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ALLERGIES AND THE ENVIRONMENT (M HERNANDEZ, SECTION EDITOR)

Impact of Particulate Air Pollution on Cardiovascular Health

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Abstract

Purpose of Review Air pollution is established as an independent risk factor for cardiovascular diseases (CVDs). Ambient particulate matter (PM), a principal component of air pollutant, has been considered as a main culprit of the adverse effects of air pollution on human health.

Recent Findings Extensive epidemiological and toxicological studies have demonstrated particulate air pollution is positively associated with the development of CVDs. Short-term PM exposure can trigger acute cardiovascular events while long-term exposure over years augments cardiovascular risk to an even greater extent and can reduce life expectancy by a few years. Inhalation of PM affects heart rate variability, blood pressure, vascular tone, blood coagulability, and the progression of atherosclerosis. The potential molecular mechanisms of PM-caused CVDs include direct toxicity to the cardiovascular system or indirect injury by inducing systemic inflammation and oxidative stress in circulation.

Summary This review mainly focuses on the acute and chronic effects of ambient PM exposure on the development of cardiovascular diseases and the possible mechanisms for PM-induced increases in cardiovascular morbidity and mortality. Additionally, we summarized some appropriate interventions to attenuate PM air pollution-induced cardiovascular adverse effects, which may promote great benefits to public health.

Keywords Particulate matter · Cardiovascular disease · Oxidative stress · Inflammation · Intervention

Abbreviations

CVDs	Cardiovascular diseases
PM	Particulate matter
PM_{10}	PM with an aerodynamic diameter less than 10 μm
$PM_{2.5–10}$	PM with an aerodynamic diameter 2.5–10 μm
$PM_{2.5}$	PM with an aerodynamic diameter less than 2.5 μm
UFPs/$PM_{0.1}$	PM with an aerodynamic diameter less than 0.1 μm
BC	Black carbon
DEP	Diesel exhaust particles
HRV	Heart rate variability
CHF	Congestive heart failure
CHD	Coronary heart disease
RRs	Relative risk ratios
HRs	Hazard ratios
IL	Interleukin
TNF-α	Tumor necrosis factor-α
GM-CSF	Granulocyte macrophage colony-stimulating factor
CRP	C-reactive protein
ROS	Reactive oxygen species
t-PA	Tissue plasminogen activator
PAI-1	Plasminogen activator inhibitor
FMD	Flow-mediated dilation
PUFAs	Polyunsaturated fatty acids
GSTM1	Glutathione S-transferase M1

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Introduction

Ambient air pollution is the largest single environmental risk factor that causes more than 3.9 million premature deaths worldwide, particularly in developing countries with rapid industrialization and urbanization. Among diverse air pollutants, particulate matter (PM) is an important component and a complex mixture of microscopic solid and liquid droplets suspended in the air. Inhalation of PM can lead to multiple adverse health effects in human being, depending on their original source of emission or formation, chemical components, varying size, surface areas, and concentrations [1, 2]. Based on aerodynamic size, PM is generally classified into inhalable (≤ 10 μm; PM_{10}), coarse (2.5–10 μm; $PM_{2.5–10}$), fine (≤ 2.5 μm; $PM_{2.5}$), and ultrafine (≤ 0.1 μm; $PM_{0.1}$) particles. The smaller particles could be more pathogenic [3], as a result of their greater propensity to induce systemic pro-oxidant and pro-inflammatory effects [4].

Cardiovascular diseases (CVDs) are the leading cause of mortality and a major health burden in developed countries and have the similar profile in many Asian countries. In fact, clinical and epidemiological studies have unequivocally indicated positive correlation between the exposure to ambient PM and increased morbidity and mortality of CVDs [5, 6], even the levels of PM at or below existing air quality standards [7]. In particularly, the smaller particles (e.g., $PM_{2.5}$ and $PM_{0.1}$) may pose a higher risk for cardiovascular disorders [3, 8]. This review mainly focuses on the acute and chronic effects of ambient PM exposure on the development of CVDs and the possible mechanisms for PM-induced increases in cardiovascular morbidity and mortality. Additionally, we summarized some appropriate interventions to attenuate PM air pollution-induced cardiovascular adverse effects, which may promote great benefits to public health.

PM Inhalation Induces Cardiovascular Effects

Numerous epidemiologic studies have demonstrated the associations between short- and long-term exposures to ambient air pollution and increased risk for cardiovascular events, including myocardial infarction (MI), congestive heart failure (CHF), and stroke.

Short-Term Effects Observational studies have documented that short-term exposure to increased PM is directly linked to increased morbidity of CVDs. Zanobetti and colleagues found an increase of 1.89% in CVDs, 2.25% in MI, and 1.85% in CHF admissions for a 10 μg/m^3 increase in 2-day averaged $PM_{2.5}$ concentration in 26 US communities [9]. In Shanghai, China, an 8-year period of observation study revealed that a 10 μg/m^3 increase in the concentration of 2-day PM_{10} and $PM_{2.5}$ resulted in increased hospital admissions for coronary heart disease (CHD) (0.23 and 0.74%, respectively) [10]. $PM_{2.5}$ exposure in the USA was generally lower than exposures observed in China. The differential effect magnitudes between the USA and China may be due to pollution levels, individual activities, and population susceptibility in different locations. In addition, existing studies indicate that ambient PM is strongly associated with increased cardiovascular morbidity even at very low levels of exposure.

The positive relationship between CVD mortality and PM exposure has been demonstrated in several large time-series and case-cross-over studies. Kan and colleagues reported an increase in PM_{10} level (2-day moving average concentrations) by 10 μg/m^3 was significantly associated with increases of 0.54% [11] and 0.36% [12] in daily stroke and CHD over the eight Chinese cities, respectively. This is the first multicity study in China, or even in other developing countries, to report the acute effect of PM air pollution on stroke and CHD mortality and similarly, a recent study conducted by the same group to evaluate short-term associations between $PM_{2.5}$ and daily cause-specific mortality in 272 representative Chinese cities. Each 10 μg/m^3 increase in 2-day moving average of $PM_{2.5}$ concentrations was associated with an increment of 0.22% in mortality from total non-accidental causes, 0.27% from cardiovascular diseases, 0.39% from hypertension, 0.30% from CHD, and 0.23% from stroke [13]. In addition, several time-series studies have been conducted worldwide in recent years to address the daily PM-related CVDs mortality [14–17].

Long-Term Effects Chronic ambient PM exposure is known to impair cardiovascular function, exacerbate disease, and increase cardiovascular mortality and morbidity. There is persuasive evidence on the negative impact of PM air pollution on cardiovascular events and outcomes, including electrocardiographic changes (e.g., reduced heart rate variability), endothelial dysfunction, atherosclerosis, and thrombosis [18–21].

Long-term effects of air pollution on mortality are investigated through cohort studies. Previous two landmark cohort studies of the Harvard Six Cities Study [22, 23] and American Cancer Society Study [24, 25] have repeatedly demonstrated the close positive relationship between levels of $PM_{2.5}$ and cardiopulmonary mortality. Large cohort studies have shown that long-term exposure to relatively low levels of PM is associated with cardiovascular mortality in North America and Europe [26–28]. Nevertheless, few studies have assessed the association of CVDs with high-level air pollutants. A retrospective cohort study, containing 39,054 subjects from four cities in northern China, was conducted for mortality of all-cause and specific cardiovascular diseases from 1998 to 2009. For each 10 μg/m^3 increase in PM_{10}, mortality relative risk ratios (RRs) of all-causes, CVDs, ischemic heart disease, heart failure, and cerebrovascular disease were increased by 1.24, 1.23, 1.37, 1.11, and 1.23%, respectively [29]. These findings

were strengthened by a Hong Kong cohort study of 66,820 participants (≥ 65 years of age), which demonstrated mortality hazard ratios (HRs) per 10 μg/m^3 increase in $PM_{2.5}$ were associated with an increase of 1.14% for all natural causes, 1.22% for CVDs, 1.42 for ischemic heart disease, and 1.24% for cerebrovascular disease [30]. However, a meta-analysis of 22 European cohort studies did not find any association between PM and cardiovascular mortality [31]. This discrepancy could be due to the changes in cardiovascular risk profile (e.g., reduced smoking, increased medication, and medical treatment). Compared with short-term studies, long-term cohort studies suggest consistently higher relative risk. The most likely explanation is that chronic studies can capture cumulative health effects due to long-term air pollutant exposure [19].

Possible Mechanisms of PM-Induced Cardiovascular Effects

A number of PM-related mechanisms have been proposed to play a role in pathways leading to CVDs; however, these mechanisms may be associated with direct and indirect toxic effects of PM in the cardiovascular system [32, 33]. The main mechanisms involve, but not limited to, direct translocation of PM, in particular ultrafine particles (UFPs), into the blood stream; systemic inflammation and oxidative stress; abnormal coagulation function and vascular dysfunction; and disturbance of the autonomic nervous system induced by PM.

Direct and Acute Effects of UFPs

Among diverse air pollutants, UFPs are extremely small in size, large in quantity and surface area, and most importantly, capable of passing through the air-blood barrier. UFPs, even at low concentration, were shown to translocate into the blood circulation and can reach the heart and other remote organs [34, 35]. These results suggest that UFPs could induce direct cardiovascular toxic effects independent of their passage through the lungs. After deposit on vascular endothelium, the UFPs can promote oxidative stress and inflammation, resulting in atherosclerotic plaque instability, and finally the formation of thrombus [36]. In an animal study, increased left ventricle ejection fraction and premature ventricular beats were observed in rats intravenously injected with UFPs [37]. The finding from this study implied that inotropic effect of UFPs may be harmful to patients with pre-existing coronary artery disease, by increasing the oxygen demand and aggravating the ischemic symptom. The in vitro study of UFPs on cardiac performance demonstrated that the direct effects of UFPs most likely could be explained by their ability to generate reactive oxygen species (ROS), which can cause myocardial stunning and endothelial dysfunction [38, 39]. Taken together, UFPs can directly and acutely affect cardiac contractility and coronary flow. Nonetheless, more researches on human are needed to examine the capability of UFPs to induce adverse cardiovascular effects and directly, cardiac performance.

System Inflammation and Oxidative Stress

It has been proposed that inhaled PM may trigger inflammation-related cascade in the respiratory tract, in particular, $PM_{2.5}$ and UFPs can lead to systemic inflammation, increasing the risk of CVDs. Indeed, following exposure to concentrated ambient PM [40] and diesel exhaust particles (DEP) [41], local inflammation and oxidative stress can release from lung cells into bronchial fluid and the blood stream of several representative inflammatory markers, such as the cytokines interleukin (IL)-1β, IL-6, interferon-γ, granulocyte macrophage colony-stimulating factor (GM-CSF) [42], and tumor necrosis factor-α (TNF-α) [43]. Brook et al. showed that exposure to concentrated PM for 2 h induced increases in total white blood cell and neutrophil counts immediately [44]. This was strengthened by the panel studies that showed associations between ambient PM exposure and the acute phase response, as evidenced by increases in C-reactive protein (CRP) [45], fibrinogen [46], plasma viscosity [47], and altered leucocyte expression of adhesion molecules [48]. In addition, a ROS-mediated mechanism was involved in PM-triggered pro-inflammatory pathway [49], which linked with atherosclerosis, vascular dysfunction, cardiac arrhythmias, and myocardial injury.

Abnormal Coagulation Function

Another potential mechanism for ambient PM-induced cardiovascular detrimental effect is the abnormal activation of the hemostatic system. In response to vessel injury, the human body relies on the coagulation factors to strengthen and complete thrombus formation initiated by platelet activity, with fibrinogen being central to this process. A previous study has shown that PM exposure was linked to prothrombin time (PT), endogenous thrombin potentials (ETPs), and fibrinogen, which provided the evidence of long-term effects on coagulation [50]. Similarly, a recent study has demonstrated that the increase in fibrinogen levels was associated with increased black carbon (BC), $PM_{2.5}$, and UFP at multiple lag times [51]. Toxicological studies have demonstrated that instillation of DEP reduced the time to thrombotic occlusion in vivo and increased platelet-monocyte aggregates via inhibiting tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI)-1 release from human umbilical vein endothelial cells (HUVECs) [52].

Vascular Dysfunction

The endothelium plays a critical role in regulating blood pressure, atherogenesis, and thrombosis; thus, endothelial dysfunction could contribute to cardiovascular dysfunction associated with PM exposure. A large multicity cohort study has shown long-term PM exposure was significantly associated with reduced endothelial function by decreasing flow-mediated dilation (FMD) and vasoconstriction [53]. In support of this observation, recent studies have shown that PM exposure could induce endothelial cell apoptosis via various inflammatory signaling pathways [54–56].

Disturbance of the Autonomic Nervous System

PM air pollution has been shown to disrupt the autonomic nervous system [57]. Heart rate variability (HRV) refers to the cyclical changes of sinus rhythm, and is a well-defined indicator of cardiac autonomic function. Epidemiological studies have demonstrated that PM air pollution is associated with decreased HRV such as SDNN and rMSSD [58–60]. Moreover, blood pressure (BP), heart rate (HR), and rMSSD among the elderly were affected by the total mass of $PM_{2.5}$ [61]. Recently, a randomized cross-over study has reported that acute exposure to PM affects parasympathetic control of heart function and increases methylation of a pro-inflammatory gene in healthy individuals. This study suggested PM exposure was sufficient to trigger parasympathetic dysautonomia, independently from changes in sympathetic control, and inflammation [62].

Dietary and Pharmacological Intervention

Inflammation and oxidative stress pathways have been proposed to mediate the adverse cardiovascular effects of PM air pollution [4]. It is therefore reasonable to propose the use of anti-inflammatory and antioxidant dietary supplements or medications as an intervention approach to blunt these pathways and reduce the CVD risk of PM exposure [63]. Controlled human and animal studies have demonstrated that antioxidant vitamins, polyunsaturated fatty acids (PUFAs), or medications with anti-inflammatory or antioxidant properties can alleviate PM-induced cardiopulmonary effects.

Pharmacological Intervention

Statins are wildly recognized as one of the most effective therapeutic strategies in the treatment and prevention of CVDs. A panel study has found that statins eliminated the effects of $PM_{2.5}$ on HRV mediated by oxidative stress in subjects lacking of glutathione S-transferase M1 (GSTM1) allele [64]. In another panel study, stain was shown to mitigate vascular inflammatory/endothelial response induced by BC [65]. Moreover, a strong association between long-term $PM_{2.5}$ exposure and levels of the inflammatory marker CRP among certain susceptible subgroups, and CRP levels was lower in those individuals taking statins [66].

Dietary Intervention

Besides pharmacological interventions, intake of essential nutrients from dietary supplement such as antioxidant vitamins C and E and PUFAs is relatively safe. The results from animal and in vitro studies have suggested that vitamin C and vitamin E could prevent PM-induced cardiovascular injury through suppression of oxidative stress [67–70]. However, in humans, vitamins C and E in cardiovascular disease prevention seem to be less effective [71–74], or even increasing all-cause mortality when supplemented with high-dose vitamin E ($\geq$ 400 IU/d) [75]. Therefore, more studies are needed to examine the efficacy of antioxidant vitamins C and E or the combination on ambient PM-induced adverse cardiovascular effects.

Another dietary supplement PUFA has shown promising protection against air pollution-induced detrimental effects on the cardiovascular system. Romieu and colleague found that fish oil supplementation appeared to significantly diminish the time- and frequency-domain HRV associated with $PM_{2.5}$ exposure [76]. Similarly, Tong and colleague in a controlled human study also observed that omega-3 PUFAs could antagonize PM-induced alterations of HRV, cardiac repolarization indices, and lipids changes in middle-aged healthy adults [77]. In addition, epidemiological and clinical studies have reported that PM air pollution exposure might increase QT intervals in coronary artery disease patients. Supplementation of fish or omega-3 PUFAs could decrease the QT interval prolongation and susceptibility of the heart to atrial and ventricular arrhythmia [78–80]. Olive oil is a rich source of the omega-9 PUFAs oleic acid, which can decrease blood lipid and platelet aggregation along with improving endothelial function [81–83]. A recent study showed that intake of olive oil could blunt endothelial dysfunction induced by exposure to concentrated ambient PM, accompanied with an increase in tissue plasminogen activator (t-PA) in blood [84].

Conclusions

Epidemiologic and toxicological studies have demonstrated that particulate air pollution is directly associated with adverse cardiovascular events. The underlying mechanisms of PM-caused CVDs may include direct damage by $PM_{2.5}$ and UFPs translocating from the lung to the circulation and remote localization to the heart, or indirect injury by inducing systemic inflammation and oxidative stress, abnormal coagulation function, vascular dysfunction and disturbance of the

autonomic nervous system, and ultimately leading to heart and vascular damage. A better understanding of the mechanisms underlying the adverse effects of particulate air pollution on CVDs is key in helping to improve environmental health policy and also in providing advices for individuals at risk. In addition, some studies are continuously exploring the new and effective therapeutic approaches, which may promote great benefits to public health by reducing the risk of CVDs.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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