clearance and retention, cellular oxidative stress responses and pro-inflammatory effects locally and systemically. Furthermore, the development of nanotechnology brings increasing production of nanomaterials and engineered nanoparticles and raises concerns on human exposure and health effects.

Keywords: Air pollution, particulate matters, nanoparticles, systemic effects, cardiovascular diseases

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Introduction

The World Health Organization, estimate that 4.2 million deaths were caused by ambient air pollution in 2016. Worldwide, 16% generated by lung cancer, 17% because of ischemic heart disease and stroke, and around 26% of the deaths were due to respiratory infection caused by ambient air pollution [1]. Because of the aging population and despite to all notable advances in treatment and management, cardiovascular disease (CVD) remains the most important cause of mortality for all population and prevalence is on the rise (First American Heart Association: 1+AHA). During human evolution they have created complex personal

environments which have a powerful determinant of general health. If CVD are in a considerable proportion preventable, and considering that the pathology is influenced in a great proportion by environmental factors, it is important to identify how, why and which components of the environment affect CVD.

Various epidemiological studies have shown the association between ambient air particulate matter (PM) exposures with the pathology of cardiovascular system [2-4].

American Health Association group estimated that exposure to air pollution with PM lead to acute cardiovascular morbidity and mortality, and long-term exposure to this type of pollution reduces life expectancy by several years [5, 6]. Also, in 2004, there was published the first scientific statement regarding cardiovascular health consequences of air pollution and led to the conclusion that the effects are greater than for pulmonary diseases [7-9].

Air pollution is caused by the introduction into the atmosphere of dangerous foreign constituents that cause changes in the gaseous envelope of the atmosphere, damaging the functions that make it possible to survive on earth. These pollutants can come from natural sources (soil erosion, volcanic eruptions, forest fires, pollen) and from road traffic, exhaust gases, heavy metals, street dust, smoke, industrial emissions. All these pollutants eliminated in the atmosphere become toxic for the environment but also for the living organisms that is exposed daily. Currently, one of the most discussed and studied issues regarding ambient air quality is particulate matter pollution.

Air pollution is composed by a mixture of particulate matters, PMs, and gaseous substances. PMs are made as heterogeneous aggregations of ultra-fine particles which are found in dust, smoke, dirt, soot and liquid droplets and can affect human health if the exposure is prolonged. The most important sources are factories, cars, construction activity, fires, and natural sources: power plants, volcanic emissions, and sea spray [9].

PMs are complex systems of organic, inorganic and biological components such as nitrates, sulfates, carbon, spores, molds, bacteria that can generate chemical reactions and harmful effects on both the environment and human health [9].

Particles can be classified in various ways, but the most important one is based on size, especially because the toxicity of particles increases as their size decreases [10-20]. According to this, PMs are divided into four categories:

- coarse particles (PM10) with diameter range of 2.5–10 μm,
- fine particles (PM2.5) with diameter range of 2.5-1.0 μm,
- ultrafine particles (PM0.1, UFPs) with diameter range of 0.1-1μm,
- nanoparticles (NPs) with diameter < 100n.

The last category describe particles with size range less than 100 nm, NPs, that are considered to occur in atmospheric air due to engineered nanoparticles produced by advanced nanotechnology.

Exposure to different concentrations of particulate matters is considered the most important concern of health all over the world. The statement is based on estimation of the deaths using information integrating exposure and risk from different particle sources (outdoor and indoor air pollution and passive/active smoking) [21].

Two mechanisms (direct and indirect) are described, where exposure to air pollution contributes to cardiovascular disease, by pro-inflammatory cytokines that once in circulation affect the heart. Once in the lung, numerous studies show that PM2.5 and PM0.1 can diffuse into the blood directly affecting the heart and the circulatory system [22]. Several new studies corroborate the elevated risk of myocardial infarction (MI), stroke, arrhythmia, and heart failure associated with exposure to PMs [9, 23].

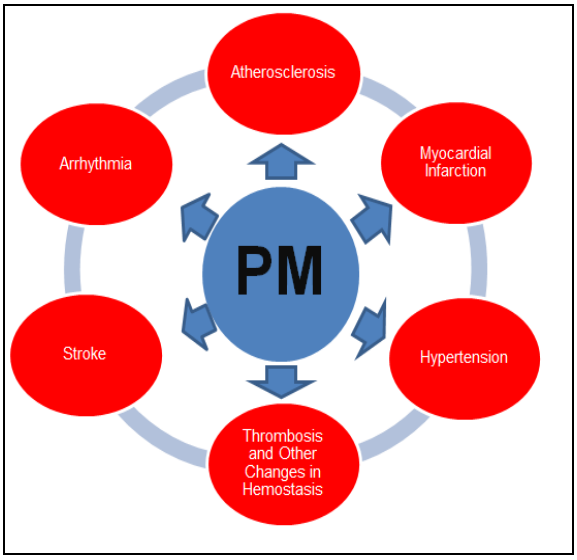

Figure 1. Pathological connection between PM and cardiovascular diseases.

Over decades, multiple studies have shown the implications of these particulate matters on cardiovascular diseases (Figure 1) that may occur under PM air exposure [24, 25].

Due to the fact that cardiovascular diseases are the first cause of death in developed countries, their risk factors were studied during the time and clearly identified. These include hypertension, obesity, dyslipidemia, diabetes and smoking. However, there are a large number of patients with myocardial infarction or stroke, where these pathological conditions are missing, which also demonstrates the co-existence of other additional factors that contribute to the onset of these diseases [24, 25]. Lately inflammation, elevated pro-thrombotic

factors and elevated lipoprotein were described as important risk factors for cardiovascular disease [26, 27].

For understanding the pathogenesis of a disease, the pathogenic mechanisms, depending on the duration of exposure to PM, are shown in two ways of action of PM on the cardiovascular system, under direct mechanism and indirect mechanism, given in Figure 2.

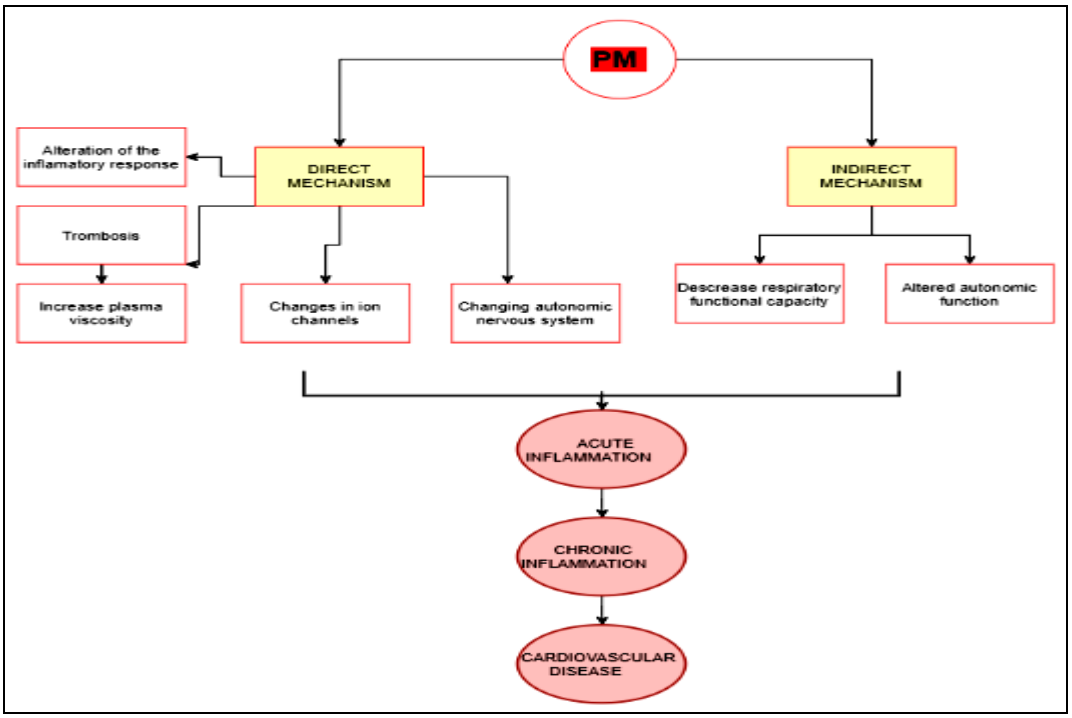

Figure 2. Pathogenic mechanisms of PM pollution on the cardiovascular system

According to the evidence of Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society (CEOHA-ATS), particulate matters pollution leads to increased mortality and morbidity of cardiopulmonary disease [28].

1. Direct mechanism

Air pollution causes important changes in blood composition with toxic effects. These are more pregnant for people with previous cardiovascular disease. The observation helps clarifying the mechanisms by which particles trigger the damage to target organs, being in the center of particle toxicology and offering a better understand of the biological effects [29, 30].

1.1. Alteration of the inflammatory response

In vitro and in vivo studies have shown that in case of exposure to PM, the biological response includes increased pro-inflammatory cytokine production, regulation and proliferation of redox and transcriptional activation of redox sensitive genes, which cause endothelial dysfunction of the blood vessels [31, 32].

Endothelial dysfunction consists of the alteration of the inflammatory response, the loss of vascular tone control and the modulation of the coagulation cascade [33].

Oxidative stress due to air pollution is the main factor that causes adverse effects on vascular integrity and functioning [34]. Oxidative stress results from disturbing the balance between the production of reactive oxygen species (ROS) - the damaging factor and antioxidants (for example: ascorbate, glutathione and tocopherol), that have the ability to defend the body. This process takes place predominantly in mitochondria. Myocardial muscle fiber needs high amount of oxygen in order to perform its activity, therefore, multiple mitochondria are present here [31, 34]. Therefore, in PM exposure, cardiac myocytes are prone to the occurrence of oxidative stress which determines vasoconstriction and act as a cytotoxic molecule that causes oxidative damage to proteins, lipids, DNA. This will contribute to muscle dysfunction and also plays an important role in the appearance and development of atherosclerosis features contributing to the progression of cardiovascular disease [30-35].

In the following, a representative scheme on the alteration of the inflammatory response to airborne PM exposure is highlighted in Figure 3.

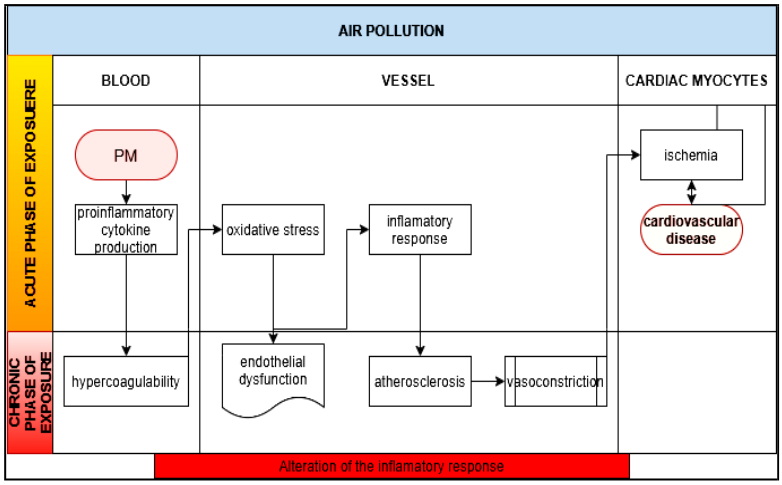

Figure 3. The alteration of the inflammatory response due to PM pollution

Initial endogenous protection occurs in the lungs due to the surfactant, which consists of an assembly of proteins, phospholipids (which are continuously

renewed) and alveolar macrophages. The liquid prevents the systemic penetration of the pollutant particles [34]. An increase of the oxidative stress at the level of the lung epithelium determines a higher permeability, allowing the PM passage. The macrophages loaded with these particles will move into the interstitial space. From this point, they are able to pass through the bloodstream, reaching other organs, especially at the heart level [36].

Studies have shown that after PM exposure by endotracheal instillation, in the acute phase, vascular dysfunction occurs at the level of systemic vessels and the release of myeloperoxidase from leukocytes in the pro-inflammatory circulation is present [37].

Laing et al. demonstrated that after 10 weeks of exposure to PM2.5 in an average total body concentration of 74.6 $\mu g/m^3$, an increase in oxidative stress in pulmonary and liver tissues of mice was observed [38].

The presence of toxic components such as heavy metals, hydrocarbons and other organic chemicals on the surface of PM circulating interacts with the vascular endothelium, producing oxidative stress and damaging the endothelial wall directly, causing damage to the vessels [39].

The diesel exhaust particles (DEP) effect was observed in different studies, including human volunteers, cell cultures or animal models. It led to the activation of cytokines (IL-8, COX-2 and IL-6, CYP1A1) and the onset of oxidative stress in the lungs with cytotoxic effect by DNA damage [40, 41].

A pilot study in 2013 has shown that exposure to ZnO particles in rats determines an intense inflammatory response and significantly decreases antioxidant substances. It also promotes atherosclerotic changes such as increased vascular wall thickness, dendritic damage and migration of smooth muscle cells in the end, changes that are comparable to the effects of a high-fat diet [42].

One study showed that elderly and diabetic individuals are more likely to be exposed to PM, suggesting that impairment of antioxidant protection due to aging or preexistence of oxidative stress can cause cardiovascular disease due to air pollution [43, 44].

The MONICA study (monitoring trends and determinants in cardiovascular disease) in Augsburg, Germany, highlights the increase in plasma viscosity due to fibrinogen and other plasma proteins such as α2-macroglobulin and immunoglobulin M. Their concentration in blood is directly proportional to air pollution [27].

Lead exposure generate reactive oxygen species by the depletion of glutathione and protein-bound sulfhydryl groups, leading to oxidative stress and nitric oxide production, highlighting the effect of air pollutants in the environment and over the health of the population [45].

Inhalation of PMs, particularly PM0.1, has a negative effect over the cardiovascular pathology by two mechanisms. Initially, in the lungs it causes an

inflammatory response with sequential release of pro-inflammatory cytokines that enter into circulation and help to maintain a state of hypercoagulability. A second mechanism is due to the reduced size of PM0.1 that can pass directly into the bloodstream where either, interacts directly with vascular endothelium contributing to atherosclerotic plaque formation, or causing local oxidative stress with pro-inflammatory effects similar to those produced at the pulmonary level [46, 47].

The exposure to air pollution is responsible for a significant impact on public health and substantially reduces human longevity [48-57].

The NPs accumulated in the blood cause the activation of circulating leukocytes in response of the immune system to the aggression of these particles. Thus, NPs reach the inside of the leukocytes through the process of phagocytosis where they accumulate significantly. Another process by which NPs reach the inside of leukocytes occurs due to plasma proteins (albumin, fibrinogen, apolipoprotein, complement and immunoglobulins) that adhere to the surface of NPs, marking them as foreign material, to make them visible in the phagocytosis process. The accumulation of large amounts of NPs in the plasma causes the stimulation of protein production and alteration of leukocyte functions that trigger pro-inflammatory responses such as chemotaxis, activation of cytokine secretion, phagocytosis that ultimately causes DNA damage and cell death (apoptosis) [49-54].

Durocher et al. showed that gold nanoparticles (AuNPs) stimulate leukocyte activity, both in vitro and in vivo, by activating inflammatory intracellular signaling pathways and releasing into circulation numerous cells that affect vascular walls [55]. The influence of nano-selenium (nano-Se) on leukocytes was also studied [56, 57]. Table 1 presents the effects of various airborne particles on the inflammatory response and blood vessels damage.

Table 1. Alteration of the inflammatory response caused by different types of airborne particles

Alteration of the inflammatory response		
PARTICLES	***CONDITIONS***	***Ref.***
PM0.1	Hypercoagulability	[46, 47]
PM2.5	Increase in oxidative stress	[38]
Heavy metals	Damage to the blood vessels	[39]
Hydrocarbons		
other organic chemicals on the surface of PM		
DEP	DNA damage	[40, 41]
Lead	Generate reactive oxygen species	[45]
Pure carbon particles	Systemic inflammatory changes	
AuNPs	Affect vascular walls	[55]
Nano-Se	exaggerated and long-lasting inflammatory response	[56, 57]

1.2. Thrombosis and increased plasma viscosity

Increasing plasma viscosity is associated with an increased risk of developing myocardial infarction or the occurrence of angina by reducing blood flow in the coronary vessels.

PM by the inflammatory process induced on endothelium and the respiratory system triggers the growth of acute phase reactants such as reactive C protein (CRP), interleukin 6, interleukin 1, D-dimers and fibrinogen. These reactants are high molecular weight molecules that increase the viscosity of the plasma [58]. So, the air pollution increases the risk of thrombosis illustrated in Figure 4.

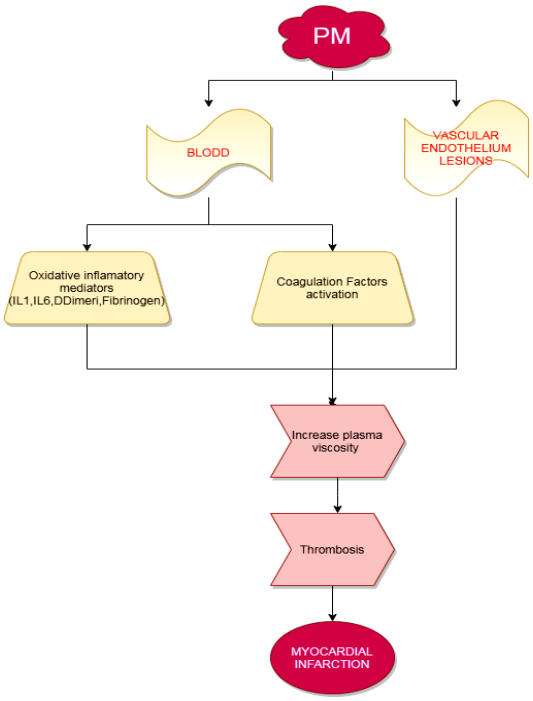

Figure 4. Pollution impact in thrombosis and increased plasma viscosity

Air pollution due to forest fires and exposure to PM10 urban causes increased serum levels of interleukin 6, interleukin 1 and pulmonary macrophages in healthy male subjects. Interleukin-6 is directly involved in regulating the synthesis of C-reactive protein (CRP) in the liver, and it is a marker of infection and inflammation closely related to the risk of cardiovascular disease [58].

This is due to the fact that this protein contributes to the formation of sparkling cells, to recruitment in the arterial wall of monocytes, stimulation of pro-thrombotic factors and expression of adhesion molecules [37, 59].

Exposure to PM also leads to increased fibrinogen levels, an independent risk factor for MI and stroke, being a key component in blood clotting and

thrombosis by increasing blood viscosity. At the same time fibrinogen degradation results in fibrin Bb15-42 and untransformed fibrin, and proteolytic enzyme-mediated fibrinolysis results in D-dimers that are considered marker of hypercoagulability. This increase in viscosity causes the activation of factor XIII with increased blood coagulation and the risk of thrombosis [60].

Three factors are essential for the production of occlusive arterial thrombosis: - vascular endothelial injury produced by direct PM action, which is considered the primary factor in triggering thrombosis, creating a favorable environment for platelet adhesion; - slowing blood flow or vascular stasis favoring coagulation through hypoxia, platelet and erythrocyte aggregation; - hypercoagulability caused by the increased viscosity of blood plasma and secondary cellular thrombogenesis. Hypercoagulability or thrombophilia is the increased tendency of blood to thrombose.

If these conditions are met, a thrombus begins to form rapidly, resulting serious embolism that could cause myocardial infarction or stroke. The mechanisms responsible for platelet activation and growth of fibrinogen are elucidated, all of which support the notion that air pollution promotes the occurrence of ischemic events.

A study in the Lombardy region of Italy on 1.218 people analyzed the correlation between air pollution levels and changes in coagulation parameters indicating shorter prothrombin time when atmospheric pollution was increased [61].

Peters et al. demonstrated that exposure to PM10 alter the viscosity of the plasma and increase level of fibrinogen which contribute to procoagulant state [62, 63].

The PM10 also stimulates the bone marrow with the release of a large number of white cells in the circulation, creating a pro-inflammatory status, all these changes being trigger for ischemic conditions [64, 65].

Moreover, daily exposure to high levels of PM2.5 along with its components, including black carbon, sulphate, nitrate or ammonium particles, has significantly increased addressability to a medical service for various respiratory and cardiovascular conditions. According to this study, the cardiovascular pathology was mainly represented by hypertension and acute myocardial infarction, and the most affected age group was between 0 and 14 years due to the fact that the respiratory frequency is higher and, implicitly, the amount of air intake is increased [66].

Researchers from the United Kingdom and Sweden had shown that exposure to diesel inhalation in 20 healthy people has prompted the increased in platelets, neutrophils and monocytes, having prothrombotic effects [67].

Numerous epidemiological studies have demonstrated a clear association between increasing concentrations of SO_2 in the atmosphere and increasing the levels of reactive C and, implicitly, plasma viscosity [48, 68, 69].

The presence of UFPs in circulation can destabilize pre-existing atherosclerotic plaques or cause lesions of the vascular endothelium leading to acute coronary events (myocardial infarction, stable or unstable angina pectoris). At the same time, these particles in circulation can influence the thrombosis process through their direct interaction with coagulation factors [70-72].

The NPs, depending on the material from which they come, have properties such as solubility, transparency and rapid absorption in different environments. Thus, a correlation was demonstrated between human exposure to NPs and the occurrence of myocardial infarction at 2 hours, fast, or at 24 hours, late. The rapid onset of myocardial infarction may be due to the NPs property of rapidly affecting the myocardial cell, after inhalation and direct passage into the blood. The late onset could be explained by the direct effect of NPs on pre-existing atheromatous plaques that it destabilizes, with their release into circulation leading to occlusion of the coronary arteries and the occurrence of myocardial infarction [73-76]. An Ohio study evaluated the action of nanoparticles on platelet aggregation that causes vascular thrombosis. Thus injection with various nanoparticles ($FeCl_3$) or mixed carbon nanoparticles) accelerated the development of thrombosis of the carotid artery in rats by increasing blood platelet levels and the release into circulation of numerous enzymes that cause activation of clotting pathways [77, 78]. Table 2 shows the conditions in thrombosis and increased plasma viscosity due to airborne particles effects.

Table 2. Thrombosis and increased plasma viscosity caused by various airborne particles.

Thrombosis and increased plasma viscosity		
PARTICLE	***CONDITIONS***	***Ref***
PM10	Vasoreactivity	
	Atherosclerosis	
	Occlusive arterial thrombosis	
	Ischemic phenomena	[62, 65]
PM2.5	Hypertension	
	Acute myocardial infarction	[66]
BLACK CARBON	Acute myocardial infarction	[66]
SULPHAT	Hypertension	[66]
NITRATE	Acute myocardial infarction	[66]
AMMONIUM	Acute myocardial infarction	[66]
DIESEL	Prothrombotic	[67]
SO_2	Discrease vagal cardiac control	[48]
UFPs	Myocardial infarction	
	Stable or Unstable angina pectoris	[70-72]
NP ($FeCl_3$ / C)	Myocardial infarction	[77-78]
	Thrombosis of the carotid artery	

1.3 Changes in ion channels

The contractile function of the heart assures the distribution of blood throughout the body and is achieved by ion channels. Calcium channels are the most abundant in the myocardial muscle fiber. Pollutant particles can directly affect these Ca-dependent channels contributing to myocardial dysfunction and arrhythmias. PM modifies the properties of Ca^{2+} channel protein (Na^{+}, Ca^{2+} exchange protein and L-type Ca^{2+} protein) resulting changes in excitation coupling in myocardial contractility that cause cardiac rhythm disorders [22].

Abramson et al. argue that antimony and heavy metals are the major PM that cause changes in myocardial contractility [79]. Lead inhibits the transcellular calcium transport system and alters intracellular homeostasis due to its similarity with this ion, causing the occurrence of rhythm disorders [80].

A London study examined the association between various regional atmospheric pollutants and the occurrence of rhythm disorders in patients with implantable defibrillators. Of these pollutants with a greater significance were the sulphate particles [81].

Increasing the PM2.5 concentration in atmospheric air has been associated with fibrillation / atrial flutter, ventricular extrasystoles and increased P wave in healthy people, according to a study in Pennsylvania [82, 83].

Ozone was also implicated in appearance of arrhythmias, causing bradycardia [84].

Transient receptor potential (TRP) cation channels are found in the upper and lower respiratory tract and in various cell types such as neurons and function as environmental sensors for the nerves of the airways. TRP activation has been demonstrated in vitro using genetically modified mouse tissues on which Diesel Engine Exhaust Particles (DEP) were instilled. This activation led to the stimulation of the sensory nerves of the airways causing airflow obstruction by bronchoconstriction. In humans, DEPs and other toxic irritants cause vague nerve irritation, causing and coughing as a reflex mechanism [85-88].

The chemical mechanisms that occur at the interface of cell membranes with nanoparticles can be chemical or physical [89]. The chemical mechanisms are characterized by the production of reactive oxygen species (ROS), with disruption of trans-membrane ionic concentrations or the formation of toxic cellular compounds that can eventually cause cell damage [90, 91].

An in vivo study showed that pulmonary instilled titanium dioxide (TiO_2) has an antagonistic effect on the fast sodium channel (Na^{+}) [92]. Silver nanoparticles (AgNPs) bind to the calcium receptor leading to an increase in its intracellular concentration or alteration of its trans-membrane transport [93].

In nanotoxicology studies, exposure to increased concentrations of nanoparticles contributes directly or indirectly to the regulation of myocardial excitability threshold (contractility or relaxation), thus increasing the possibility of

arrhythmia, and these repercussions can be detected in electrophysiological evaluation. AuNPs through the blocking effect of K^+ channels determines the prolongation of the QT interval with the risk of increasing the frequency of ventricular tachycardia [94].

The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

In mice, treatment with AgNPs causes changes in the Na^+ and K^+ channels causing blockage of unnecessary impulses involved in atrioventricular conduction, with effects such as sinus bradycardia or asystole [95].

Changes in ionic channels caused by different types of particles and correlated with various diseases or disorders are given in Table 3.

Table 3. Changes in ionic channels caused by different types of particles correlated with various diseases or disorders

Changes in ionic channels		
PARTICLE	**CONDITIONS**	**Ref**
PM2.5	Atrial fibrillation	
	Atrial flutter	
	Extrasystoles	[82, 83]
Heavy metals	Altered myocardial contractility	[79]
Lead	Rhythm disorders	[80]
SULPHATE particles	Arrhythmia	[81]
Ozone	Bradycardia	[84]
DEP	Vagus nerve irritation	[85-88]
TiO_2	Cell damage	[92]
Au NPs	Ventricular tachycardia	[94]
Ag NPs	Sinus bradycardia	
	Asystole	[95]

1.4 Changing autonomic nervous system

Air pollution can affect the heart function through the autonomic nervous system. Cardiac frequency is determined by spontaneous and periodic depolarization of the sinoatrial node from the heart wall whose function is

mediated by the sympathetic and parasympathetic autonomic nervous system. The heart rate (HR) variability is being defined as the oscillation between the heartbeats. This variability in heart rate depends on the needs and consumption to which the body is subjected, being achieved through the sympathetic or parasympathetic nervous system, that causes effects on vascular tone. The heart rate variability can be evaluated by time or frequency. Thus, depending on the time (the millisecond interval between two heartbeats), we have bradycardia and tachycardia and, depending on the frequency, it is classified as low or high frequencies [96-99].

A mechanism for activating the autonomic nervous system is achieved by stimulating the nerve endings of the lungs by PM which causes the release of different type of neuropeptides, given in Figure 5. They determine a neurogenic inflammation at this level with triggering reflexes that induce various vascular processes, such as vasodilatation, vasoconstriction, plasma extravasation and exudation [96].

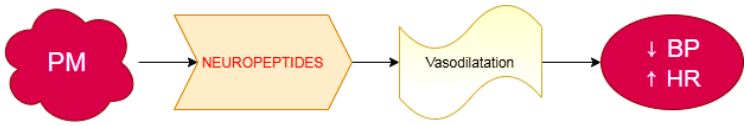

Figure 5. Pollution effects in changing of autonomic nervous system leading to decreased blood pressure (BP) and increased heart rate (HR).

Numerous studies have demonstrated the association between atmospheric pollution and changes in heart rate with implications for cardiovascular morbidity and mortality [98].

The combined effects of pollution on the heart rate were studied, thus it was shown that exposure to PM2.5 - PM10 for a short duration (1-4 hours) accelerate the heart rate, and as well a prolonged exposure (over 8 hours) for particles smaller than 2.5 μm [100].

In a study of 384 subjects, the increase in PM2.5 concentration in atmospheric air was associated with a 15% decrease in cardiac frequency variability and ozone was associated with a 21% reduction [99]. Boston residents who were exposed to PM2.5 at a concentration of 15.5 g/m^3 were associated with reduced cardiac frequency variability with bradycardia. Exposure to a concentration of 100 μg/m^3 PM10 is associated with an increase in heart rate between 5 and 10 bpm, all of which suggesting that air pollution with these particles produces changes in autonomic nervous system function with implications for cardiovascular disease morbidity [101].

A study in Massachusetts has shown that long-term exposure to air pollution due to traffic increases lead levels in the human body. The higher the lead

deposits are, the more susceptible to secondary pollutants such as sulphate and ozone the body is, causing new impaired cardiac autonomy [99, 102].

Numerous studies have shown that short-term exposure to SO_2 decreases the effectiveness of vagal cardiac control, with decreasing cardiac frequency variability [100, 102, 103].

Purely elemental carbon particles resulting from combustion perform a minimum vagal stimulation but without producing clinically significant effects on the cardiovascular system.

One study from eight European countries shows the correlation between inhalation of NO_2 particles and increased incidence of ventricular arrhythmia and ventricular tachycardia in patients with implantable defibrillators [103].

Direct inhalation of NPs could result in impaired cardiac autonomic function with an effect on the circulatory system. NPs cause automatic cardiac dysfunction by stimulating the vagal sensory nerves or by local lung inflammation [104]. The Lagendorff heart model (LH) is a model used to evaluate the self-regulatory function of the heart in an experiment designed to study the direct effects of infusions with TiO_2, SiO_2 or Printex90 NPs. Exposure to these NPs induced a significant increase in heart rate with perceived changes in arrhythmia-type electrocardiographic recording. Specifically, Stampfl has shown that direct injection of TiO_2 and Printex90 causes the release of catecholamine-like substances in the sympathetic nervous system, which determine an increase in heart rate and compensatory coronary flow. Electrocardiogram recordings revealed changes specific to myocardial infarction or atrio-ventricular block [105].

It appears that pulmonary exposure by inhalation of nanoparticles can locally cause irritation, which activates lung sensory receptors. Subsequently, a sensory signal is generated which is transmitted from the nerve ganglia to the autonomic nervous system which regulates cardiovascular function. The results of some studies showed that the biological changes induced by $UFTiO_2$ in the heart after lung exposure were probably not due to translocation of nanoparticles in the respiratory system but due to direct interactions with the heart, because coronary $UFTiO_2$ levels were below detection levels.

At the same time, it was found that pulmonary exposure to $UFTiO_2$ greatly increased substance P, which is a neurotransmitter secreted in the nerve ganglia that causes the activation of sensory receptors in the periphery with the deterioration of cardiac diastolic function and increased blood pressure [106,107].

The instillation of single-walled carbon nanotubes (SWCNTs) in rats reduced the number of vascular baroreceptors, thus affecting the autonomic regulation of cardiovascular control with detectable changes on the electrocardiogram [108-110]. Changes in autonomic nervous system caused by different types of particles are correlated with various diseases and disorders, as shown in Table 4.

Table 4. Changes in autonomic nervous system caused by different types of particles are correlated with various diseases and disorders.

Changing autonomic nervous system		
PARTICLE	**CONDITIONS**	**Ref.**
PM2.5	Bradycardia	[100]
PM10	Bradycardia	[101]
LEAD	Impaired cardiac autonomy	[99, 102]
SO_2	Decreased vagal cardiac control	[100]
CARBON PARTICLE	Bradycardia	[103]
NO_2	Ventricular tachycardia	[103]
TiO_2, SiO_2, Printex90 NP	Arrhythmia	
	Atrio-ventricular block	[105]
UFTiO_2	Increased blood pressure	[106, 107]
SWCNTs	Changes on the electrocardiogram	[108-110]

It is observed that these pollutants most often cause bradycardia, ventricular tachycardia, arrhythmia, electrocardiogram changes and increased blood pressure. There are diseases that worsen over time and that, if left untreated, lead to death among the population. That is why it is important to know as much information about air pollution as possible so that the impact on health can be counteracted.

2. Indirect mechanisms

Indirect mechanisms of PM pollution effects on the cardiovascular system lead to *cardiac toxicity* by altering *autonomic nervous system* and decreasing respiratory capacity as summarized in Figure 6.

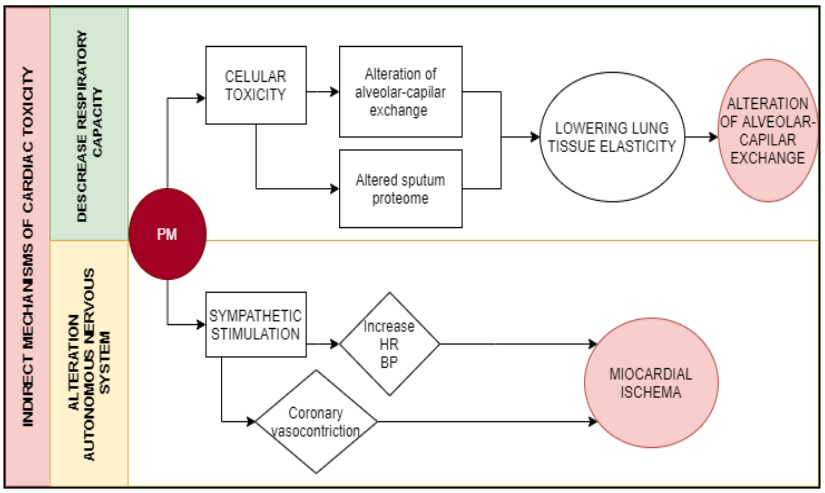

Figure 6. Indirect mechanisms of cardiac toxicity. The influence of PM pollution on respiratory capacity and on autonomic nervous system.

2.1 Decreased respiratory functional capacity

The pathogenesis of pulmonary inflammatory diseases is influenced by several factors including sex, hormones and air quality. The number of women diagnosed with asthma, emphysema, chronic obstructive pulmonary disease (COPD) or lung cancer has increased significantly in the last decade compared to men [111].

Changing lung function means lowering lung tissue elasticity that helps maintain airway permeability associated with alveolar-capillary exchange alteration [112, 113].

Numerous experiments have shown that certain nanoparticles inhaled even in small quantities pass into the bloodstream or even into the olfactory center of the brain [112, 113].

In order to protect the respiratory system from the harmful action of pollution, the respiratory tract capping fluid is involved, which is made up of numerous immune cells and plasma derived factors with the role of capturing and destroying the foreign agents of the body [114, 115].

A study on rats exposed to silica particles showed that after a period of 20 days a microscopic inflammatory reaction at the alveolar level occurs. Moreover, exposure over several days was correlated with hyperplasia of the alveolar epithelium up to fibrosis, with impaired lung capacity over time. At the same time, even if exposure to silica was interrupted, pulmonary changes evolved over time leading to decrease lung function [116].

Exposure to 10 μg/m^3 PM2.5 is associated with a significant increase in mortality and morbidity through chronic lung cord which is characterized by irreversible and progressive limitation of airflow [111].

Titanium dioxide (TiO_2) is the basic material in most commercial products, thus increasing exposure within populations [117]. Studies have shown local and systemic effects, intensification of pre-existing symptoms and including damage to organs through the absorption of nanoparticles from the lungs and gastrointestinal tract into the systemic circulation and brain.

The US Health Effects Institute supports the direct correlation between various air pollutants (especially the one related to traffic) and the more frequent exacerbation of chronic lung diseases such as asthma that causes decreased lung function in both children and the elderly [118].

A study in America investigated 135 volunteers, 40 of whom were healthy and the rest with cardiac disease and obstructive pulmonary disease, carried out for 2 years analyzed the symptoms that appeared after comparative walks in areas with high carbon black concentration, NO_2, PM10, PM2.5 and ultrafine particles and in green areas. They demonstrated that after exposure to pollutants, volunteers with lung and heart disease had more cough, sputum, difficulty breathing and wheezing compared to walking through the green spaces in the park. In the case of healthy volunteers, the beneficial effects produced by walking in the green space were counterbalanced after exposure to traffic-related pollutants. In all participants, regardless of their disease status, it led to a decrease in lung function, *forced expiratory volume* in the first second [FEV1] and *forced vital capacity* [FVC] and an increase in *pulse wave velocity* [119].

The presence of ozone in the environment produces inflammation of the airways, together with the growth of leukocytes in the transient sputum, all of which cause a decrease in lung capacity regardless of the type of effort made [120, 121].

Exposure in utero, in the last trimester of pregnancy, to UFP was associated with an increased risk of developing asthma in children up to the age of 6 years. The statement is based on a large study from Canada, involving numerous pregnant women [122].

Inhalation of the NPs (especially ZnO) causes the accumulation of neurotrophils in the lung and exposure over time determines the hyperreactivity of the airways which may lead to an increased risk of developing asthma [123, 124].

Decreased respiratory functional capacity is caused by a number of pollutants listed in Table 5. These include PM2.5, Si, P, PM10, TiO_2, NO_2, Ozone, UFPs and ZnO NPs.

Table 5. Respiratory functional capacity altered by different airborne particles and their influence on various diseases and disorders.

Respiratory functional capacity		
PARTICLE	***CONDITIONS***	***Ref.***
PM2.5	Chronic lung COPD	[117]
Si, P	Hyperplasia of alveolar epithelium	[116]
PM10	Wheezing/ cough	[119]
TiO_2	Pulmonary fibrosis	[117]
NO_2	Difficulty breathing	[119]
Ozone	Inflammation in lungs	[120, 121]
UFPs	Hyperreactivity	[122]
ZnO NP	Asthma	[123, 124]

As a result of exposure to these constituents are chronic lung COPD, pulmonary fibrosis, asthma, difficulty breathing, lungs inflammation, hyperplasia of alveolar epithelium, chronic lung disease and hyperreactivity.

2.2 Involve altered autonomic function

The autonomic nervous system controls the vegetative function of the organs. At the cardiac level there are two types of receptors (chemoreceptors): central (brain) and peripheral (at the bifurcation of the carotid artery) that control autonomic activity. Activation of peripheral chemoreceptors occurs mainly by decreased O_2 levels, increased CO_2 concentration, changes in pH or body temperature [125].

In response to hypoxia, these chemoreceptors trigger increases in sympathetic tone leading to increases in blood pressure (BP) and heart rate (HR), as well as increased ventilation. If the sympathetic tone is maintained for long periods of time, it causes an increased mortality rate in people with heart disease. Exposure to PM and ozone causes a decrease in the level of O_2 in the blood and determines the activation of the chemoreflex [126]. The *chemoreflexes* are important modulators of sympathetic activation.

Long-term traffic exposure, exposure to environmental tobacco smoke, SO_2, and NO_2 were correlated with abnormal cardiopulmonary sensitivity responses to hypoxia, indicating changes in carotid body activity that increase systolic, diastolic, and mean arterial BP during exposure, and decreased cardiac

contractility after exposure. Wang et al. shows that cardiac arrhythmias associated with heart failure mice were due to changes in carotid sensitivity induced by exposure to particles. Exposure to acrolein causes significant decreases in O_2 pressure and significant increases in CO_2 pressure in the blood, suggesting that carotid body activation may have been triggered by hypercapnia and / or hypoxia [125-127].

The atmospheric pollutants determine the modification of the autonomic nervous system at the level of the upper respiratory tract by activating chemoreflexes such as cough, sensation of congestion in the chest, bronchoconstriction with hypersecretion of mucus and decrease of the respiratory frequency. These vagal reflexes occur by estimating the demyelinated nerve fibers from the nose to the alveoli. Thus, the dysregularities of the respiratory frequency determine the activation of the baroreceptors with the consecutive increase of the heart rate and implicitly of the systolic blood pressure [128-130].

The changes in autonomic function are due to various PMs and NPs from polluted air and led to conditions such as hypoxia, arrhythmia, decreased lung function, cough and bronchoconstriction, which are included in Table 6.

Table 6. The altered function of the autonomic nervous system caused by various types of PM and NPs is correlated with various diseases and disorders

Altered autonomic function		
PARTICLE	**CONDITIONS**	**Ref.**
PM	Hypoxia	[126]
Ozone		
Cigarette smoke	Decreased lung function	[131-133]
O_3		
SO_2		
NO_2		
Chlorine	Coughing	
	Wheezing	
	Decreased respiratory rate	[134]
UFPs	Arrhythmias	
	Bronchoconstriction	[135,136]

Cigarette smoke, O_3, SO_2 as well as acrolein stimulate these nerve regions, ultimately causing decreased lung function and increasing the rate of hospitalization among patients with chronic lung disease [131-133].

Chlorine- containing volatile substances cause respiratory tract irritation, coughing, wheezing with decreased respiratory rate in mice [134].

UFPs reaching the alveolar level are transported by nerve threads to the ganglion structures of the sympathetic and parasympathetic nervous system

responsible for the occurrence of harmful effects, such as arrhythmias or bronchoconstriction, with the decrease of the oxygenation level at the level of the organs, especially of the brain [135, 136].

The growing PMs and NPs pollution has led to important public health issues. The negative impacts of polluted air highlighted in this review make us aware that the situation in which we find ourselves must be changed. Thus, informing and educating the population is fundamental to try to reduce the negative impact and take measures to improve air quality. The use of multiple strategies to tackle air pollution and especially NPs from vehicles is likely to be accompanied by improvements in cardiovascular health.

3. Nanoscale interactions

Various types of nanoparticles, NPs, are known to have beneficial effects on the health of mankind due to their antimicrobial, anti-inflammatory and anti-cancer activity, or to have harmful effects, particularly airborne toxic particles, especially due to their ability for binding to cell membrane.

The interaction between nanoparticles and the cell membrane has been discussed as a distinctive issue in the field of colloids and interface science, taking into account that biomolecules, like lipids, fatty acids, proteins, drugs and vitamins can be structured as nanoparticles in various fluids. In this respect, the models for cell membrane are frequently used, namely Langmuir monolayers of various lipids extracted from various cell membranes and self-assembled at air-water interface [137-143] and at oil/water interface [144], carotenoid pigments [145-157] and fatty acids [158-160] spread as monolayers at fluid interfaces.

The interfacial mechanism of anesthesia was determined from the interaction of anesthetic molecules with Langmuir monolayers of fatty acids [161-163], phospholipids [164, 165] and membrane systems [165-167] using nanoscale kinetics and nanoscale thermodynamics approaches. Different biomolecules, like anti-oxidants [168, 169] and proteins [170, 171] are also studied in regard with the nanostructure formation in various fluid media.

Supramolecular organization and nano structuration of collagen and anti-cancer drugs in self-assembled as model membrane systems are investigated by Langmuir and Langmuir-Blodgett techniques [172-175]. Methods for delivering active agents to mammalian brains in a complex with essential fatty acids conjugated to a polycationic carrier were developed through Langmuir and Langmuir-Blodgett self- assemblies of nanoparticles to cross blood- brain- barrier (BBB) [176-180].

The effect of drug nanoparticles on lipid domains created at interfaces was determined through Langmuir-Blodgett technique [181-186]. This technique opens a new tool for the investigation of colloidal gold nanoparticles, GNPs, self-assembled at the air-water interface [187-190]. The effects if the surface pressure

on the formation of monolayers of nanoparticles are assessed by Langmuir Blodgett technique [191-203].

The interaction between lung surfactant and various nanoparticles is investigated at fluid interfaces for toxicity assessments [204-216], as well as for GNPs as pollutants [210].

The role of size and surface charge in the interaction of nanoparticles with lung model surfactants is investigated [215, 216]. The interaction of nanoparticles with various cell membranes are assessed [217-221] to obtain knowledge on the entry of particles into the cells correlated with the importance of nanoparticles properties and with chemical composition of membrane systems. These studies can offer insights into the interaction mechanisms of corona particles, e.g., GNPs coated with a layer of biomolecules with cell membranes and membrane models, to better understand the attack of corona virus, Covid-19, to the lung.

The above studies revealed the importance of coating layer on the nanoparticles in their interaction with cell membrane systems. Therefore, the engineered nanoparticles of GNPs and AgNPs, each particle coated with a controlled layer of biomolecules, as functionalized nanoparticles [219, 222-248] are very useful to be evaluated in interaction with cell membranes and with model Langmuir and Langmuir-Blodgett membranes to assess their mechanism of action in vivo used as drug delivery vehicles targeted to their place of action.

These future studies are crucial especially because GNPs and AgNPs are highly expected to be strong candidates to be used as next-generation antimicrobial and anti-inflammatory innovative materials, also because they can reduce the emergence of multidrug-resistant bacteria. The interaction between nanomaterials, particularly their constitutive NPs, and the cell membrane is also important to evaluate their potential cytotoxicity.

Since the interaction of nanoparticles with cell membranes is also dependent on the chemical and physical nature of the nanoparticle and on the composition and structure of cell membrane surface, it is critical to understand how nanoparticles interact with cell membranes by using membrane models, such as Langmuir and Langmuir-Blodgett techniques to illustrate the antimicrobial and anticancer mechanism of membrane-binding nanoparticles and nanomaterials.

Conclusions

The size, shape and charge of airborne PM2.5 and especially NPs have a strong effect on their interactions with living cells, influencing uptake efficiency, internalization selection, intracellular localization and cytotoxicity, with vast impact particularly on lung and cardiovascular systems.

The underlying mechanisms implied in development of various pathologies after the endemic exposure to PM, particularly cardio-pulmonary afflictions are

continuously analyzed and studied. The regional type of exposure has been described by different data from the literature; still the individual level of exposure to PM has not been quantified and fully described. Even if the studies show a direct correlation between high exposure to PM and the alteration of individual health, the long-term effects are still not completely elucidated.

A great number of clinical studies and epidemiological data provide strong evidence that prolonged PM exposure leads to detrimental cardiovascular function. The mechanisms may be direct and indirect. Further research is needed in order to explore the effects of PM and NPs as well the corresponding response pathways, specifically the nature of the effect and time course of the response.

Clinicians should be aware of the risks and consequences of exposure to PM and NPs and should continuously approach this topic since the rates of industrialization are unlikely to decrease.

At the cardiovascular level, studies around the world are beginning to show that both short-term and long-term exposures to PM and NPs can lead to ischemia and myocardial infarction, heart failure, arrhythmias, strokes and increased cardiovascular mortality. *In vivo* and *in vitro* toxicological experiments on regional animals or human groups support the occurrence of acute events that are directly related to the amount of PMs and NPs. At the same time, the continuous inhalation of PMs and NPs in the pulmonary tree can cause remote effects on the cardiovascular system through numerous indirect mechanisms.

The strong associations between air pollution and cardiovascular dysfunction have been repeatedly demonstrated and have even led to legal changes for the automotive industry. The precise and complete mechanisms that underlie this association have yet to be definitively established, but clear evidence exists that many of the adverse health effects are attributable to combustion-derived nanoparticles. Either through direct translocation into the circulation or via secondary pulmonary derived mediators, PM augments atherogenesis and causes acute adverse thrombotic and vascular effects, which seem to be mediated by proinflammatory and oxidative pathways. Improving air quality standards, reducing personal exposures, and the redesign of engine and fuel technologies could all have a role in reducing air pollution and its consequences for cardiovascular morbidity and mortality.

Taking into consideration the negative impact over individual health of air pollution, the need of continuous education for general population is required. Lifestyle measure is needed in order to minimize the exposure to different pollutants. Moreover, the collection of data may be useful indicators in order to elaborate regional legislative strategies.

Current studies addressing the acute toxicological or therapeutic potential of NPs need to be complemented by systematic investigations *in vivo* exposure

models to NPs. This future research will need to include the dose-response relationships.

Finally, the decision where NPs are beneficial or harmful is a difficult issue. Definitely, future investigations need to define the characteristics of NPs responsible for a certain effect based on scientific evidence with the greatest benefit of safe nanomaterial applications in medicine and decreasing the risks of ambient harmful NPs for society.

Abbreviations

PM – particulate matter
NPs – nanoparticles
AgNPs – silver nanoparticles
AuNPs – gold nanoparticles
BP – blood pressure
HR – heart rate
1+AHA – First American Heart Association
CVD – cardiovascular diseases
COPD – chronic obstructive pulmonary disease
CEOHA-ATS - Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society
ROS – reactive oxygen species
DEP – diesel exhaust particles
MONICA – monitoring trends and determinants in cardiovascular disease
CRP – reactive C protein
UFPs – ultrafine particles
TRP – transient receptor potential
LH – Lagendorff heart model
SWCNTs – single-walled carbon nanotubes
FEV1 – forced expiratory volume in the first second
FVC – forced vital capacity

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