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Exposure to Urban Air Pollution Nanoparticles: Oxidative Stress and Cardiovascular Disease

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ABSTRACT

It is estimated that more than two-thirds of air pollution-related deaths are due to cardiovascular causes. Significant studies have now indicated that exposure to urban air pollutants is known to be a source of oxidative stress and inflammation that causes cardiovascular disease. Nitrogen oxides, Particulate Matter (PM) such as coarse particle (PM10, PM <10 μm), fine particles (PM2.5, PM <2.5 μm) and Ultra-Fine Particles (UFPs or PM0.1, PM <0.1 μm), and ozone and transition metals are oxidant potent capable of producing Reactive Oxygen Species (ROS). Although several biological mechanisms are involved in cardiovascular disease, oxidative stress is an important observation in many levels of cardiovascular failure due to exposure to air pollutants. This mini-review cites evidence that oxidative stress is a key pathway for various cardiovascular measures of exposure to air pollution.

INTRODUCTION

Exposure to air pollutants has far-reaching implications for biodiversity, and its human health effects have made it internationally important. Air pollutants exposure is the fifth risk factor for all-cause mortality and the number one environmental risk factor for mortality [1]. Recently, air pollutants it has been revealed to have effects all over the human body [2,3], however, their effects cardiovascular system, especially are disproportionate in terms of disease and mortality. In fact, due to the high prevalence of the cardiovascular disease worldwide and the inherent mortality of many cardiovascular diseases, more than 65% of air pollution deaths are due to cardiovascular causes, especially cerebrovascular disease and ischemic heart disease [1,4]. In addition, cardiovascular complications may play an important role in the air pollution impact on the progression of the diseases in other organs [5]. Oxidative stress has been shown to play a major role in cardiovascular disease of air pollution. This topic was examined in detail in 2012 [6], and the 2010-2016 data were expertly reviewed [7]. The aim of this study is to provide a mini-review of the oxidative stress role in cardiovascular effects of exposure to urban air pollution nanoparticles by surveying evidence in various aspects of cardiovascular pathophysiology.

Exposure to air pollution

Air pollution involves a range of materials derived from various sources and the chemical reactions in atmosphere. Airborne pollutants can come from both human resources (e.g. power plants, industry, traffic, cooking, home heating, construction, agriculture, mechanical wear, etc.) and natural sources (e.g. volcanic
eruptions, forest resources, airborne dust and mildew) [8,9]. Although indoor air pollution has been particularly important in terms of disease burden in developing countries, ambient air pollution refers to outdoor air pollutants and has historically received the most attention [9-11]. The many studies on ambient air pollution focus on urban air pollution; for other reasons, higher levels of traffic emissions, high urban population densities, and increasing urbanization of communities around the world. Urban air pollution is a complex mixture of chemicals. Gaseous pollutants such as CO₂, SO₂, CO, NO₂, and O₃ that are present in varying amounts, have potential to cause short-term and long-term health effects, possibly as additives in a manner to particulate matter [9,12,13]. Many of these gases have oxidative properties and the induction of oxidative stress (along with inflammation) is a possible mechanism through which it can affect human health [14]. Semi-volatile species such as naphthalene, formaldehyde, Poly Aromatic Hydrocarbons (PAHs), benzene, exist as liquid droplets, but can also be transported between gas phases and particulate phases of the air pollution [15]. In addition, there are many sources of PM. PM is classified according to the size of the particle. Coarse particle is particle with a diameter of 10μm or less (PM10), fine particles with a diameter of 2.5μm or less (PM2.5), and Ultrafine Particles (UFPs or nanoparticles) with a diameter of 100 nanometers or less. (PM0.1) (Figure 1). Particulate matters are monitored in environment through fixed monitoring networks that measure PM2.5 and PM10. At present, it is not possible to measure very fine PM using very large monitoring networks in environment. Organic and elemental carbon is an important part of ambient PM (especially those obtained from traffic combustion) but non-carbon compounds such as sea salt, various mineral dust, ammonium, sulfates, nitrates, etc. are also present [16,17]. Particle composition is one of the key physicochemical properties that determine the biological response to PM inhalation. Organic carbon species (PAHs, nitro PAHs, quinones, alkanes, alkenes, alkyl benzenes, etc.) and active oxidation transfer metals often play a role in health effects of ambient PM and availability of the these chemicals on PM surface has a biological effect on these particles [18,19]. In addition, the sizes of particles are a very important factor for PM health effects. The size is a determinant of penetration into the lungs and the ability (or inability) mechanisms of biological clearance to remove inhaled PM [20,21]. The particle size also has a very important effect on PM relative surface area, with small particles having an area greater than mass equivalent to a particle larger than the same substance (although this is partly due to the agglomeration of particles in air and the biological fluids). Accordingly, PM2.5 is often more important to health associations than PM10 [9,22]. There is a perception that UFPs can pose a greater health risk due to their greater reactive relative surface area and their ability to deep penetrate into the lungs alveoli and bloodstream [23,24]. Vehicle exhaust is an eminent source of UFPs in urban air pollutants, and Diesel Exhaust Particles (DEPs) is of particular interest due to its higher PM ratio compared to petrol/ gasoline engine emissions as well as the tendency to correlate with high levels of co-pollutants such as NOₓ [25,26]. Many of the above air pollutants and their constituent compound have the ability to induce health effects. However, in relation to the cardiovascular system, the composition of the PM is more important for epidemiological associations [9,27]. For this reason, this study will focus on cardiovascular measures of PM and in particular the vehicle emissions as outstanding sources of UFPs.

**Epidemiological evidence overview of air pollution and cardiovascular disease**

The air pollution exposure cardiovascular effects were highlighted in the early 1990s. Examining the relationship between exposure to PM2.5 and death from cardiovascular disease, in 1993, a completely linear relationship was observed between the level of PM2.5 and the rate of cardiovascular disease and mortality [28]. In the USA, in polluted cities with level of PM2.5 (11 - 30μg / m³), the adjusted cardiopulmonary mortality ratio was 1.37 (95% CI: 1.11–1.68) [29]. In the other study in the United States, it
was estimated that a decrease of 10μg/m³ PM2.5 was cause increase the average life expectancy by approximately 7 months. In addition, a study on women in the USA indicated that long-term air pollution exposure caused a 24% increase in risk of the cardiovascular event and alarming 76% increase in the cardiovascular disease death risk [30]. Finally, a basic study in across Los Angeles, USA, showed an association between exposure to PM2.5 and atherosclerosis (chronic vascular disease that underlies coronary artery disease and many other cardiovascular diseases). A difference of 10μg/m³ PM2.5 was related to a 4-6% increase in Carotid-Intima Thickness (CIMT) [31]. Long-term and short-term air pollution exposure is related to mortality and cardiovascular events (such as heart attack or stroke) Using data from the three large US cohorts. Prolonged air pollution exposure (1-4 years) was related with an 8-18% increase in the cardiovascular mortality per 30μg/m³ PM2.5 [32].

An 8-year follow-up of people living in near to a main road indicates almost a doubling of risk of the cardiovascular death [33]. In the short term exposure, increased coronary events [34] and cardiovascular mortality [35,36] were associated with air pollution PM on the same day and before. The trac air pollution coronary effects or may occur even earlier, as people with a heart attack may have been in traffic 1-2 hours beforehand [37,38].

Our previous studies have well demonstrated the effects of urban air pollution nanoparticles exposure on oxidative stress and inflammation in the central nervous system and neurotoxicity and behavioral changes associated with anxiety and depression and impaired memory and learning [39-44].

However, dose-response relationship between the cardiovascular mortality and exposure to PM, especially at low and high doses, needs further investigation. Current evidence suggests that there is a linear relationship between exposure to moderate PM levels and mortality, followed by an increase in mortality rates to higher levels ("superliner") [45-47].

It is important to note that relatively low levels of air pollution can also increase cardiovascular disease in the long run [46]. However, this is true for PM2.5 levels, which are currently lower than international guidelines (e.g. World Health Organization; annual PM2.5 <10μg/m³) [48,49]. The volume of epidemiological evidence goes far beyond mortality and widespread criteria for complications. Indeed, air pollution has been shown to be associated with most cardiovascular disorders, including coronary artery disease [30,50,51], arrhythmias and cardiac arrest [52,53], acute myocardial infarction [54,55] Related are heart failure [54,56], cerebrovascular disease [13,50,57], peripheral arterial disease [58,59] and venous thromboembolism [60,61]. Comprehensive review of evidence suggests that there is a strong causal link between a wide range of the cardiovascular endpoints and exposure to air pollution [62].

"Evidence suggests a causal relationship between PM2.5 exposure and cardiovascular morbidity and mortality" [9]. Recent studies have strengthened the weight of this evidence. Another study concluded that "there is now ample evidence that exposure to urban air pollution contributes to cardiovascular disease and mortality, supported by credible evidence of a number of possible mechanisms." It also emphasizes that "air pollution should be considered as one of several major modifiable risk factors in the prevention and management of cardiovascular disease" [63].

Oxidative stress following exposure to air pollution in cardiovascular disease

Oxidative stress was proven as a key pathway in the field of cardiovascular effects of exposure to air pollution [64-66]. Both controlled exposure and epidemiological studies in humans have provided the strong evidence for oxidative pathways, and these foundations have been established by a network of mechanical studies in cellular and animals models [7]. The AHA statement in 2010 concluded that "at the molecular level, oxidative stress as a very important cause and effect of PM-mediated cardiovascular effects has a good empirical basis" [9]. This mini-review emphasizes the role of the oxidative stress in the cardiovascular disease of exposure to air pollutants nanoparticles (Figure 2). Extensive effects of UFPs-induced oxidative stress have been investigated [65,67]. Studies have identified linking both cardiovascular function and air pollution exposure to the mechanical evidence for oxidative stress (such as identifying the source of free radicals, measuring the biomarker of oxidative stress, assessing the oxidative potential of a...
contaminant, exploring genetic polymorphisms that cause altered sensitivity to oxidative stress, or preventing/ reversing antioxidant compounds). In addition, based on an examination of various aspects of the cardiovascular system, it is clear that the oxidative stress is an important and common mechanism in many different processes that link cardiovascular mortality to air pollution exposure.

**Air pollution nanoparticles and cardiovascular disease**

Many studies have indicated that fine PM exposure causes coagulation changes and systemic inflammation predisposing to ischemic cardiovascular disease, as measured by elevated C – Reactive Protein (CRP), platelets, circulating polymorphonuclear leukocytes, plasma viscosity, fibrinogen and other markers.

PM promotes vascular inflammation, endothelial dysfunction and atherosclerosis [3]. Previous findings mainly have attributed this effect to PM2.5, but most studies show a far greater effect for PM0.1. In fact, new researches show that PM0.1 has a main role in essentially all of these factors [68]. PM0.1 also causes loss of sympathovagal balance, increased heart rate variability, hemostatic function, and altered inflammatory in exposed humans [69]. Even short-term exposure to PM0.1 can cause cardiovascular effects. In the middle-aged patients with metabolic syndrome following PM0.1 exposure for 2h, have been observed decreased blood plasminogen, electrocardiographic changes, thrombomodulin, increased serum CRP, and amyloid A [70]. Many studies have indicated an association between heart disease and chronic UFPs exposure. A 33,831 Dutch residents prospective study found that prolonged UFPs exposure was related to an increased risk of myocardial infarction, cardiovascular disease, and heart failure [71]. Among Toronto residents from 1996 to 2012, an increase in exposure to PM0.1 in adults was related to an increased acute myocardial infarction incidence and heart failure. Although NO2 was also independently related to an increased incidence of heart failure, adjustment for NO2 and PM2.5 did not change this association [72]. Mobile monitoring has shown that annually-averaged number of airborne particles exposure is associated with hypertension, ischemic heart disease, and stroke [73]. Other research have also report an increase in thrombotic and ischemic stroke with exposure to PM0.1 [74]. And worse microvascular function and increased blood pressure with UFPs (PM0.1) but not with fine (PM2.5) and coarse (PM10) particles [68,75]. Particle size is correlated with total cardiovascular mortality. As the particle size decreases, this correlation becomes stronger. UFPs (PM <0.5μm) have the highest correlation [76,77]. No correlation was found for mass concentrations coarse particles (PM1, and larger) [77].

Particles 10–50 nm mostly indicate this finding that the number of particles is correlated with the cardiovascular disease related emergency department visits, with a delay of 4 to 10 days. Exposure to PM0.1 is reported to account for more than 7% of the emergency department visits [78]. The strongest immediate effect correlate was found with PM 30–100–nm (within 2 days), despite a concentration of small mass. The immediate effect associated with mass concentration was with the 1–5 μm particles, which had a similar delayed effect to PM0.1 number [78]. Another study in California of more than 100,000 women found that the mortality from ischemic cardiac disease is more strongly related to PM0.1 than to PM2.5 [79]. Repeated biweekly submaximal exercise tests on adult patients with stable coronary cardiovascular disease showed that exposure to PM0.1 has been related to electrocardiographic ST-segment depression of >0.1 mV. Findings show that PM0.1 effect was independent of the PM2.5. CO and NOx were also related to risk for ST-segment depression, but PM10 and PM2.5 were not [80].

**CONCLUSION**

Awareness of the air pollution health effects is increasing worldwide and is now a priority on environmental and political health agenda. This awareness is reinforced by global data revealing the staggering extent of the air pollution effects on health; reaches the peak of more than a few million deaths annually. A vital stimulus for action is the wider understanding that air pollution effects are not limited to the lungs, but have effects on what each organ appears to be. The cardiovascular effects of contamination are increasingly being recognized by the mainstream. Given the high prevalence of cardiac disease worldwide and its high mortality rate, the infection effects on cardiovascular system will remain crucial. In addition, there is now strong human evidence that inhaled nanoparticles can enter the bloodstream [11,24,66], circulation is not only a means of transporting transported particles throughout the body, but the direct effect of pollutants on cardiovascular function can also contribute to these effects.

Air pollution affects various organs of the body (for example, through high blood pressure, impaired organ perfusion, changes in vascular growth, etc.) [81]. Significant progress has been made in determining biological mechanisms for air pollution cardiovascular effects. A set of interactive mechanisms has been elucidated; however, oxidative stress is a key mechanism for pathophysiological application of contamination to various aspects of cardiovascular system. It is noteworthy that oxidative stress appears as a mechanism in cardiovascular actions of air pollutants using different study approaches. The complementary findings at numerous endpoints and a variety of studies argue that oxidative stress is a vital mechanism in the association between cardiovascular disease and air pollution exposure. Whether oxidative stress is a key trigger or not just a contributing factor is challenging. However, its presence undoubtedly exacerbates the disease. The close
interaction between inflammations indicates and oxidative stress a possible means by which air pollution activities can be enhanced to produce pathophysiological effects in several organs. In addition, due to the obvious prooxidative effects of many air pollutants, and the capacity of oxidative stress to disrupt various aspects of cardiovascular function, oxidative stress may play a key mediator, not just an early phenomenon in later stages of the disease.

Reducing pollution sources should be a key strategy to reduce the burden of urban air pollution on human health. Today, given the challenges of reducing human pollution in the face of increasing urbanization and lifestyle changes, there is room for interventions that can protect against environmental pollution in the medium term. As a result, oxidative stress is the key mechanism by which air pollution exposure causes cardiovascular complications and mortality. The burden of cardiovascular disease and other diseases caused by oxidative pathways is expected to be reduced by developing strategies that reduce the production of air pollutants.

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