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Air Pollution and Other Environmental Modulators of Cardiac Function

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Abstract

Cardiovascular disease (CVD) is the leading cause of death in developed regions and a world-wide health concern. Multiple external causes of CVD are well known, including obesity, diabetes, hyperlipidemia, age, and sedentary behavior. Air pollution has been linked with the development of CVD for decades, though the mechanistic characterization remains unknown. In this comprehensive review, we detail the background and epidemiology of the effects of air pollution and other environmental modulators on the heart, including both short- and long-term consequences. Then, we provide the experimental data and current hypotheses of how pollution is able to cause the CVD, and how exposure to pollutants is exacerbated in sensitive states.

Introduction

As the population in developed regions has increased, so have the by-products of this development, with dramatic increases in air pollution levels. It is well known that air pollution can be detrimental to human health, a thought that began after events such as the London Smog of 1952, where an estimated 12,000 people died prematurely due to an unusually high amount of pollution that occurred over a five-day period (29). This and other occurrences have since led to government policies that have resulted in a drastic decrease of pollutant levels over the last several decades. Despite these measures, air pollution is still a major public health issue, leading the World Health Organization to recently declare that as a result of exposure to air pollution, seven million people died prematurely in 2012 (175).

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Current lines of research aim to examine the mechanisms behind the triggering and exacerbation of diseases by air pollution, to take measures toward refining policy and recommendations concerning exposure. The particulate matter (PM) portion of air pollution has the strongest link to cardiovascular disease, as detailed below, and therefore is the focus of most research concerning air pollution and cardiovascular health. In the present review, we will first highlight seminal epidemiological studies linking air pollution exposure with cardiovascular morbidity and mortality, describe the primary constituents of air pollution and the mechanistic pathways that contribute to health outcomes including cardiovascular disease. Finally, we will emphasize several key environmental factors that modify the relationship between air pollution exposure and disease.

Constituents of Air Pollution

It is important to characterize the composition of air pollution to understand its toxicology. Air pollution consists of a heterogeneous mixture of gases, liquid suspensions, and particles. Carbon monoxide, the oxides of nitrogen, sulfur dioxide, and ozone make up the main gaseous components of air pollution, which all can have substantial effects on health when inhaled over short or long-term periods. Epidemiological and mechanistic studies identify the PM component of air pollution as the most detrimental to human health, especially affecting the pulmonary and cardiovascular systems. The general strategy for reporting and recommendations for PM have focused upon the size of PM. PM is categorized as PM₁₀, PM_{2.5}, and PM_{0.1} indicating all PM less than 10, 2.5, and 0.1 μm in diameter, respectively. As both the density and capability of PM monitoring has improved over the last several decades, the understanding of how size plays a role in public health has evolved. PM_{2.5} has emerged as being the most relevant for health due to its ability to travel farther before settling to the ground, and its ability to locate both in the alveolar regions of the lungs and in the bloodstream. This perspective may change as more data emerges concerning the cardiovascular implications of PM_{0.1}.

Chemical analyses of certain PM sources can give insight toward the biological mechanisms causing subsequent health effects. PM from combustion sources has long been analyzed, containing metallic elements, most notably iron, copper, chromium, and nickel among many others as well as organic molecules such as polycyclic aromatic hydrocarbons (222, 253). For example, analysis of 24 different PM collection sites in Europe found organic matter to be the main constituent of PM₁₀ and PM_{2.5}, with nitrate, sulfate, and mineral dust as other major contributors (199). These and other studies lead to the consensus that PM contains a carbonaceous core connected with a variety of organic molecules and metallic elements, differing based upon the source and size of PM. Nitrogen oxides, gaseous components of air pollution, are produced mainly by combustion from vehicles and power plants and have highly variable ambient concentrations (249). Notably, nitrogen dioxide (NO₂) is important in the formation of ozone (O₃) and contributes its ambient level when interacting with hydrocarbons and sunlight (31).

Sources of Air Pollution

The majority of research concerning air pollution and cardiovascular health is concerned with outdoor air pollution residing in developing or developed countries. It cannot be ignored that significant evidence exists demonstrating that inside air also contains pollutants due to either entrance of outdoor pollution, secondhand smoke, or indoor sources such as cooking. The preeminent concern with indoor air pollution lies in regions of the world that use solid fuels as an indoor cooking and/or heating source. In fact, almost 3.5 million premature deaths occur due to exposure to household air pollution, primarily from solid fuels (145,228). The composition of indoor air pollution contains predominantly PM, carbon monoxide (CO), NO₂, and sulfur dioxide (SO₂), though at higher concentrations than found outdoors (134). A study examining the black carbon and PM_{2.5} concentrations in Tibetan households using yak dung as fuel found that residents are becoming more aware of indoor air pollution from cooking and heating, but that even households with chimneys still contained large levels of PM_{2.5} and carbon black (265). For this reason, many of the studies examining this type of indoor air pollution focus on disorders of the lungs, as the exposure levels are greater and more frequent than those that occur outdoors (93, 134). Concerning the cardiovascular system, positive association between preeclampsia/eclampsia has been found in homes that burn solid fuels (1), and increased blood pressure (19). Another study found that wood smoke exposure caused no change in blood pressure, but was able to increase arterial stiffness and decrease heart rate variability (HRV) (250). These studies indicate that indoor air pollution is able to exert the same cardiovascular changes as found in outdoor air pollution, though at different levels and composition.

Compared to outdoor air pollution, intervention for indoor air pollution is more feasible due to the smaller scale of the pollutant source. Efforts for reducing the amount of indoor air pollution in communities that use solid-fuel cooking devices have been successful. Intervention usually entails educating the households on the effects of the pollutants, and altering the exhaust or intake of the cooking system. Improved cook stoves in the homes of Honduran women reduced the personal indoor PM_{2.5} and CO levels by 73% and 87%, respectively. Women from this study with improved cook stoves reported less respiratory symptoms, but did not have any difference in lung function or blood C-reactive protein (CRP) levels compared to women that used traditional cook stoves(60). Intervention using a chimney to divert wood smoke also caused a significant reduction in respiratory symptoms with a reduction in CO by 61.6% (82). Improved cook stoves used by Guatemalan women significantly reduced diastolic blood pressure using both comparison to a traditional stove group and comparisons before-and-after intervention (153). Intervention studies have also been conducted in developed regions such as in Denmark homes, where filtration intervention was able to reduce the microvascular function in older, nonsmoking couples (35). These studies demonstrate the need for proper education concerning ventilation and filtration in homes and other buildings.

Most people encounter a mixture of both indoor and outdoor air pollution. For this reason, studies must be able to measure not only the regional outdoor exposure levels of pollutants, but also the exposure level the individual encounters. Data analysis from subjects wearing personal exposure measurement devices combined with values from outdoor sampling can

calculate the influence of factors on indoor air pollution such as outdoor air pollution or secondhand smoke (231). Investigating the sources of indoor air pollution in New York City, it was found that outdoor air only contributed to 28% of the indoor $PM_{2.5}$ as the rest was attributed to indoor sources such as cooking and smoking (113). In comparison to outdoor air pollution, a personal exposure study demonstrated $PM_{2.5}$ levels were found to be higher inside than at ambient outdoor levels, but nitrogen dioxide levels were less indoors (161). Personal exposure assessment of children in a large polluted city found a 24 h mean $PM_{2.5}$ concentration of $102.5 \mu\text{g}/\text{m}^3$, lower than the outdoor measured average concentration of $128.5 \mu\text{g}/\text{m}^3$ (87). One study examined personal exposure to $PM_{2.5}$ mass and elemental carbon (EC) portion and found increased risks of respiratory symptoms were only associated with personal levels of EC and not personal or regional $PM_{2.5}$, suggesting the need for further research concerning the relevant sampling methods (232). One study found disparity between personal sampling and traffic near the place of residence, suggesting traffic level, a factor used in many epidemiological studies, does not correlate with personal exposure levels (87). Thus, many epidemiological studies that examine regional outdoor levels of air pollution or distance from traffic only examine the outdoor component of air pollution, and cannot take into account indoor air pollution sources, filtration of outdoor pollutants, and time spent outdoors versus indoors.

Though outdoor air pollution contributes to a major portion of indoor air pollution, the largest contributor to indoor air pollution if a smoker is present is secondhand smoke (230). Though not all studies concerning secondhand smoke are exclusively for indoor exposure, its detrimental effects on the cardiovascular system cannot be overstated [for in-depth review(s), see (15, 174)]. An analysis of global deaths estimated that secondhand smoke was responsible for 369,000 deaths by ischemic heart disease during the year the study was conducted (174). Studies analyzing the effects from citywide smoking bans have also shown a reduction of incidences of myocardial infarction (MI) after the ban (16, 131). Suppressed or altered endothelial function occurs quickly after exposure to secondhand smoke and is sustained for at least 24 h (46, 119, 189, 263). Secondhand smoke has been shown to promote atherosclerotic plaque development (184) and increased MI size in rats (270). Therefore, the main health concern for indoor air pollution in developed countries is secondhand smoke.

Outside of solid fuel burning and secondhand smoke, there are several common concerns for indoor air pollution exposure (excluding occupational hazards). PM and nitrogen oxides can be produced by gas and electric stoves or space heaters, and if improperly ventilated can reach concerning concentrations (79,142,152,169). Circumstances such as ice resurfacing machines in an ice arena can also generate nitrogen dioxide and carbon monoxide to toxic levels (133,183).

Epidemiological Findings

Overall, ischemic events and related deaths are the most prominently linked cardiovascular consequences to PM exposure. Short-term increases in PM have been associated with increased hospital admissions for MI, acute coronary events, and ischemic heart disease (72,187,193,247,268) and deaths from MI (164). These studies show relevance to the fact

that short-term bouts of increased PM can exacerbate the poor coronary condition of susceptible individuals leading to an ischemic event. Epidemiological studies have also shown an increased risk for ischemic heart disease and MI onset associated with long-term exposure to areas with higher PM within the ambient air (129,135,136,190,248,269). Findings such as these have led to current lines of research examining the ability of PM to exacerbate atherosclerosis and other risk factors for ischemic heart disease.

Increases in concurrent day PM have been associated with increased hospitalizations for congestive heart failure (80, 125, 259). This was also shown when data from a cohort were analyzed with a 14-day lag time (194), which sparked interest in research seeking to detail the time course of PM exposure and heart failure. In a meta-analysis of 35 studies from around the world, it was found that increases in fine PM (PM_{2.5}; particles less than 2.5 µm in size) were associated with heart failure hospitalization and death, and decreasing PM_{2.5} by 3.9 µg/m³ would prevent nearly 8000 hospital admissions each year in the United States (225).

PM_{2.5} has become the most important size range of PM when concerned with cardiovascular health. This is evidenced at the population level, where numerous studies have linked PM_{2.5} levels with cardiovascular events and mortality. At a long-term level, in a follow-up to the Harvard Six Cities study, a 26% increase in cardiovascular-related mortality was found for every 10 µg/m³ increase in PM_{2.5}, using the 3-year average concentration (143). This is echoed in analyses of other studies such as the Women's Health Initiative study of 65,893 women, where the same increase in PM_{2.5} was associated with a 76% increase in cardiovascular-related mortality (158), and the California teacher's study where every 10 µg/m³ increase in PM_{2.5} had a 1.20 hazard ratio for mortality from ischemic heart disease (146). Short-term bouts of increased PM_{2.5} have also been linked with acute cardiovascular events. One to 3-day increases in PM_{2.5} have been associated with increased ventricular tachyarrhythmias (85), emergency room visits for cardiovascular reasons (155), including heart failure (235), and cardiovascular mortality (176).

Other components of air pollution have also been positively associated with cardiovascular disease and mortality, though not as strongly as PM. It has been shown that exposure to ozone increases the relative risk for several causes of cardiovascular mortality, most notably thrombosis mortality (121). However, ozone was not found to be associated with heart failure hospitalization or death in a recent meta-analysis of epidemiological studies concerning air pollution and heart failure, though increased PM, sulfur dioxide, nitrogen dioxide, and carbon monoxide were positively associated with these factors (225). Interestingly, in a case-crossover study, ozone was found to increase the risk of acute coronary effects, but no effect was found for sulfur or nitrogen dioxide (215). Epidemiological evidence concerning the effects of these components on the cardiovascular system is variable, perhaps due to the smaller number of studies, or volatility of each component. Therefore, the primary focus of this review is concerning the PM component of air pollution.

Evaluating air pollution-induced health effects is possible secondary to both increasing and decreasing levels of pollutants, with increasing levels of air pollution, such as those

secondary to natural events (e.g., volcanic activity and wild fires) and/or anthropogenic activity, providing the majority of evidence. For example, considerable data from time-series analyses and cohort studies worldwide describe the association between air pollution levels and mortality, with an estimated 10% increase in all-cause mortality for every 10 $\mu\text{g}/\text{m}^3$ in small particle pollutant concentration (40). A growing number of studies—often real-world quasi-experimental designs—are available to evaluate air pollution-induced health effects in reverse—that is, whether measurable health improvements are observed following reductions in air pollution.

Real-world events such as the closing of a steel mill (180), worker strike at a copper mine (195), banning of coal sales (59), restricting sulfur content in fuel (154), reducing traffic (181) and other governmental interventions to reduce air pollution levels (181) offer natural experiments to further evaluate air pollution-induced health effects. Due to considerable challenges with natural experiments, researchers are often limited only to the metrics of morbidity and mortality. However, a group of investigators recently were able to perform a more controlled study to investigate the effects of aggressive governmental pollution control preceding the 2008 Olympic Games in Beijing, China by examining markers of cardiovascular disease pathophysiology before, during, and following pollution control efforts (181). Investigators observed changes in some, but not all, inflammatory pathway markers that paralleled the temporal variation in pollutant levels (181). This study provides some of the first mechanistic data in humans describing changes associated with a reduction and re-introduction of air pollution. Such a model may afford unique information to facilitate an improved understanding on the effects of exposure timing and duration.

In addition to natural experiments, long-term trend analyses are available describing the health effects associated with reductions in air pollution. For example, follow-up analyses of the seminal Harvard Six Cities (86) and American Cancer Society (196) cohorts support health benefits as a consequence of reducing air pollution (140,191). In addition, ongoing cost-benefit analyses of the U.S. Clean Air Act continue to identify that benefits associated with improving air quality far outweigh the costs (65). However, evaluating the health benefits associated with improved air quality (e.g., climate change mitigation) are challenging due to various sources of exposures, estimates of public health benefits, and methods of analysis (30).

Mechanisms

PM exposure is able to affect the heart both directly, by translocation into the bloodstream (see below), and indirectly via interaction with the lungs. As PM is inhaled, it affects predominately bronchial and epithelial cells, as well as the pulmonary macrophages of the lungs. The response of these cells to PM involves both inflammation and oxidative stress. This response is not isolated to the lungs, but through the release of certain factors affects the cardiovascular system. The combined direct and indirect pathways of PM lead to the cardiovascular consequences of PM.

Direct pathways

Direct translocation of particles into the bloodstream—Since PM is a complex mixture of particles of differing composition, size, and charge, it is difficult to determine the capacity for translocation through the air-blood interface. There are, however, several human and animal experiments utilizing labeled particles that provide evidence for the translocation of PM into the bloodstream, and to several organs, after inhalation. After tracheal instillation of 80 nm ^{99m}Tc -labelled albumin particles in hamsters, significant radioactivity indicating particle translocation was found in the bloodstream, liver, heart, spleen, and kidneys less than 1 h after delivery (168). A similar experiment utilizing ^{192}Ir -labeled ultrafine (UFP) particles in rats found a small but significant percentage of particles in the circulation at time points up to 1 week (137). Experiments in humans have found conflicting results concerning translocation, as studies have found no clearance from the lungs (160,261,262) of ^{99m}Tc -labelled particles within 1 to 3 days, but another has found immediate clearance (166). Discrepancy between these studies and others brings attention to concerns such as particle generation, tracer leaching and detection methods. Recently, a study utilizing instilled gold particles at 20 and 200 nm in diameter in mice found notable concentrations of these particles in the liver, spleen, kidney, and heart (99). The authors also utilized fluorescent-labeled particles of the same size, and detected these particles on red blood cells, within the endocardium and cardiac ventricular tissue (99). Overall, the translocation of particles is difficult to quantify, though the current literature suggests that less than 1% of particles inhaled translocate from the lungs to the bloodstream and to other organs, such as the heart.

There is a strong need for further research in this field, as the current studies have limitations that could alter the results significantly. Only inert particles have been used, not ambient PM, and particle translocation has been shown to be a function of charge and composition (54), and solubility of particles most likely plays a large role in their translocation. The possibility also exists that organic components of PM such as polycyclic aromatic hydrocarbons could translocate into the bloodstream, though there has been no investigation of this occurring after PM inhalation. Additionally, studies conducted with labeled particles utilize inert particles. It is difficult, if not impossible, to label relevant particles such as those from diesel exhaust, which removes the factor that elements of airborne PM could cause damage to the lungs (168) as well as factors concerning the solubility and composition of PM from air pollution that could affect their translocation. Experiments using labeled particles have also been conducted using single and short-term follow-up, which is contrary to real exposure conditions to ambient PM. Lung macrophage transport could also be a factor in determining PM translocation efficiency, but this can take several weeks to occur(54), thus experiments with longer follow-up times should be conducted.

Direct effect of PM on cardiomyocytes—The direct role of PM exposure on cardiac myocyte function was determined in our laboratory by exposing freshly isolated control myocytes to concentrated diesel exhaust particles (DEP) at 0.1 $\mu\text{g}/\text{mL}$. As reported in Zuo et al. (272), direct effects of PM on cardiomyocytes were reported that became progressively worse through overnight culture. These PM-induced effects were ROS dependent, and cotreatment with antioxidants prevented the alteration in cardiomyocyte function. These results suggest a direct role of PM on isolated cardiomyocyte function. Interestingly, PM

effects of diabetic myocytes (cultured in a high glucose environment overnight) were much greater than control myocytes, in line with our hypothesis that susceptible individuals are more affected by PM. Very few other studies have been published on the direct effects of PM on isolated cardiomyocytes, and therefore we have continued this line of inquiry and have published intriguing data on cardiomyocyte function in hearts isolated from animals treated in utero (109,110,244).

Pulmonary Inflammation and Oxidative Stress—It is important to understand the effects of PM on the lungs, as this is a crucial link between PM inhalation and the heart. The dominant response of the lungs to inhalation of PM is inflammation. Evidence for a pulmonary inflammatory response can first be demonstrated in experiments with cultured lung cells treated with various PM constituents. Macrophages, the phagocytic host defense cells of the lung, have been shown to release interleukin (IL)-6, IL-8, IL-1 β , tumor necrosis factor (TNF)- α , granulocyte macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein (MIP)-2 and regulated on activation, normal T cell expressed and secreted (RANTES) protein, among other chemical messengers in response to culture with PM (25,90,128,226). The release of these factors causes recruitment of phagocytes, lymphocytes, neutrophils, and monocytes in response to PM *in vivo*. There is also a wealth of evidence that lung epithelial cells release several cytokines and chemokines when cultured with PM including IL-6, IL-8, TNF- α , IL-1 α , and GM-CSF (11,21,22, 24,45,81,97,102,120,130,165,201,227,233,251,264). Evidence from these studies has also shown that factors released by macrophages and epithelial cells differ based upon PM characteristics. Particle size plays a critical role, as the coarse (PM_{2.5}–10) fraction of PM has been shown to be responsible for most of the inflammatory responses from both cell types (24, 26, 112, 120, 177). This difference could be due to alterations in the composition of PM, which is a critical component affecting the release of certain cytokines from these cell types (112, 224, 264). The merit of these *in vitro* studies is their ability to determine how different sources and concentrations of PM affect the cellular environment of the lung, thus allowing the design of future *in vivo* studies utilizing relevant PM delivery methods.

Additionally, to examine the interaction between macrophages and lung epithelial cells, experiments using conditioned media (128, 130) or coculture (81, 96, 245) have shown that macrophages are able to amplify the epithelial cell response to PM. This phenomenon has been shown to be mediated by TNF- α release from macrophages, shown by the suppression of IL-8 release from epithelial cells treated with conditioned media from PM₁₀-exposed macrophages in the presence of TNF- α -neutralizing antibodies (130). A similar experiment using anti-TNF- α and anti-IL-1 β antibodies found reduction of the release of several mediators from epithelial cells, and the combined effect of both antibodies was strongest, suggesting that several chemical messengers are involved (128). Additional work using a lung epithelial and macrophage coculture model found a contact-dependent increase in cytokine release from the cells (245). Thus, it is clear from *in vitro* experiments that cellular contact with PM is capable of causing an inflammatory response.

Cell-based experiments are instrumental in the identification of the mechanistic pathways in which lung cells respond to PM as well as provide distinctions in chemical messaging profiles in response to varying particle sizes and types. To validate these findings, several

experiments have been conducted to examine pulmonary inflammation in response to PM *in vivo*. Analysis of bronchial alveolar lavage (BAL) fluid from rodents tracheally instilled with PM have increased cell counts, specifically containing macrophages and neutrophils (83, 116, 167, 254), indicating recruitment of inflammatory cells. Cytokines and other signaling molecules have also been found to be increased in PM-instilled mice, including levels of MIP-2, IL-6, TNF- α , and monocyte chemotactic protein (MCP)-1 (83, 116, 151, 209, 221, 254, 255). Functionally, airway aspiration of several types of PM was shown to cause hyper-responsiveness to metacholine in mice (104).

Pulmonary inflammation has also been demonstrated in human studies where BAL fluid or sputum from volunteers was examined after controlled inhalation of PM or clean air. Increased inflammatory cell counts after PM exposure were increased compared to control (2, 234), an effect that was found to be unique to the bronchiole region, and not in the alveolar region of the lungs (27). Additionally, increased IL-8 and eotaxin were found to be increased in the lungs of subjects after PM inhalation (2, 219, 234), providing further evidence that PM is capable of causing an inflammatory response. This may have led to findings such as the reduction in lung function found in children who live close to pollutant sources (41,103).

Closely related to inflammation is pulmonary oxidative stress, a major response in the lungs to PM exposure. Particles interacting with lung epithelial cells can trigger a response from pathways such as mitogen activated protein kinase (MAPK) and transcription factors such as nuclear factor (NF)- κ B, releasing certain inflammatory factors as stated above (18,33). PM both causes the release of oxidative species from lung epithelial cells, and has an innate oxidative capacity (138,218). This response has been shown to cause activation of an anti-oxidant response, via the transcription factor nuclear factor (erythroid-derived 2)-like (Nrf)2 (18). Imbalance in favor of reactive oxidative species (ROS) has been shown both *in vivo* and *in vitro* by the detection of excess ROS in the lungs (23, 114, 227). These ROS are capable of causing significant damage through protein modifications and triggering of downstream pathways.

Indirect pathways

Systemic inflammation—Systemic inflammation has been implicated as a process that alters cardiovascular health in response to PM exposure. Although pulmonary inflammation in response to PM exposure is a well-studied field, evidence for a systemic response is still emerging. Clinical studies have found associations between short-term increases in PM and increased markers of inflammation in serum. A sensitive marker of the acute phase response, plasma CRP, among other markers, has been positively associated with ambient PM concentrations at several levels, including a weak association with normal subjects(84), and a strong association with elderly, obese, diabetic, and hypertensive subjects (88, 192) and those with a history of coronary disease (77, 211). In one study, plasma CRP levels were increased in a population after an event that lead to a “spike” in ambient PM levels (188). Individual PM monitoring has also shown that PM is positively associated with CRP, as well as increased neutrophil and decreased leukocyte counts (206), solidifying the link between

PM and markers of inflammation at real-world concentrations. PM has also been found to be correlated with white blood cell counts and fibrinogen levels (182,223).

Though many of these are short-term, and thus characterize an acute inflammatory response, a few studies have found associations between long-term increased PM levels and increased white blood cell counts, CRP and fibrinogen (52, 122). One study in particular compared inflammatory markers of healthy children living in a polluted city to children in a non-polluted city, and found increases in TNF- α , CRP, IL-1 β , prostaglandin, and endothelin-1, among other factors(42). Though some studies found no positive associations between PM and systemic inflammatory markers (95, 237, 273) there still exist several clinical studies suggesting that PM is capable of inducing a systemic inflammatory response.

Laboratory experiments have been able to examine the capability of PM in causing systemic inflammation to confirm the evidence found in epidemiological studies. Mice exposed to PM through various deliveries were found to have increased serum inflammatory cell numbers and levels of CRP, IL-1 β , MCP-1, and TNF- α (98,132,167). These studies have shown that inflammation in response to PM exposure is not limited to the lungs. PM exposure in animals has also been shown to shorten polymorphonuclear leukocyte (PMN) transit time through bone marrow and increase circulating band neutrophils (111,163,246). Band neutrophil counts have also been found in a human population following an event with increased ambient PM (243). Other experiments using tracheally instilled media from cells conditioned with PM found the same reduction in PMN transit time found with instilling the particles directly (96,162), indicating that factors released by lung cells in response to PM are responsible for the systemic response found in these models.

Though it is clear from these and other experiments that PM exposure is capable of producing a systemic response evident in the bloodstream, it is also important to elucidate inflammatory damage to the organ systems involved, such as the heart. This has been shown in a long-term model of PM exposure, where mice exposed to PM had increased vascular macrophage infiltration (238).

Systemic oxidative stress—Systemic oxidative stress, a process closely linked to inflammation, has also been found to be associated with PM exposure, though evidence for this is difficult to obtain and thus limited in humans. This can be detected by alteration of certain markers in the circulation, or by examining factors produced at the cellular level by affected organs. Increased PM over short-term periods has been significantly associated with increased plasma homocysteine, a marker of oxidative stress, in smokers(9), elderly men (178) and in healthy subjects (203). PM levels were also shown to be positively associated with increased 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, in healthy individuals (57). Controlled exposure studies have also shown increased DNA strand breaks and formamidopyrimidine DNA glycolase sites (36), purine oxidation (252) and increased plasma malondialdehyde (229) in humans exposed to PM compared to control. Oxidative stress was further solidified as a mechanism responding to PM exposure when it was shown that supplementation with omega-3 fatty acids was able to reduce the effects of PM on Cu/Zn superoxide dismutase (SOD) activity and GSH plasma levels in an elderly cohort (210). Cardiovascular dysfunction as a result of air pollution exposure may be

as a result of oxidative damage to tissue, which may not be detectable in the bloodstream. Therefore, clinical examination of oxidative stress after PM exposure is difficult.

Cellular exposure models have been able to confirm the capacity of PM to induce oxidative stress in several cell types, including lung cells, vascular cells, and cardiac cells. Many common PM types such as diesel exhaust particles (DEP) have been shown to produce superoxide without biological systems (138). PM exposure has been shown *in vivo* to cause increased cardiac oxidative stress as measured by increased chemiluminescence and thiobarbituric acid reactive substances (TBARS) in rats (105). The evidence of systemic oxidative stress has also been shown when PM exposure caused increased $O_2^{\cdot -}$ and NADPH oxidase expression in the aorta of mice (240). PM exposure caused increased tissue expression of the anti-oxidant genes Nrf-2, catalase, NQO-2, SOD2, GST-Ya, and ATF4 in the liver (4). Oxidative stress has been shown in the microvasculature of mice exposed to PM (172), confirmed *in vitro* where damage to pulmonary arterial endothelial cells by organic extracts of DEP were found, and reversible by the use of antioxidants, including NO synthase inhibitors (12).

Blood pressure—Increased blood pressure as a subclinical response to PM has also been demonstrated. Though the mechanism is unclear, increased blood pressure in response to PM exposure would provide an explanation for the observed cardiovascular consequences, both at the short- and long-term level. PM has been positively associated with altered blood pressure and risk of developing hypertension (66), with a robust array of studies at the population level (5,20,43,55,78,89,124,126,267) including long-term exposure (58). Though a few studies have found a small negative association or no association between PM and blood pressure (127,150), the majority of data have indicated that exposure to PM is associated with increased blood pressure, and therefore must be taken into account when considering the cause of PM-induced cardiovascular dysfunction. The disparities between these studies thus trigger the need for more experiments using individual exposures.

Detailed individual exposure studies have been conducted, and PM and increased blood pressure have been positively associated using subjects with individually monitored PM and blood pressure levels (19, 56, 147), including one study that found increased blood pressure in individuals exposed to diesel exhaust for 2 h on two separate occasions (68).

Interventional studies have also shown the effects that PM has on blood pressure. Blood pressure was decreased in subjects as they walked through Beijing air pollution with individual monitoring only after they wore a facemask designed to prevent PM inhalation (141). Similarly, blood pressure was lowered in Guatemalan women after a chimney was added to their cooking area to remove PM (153). One particular study found a positive association between personal PM levels and blood pressure, but not when community PM levels were used for analysis (39). This places particular importance on the methods used to obtain PM ambient concentration values, and calls for more individual monitoring and experimental studies. Animal exposures have also been helpful for interventional study, such as one study that found mice exposed repeatedly to PM had increased blood pressure, which was preventable by curcumin administration (167). Overall, it is clear that blood pressure is altered upon PM exposure, and the mechanisms behind blood pressure alterations should be taken into account when examining the cardiotoxicity of PM.

Coagulation and thrombosis—Exposure to PM has been linked with increased blood coagulation factors and thrombosis. Large population studies have positively associated increased PM levels with the risk of developing deep vein thrombosis (7) and venous thromboembolic disease (75). PM has been positively associated with several coagulant biomarkers such as plasminogen activator fibrinogen inhibitor-1 and fibrinogen in both healthy individuals and coronary heart disease patients (57, 236). CD40 ligand, a coagulatory marker, was increased in association with PM levels in patients with coronary heart disease (212), and von Willebrand factor has also been associated positively with PM exposure in diabetics (144). One study found that increased PM was associated with decreased prothrombin time, but no association was found between PM and activated partial thromboplastin time (8). Platelet aggregation and coagulation was associated with PM when it was measured in individuals at multiple time points for 1 year (213), but shorter-term studies such as a controlled exposure study had no effect on coagulation factors (37). Long-term exposure to higher PM over the course of one year was associated with increased procoagulant microvesicles, but not with coagulation factors such as tissue factor (91). Investigation of increased blood coagulation after PM exposure using cellular and animal models has also brought insight into the underlying mechanisms. In rodents, tissue factor was increased (239) as was plasminogen activator inhibitor, and tail vein bleeding time was shortened after PM exposure (70). Exposure of macrophages and bronchial epithelial cells *in vitro* to PM caused a pro-coagulatory response (107). Thus, there is substantial evidence that increased blood coagulation is a contributing mechanism to cardiovascular dysfunction after PM exposure.

Heart rate variability—PM exposure causes alterations in HRV, suggesting the involvement of the autonomic nervous system in the response to PM. HRV is measured over a set period of time, and a decrease in HRV is found in cardiovascular pathologies such as heart failure and diabetes. In an elderly cohort, a decrease in standard deviation of normal-to-normal beat intervals (SDNN) was associated with increased PM, but only in a subset with a certain gene polymorphism involved in the methionine cycle (6), and not in subjects with genetic hemochromatosis (*HFE*) variants (179). These studies suggest that small changes in key proteins, such as those involved in iron storage, are able to promote or prevent cardiac alterations after PM exposure. There is evidence that the effect PM has on HRV is not always a negative association, such as in a small clinical study where PM exposure was associated with increased SDNN in COPD patients, but decreased SDNN in subjects with a recent MI (260). In addition, SDNN and the root mean square of successive differences (RMSSD) in mice exposed to PM were both increased and decreased through a set time period in ApoE knockout mice (49). Exposure to a relatively high dose of PM caused a decrease in SDNN in spontaneously hypertensive rats (48) and RMSSD was decreased in rats exposed to diesel exhaust (3). In a controlled human exposure study, there was no significant impact on HRV parameters when exposed to diesel exhaust for 3 h (186). Similar results were found when PM inhalation by rats did not change the risk of supraventricular arrhythmias (258). Therefore, PM has been shown to elicit significant effects on HRV that cannot be discounted, but further study is needed with varying time-frames, PM concentrations, and comorbidities.

Atherosclerosis and vascular dysfunction—Increased atherosclerosis and vascular dysfunction have been found with PM exposure in a number of robust studies, existing due to the strong link found between PM and coronary disease in epidemiological studies. In a human cohort, PM has been positively associated with carotid intima-media thickness over a long term, with a stronger association in at-risk groups (139), and in diabetic patients, increased PM was associated with increased brachial artery flow-mediated diameter (147) and decreased nitroglycerine-related vascular activity (173). Several other factors have been shown in human studies, such as flow-mediated vasodilation reduced in individuals after PM exposure during exercise (217), increased coronary artery calcification in individuals living closer to automobile traffic (123) and endothelial impairment in healthy individuals exposed to PM (38). A controlled exposure study analyzing microvascular function found no alterations after PM exposure (37), but it remains clear that PM exposure is capable of causing vascular dysfunction in humans.

Animal experiments have brought a great deal of insight toward the vascular implications of PM exposure. Rabbits, apolipoprotein E-deficient mice (ApoE^{-/-}) and LDLR deficient mice exposed to PM had an increased volume of atherosclerotic lesions (4, 50, 171, 241) and monocyte recruitment to atherosclerotic plaques (266) with PM exposure. Long-term exposure to relevant concentrations of PM caused increased atherosclerosis and vascular inflammation in ApoE^{-/-} mice fed a high-fat chow (238). Short-term PM exposure also caused an increase in infarct size in mice with ischemia reperfusion (I/R) injury (69), and several studies have shown rodents with attenuated vascular function and morphology with PM exposure (115,156,172,197,242). Some studies have also shown that the endothelin-1 pathway is involved in the vascular response to PM (53, 149), giving rise to the need for more mechanistic studies.

Environmental Modulators

Heat stress

Attention to climate change has raised awareness to the association between elevated ambient temperature and morbidity and mortality (17). This excess morbidity and mortality related to the interaction between air pollution and extreme heat is a global public health problem that is well recognized throughout the world and predicted to intensify (117). Elevated ambient temperatures are problematic as they contribute to air pollution as well as modulate the physiological effects of exposure. For example, hot dry climates with low precipitation are well known to significantly contribute to sediment yield thereby accounting for a large proportion of ambient PM concentrations (101). Exposure to high ambient temperatures, or thermal stress, is also well recognized to affect the toxicity of environmental pollutants. In a recent *Comprehensive Physiology* review, Gordon et al. (108) thoroughly reviewed the mechanisms of thermal stress and toxicity and describe how temperature can affect an environmental toxicant's biologically relevant dose and metabolism within the body. In addition, authors also describe a relationship between ambient temperature and mortality that presents with a V-, U-, or J-shaped patterns as derived from several epidemiological studies [c.f. Fig. 23, (108)] such that mortality risk

increases at temperature extremes with a sharp increase in mortality at temperatures exceeding 20°C.

Violence, psychological stress

Epidemiological data now support that exposure to psychological stress augments susceptibility to air pollution (61), including exposure to both violence and stress (51,62,63). For example, Clougherty and colleagues have utilized a double-exposure paradigm in animals whereby rats are exposed to PM air pollution in addition to chronic social stress (64). Exposed rats demonstrated altered breathing patterns (i.e., rapid and shallow) in comparison to non-stressed rats as well as a phenotype of airway disease with systemic inflammation (e.g., elevated CRP, tumor necrosis factor- α , white blood cells). Therefore, concomitant exposure to stress and air pollution may lead to adverse health effects via an inflammatory-mediated pathway.

Comorbid conditions

Obesity and diabetes are well-known causes of CVD and cardiovascular-related death (67). Research is emerging that suggests a synergistic effect of air pollution exposure and obesity or diabetes on cardiovascular morbidity and mortality. Additional research has also indicated that increased air pollution could itself cause a greater propensity for diabetes. Whether air pollution is a factor contributing to the development of these diseases, or if they only work in conjunction with air pollution to cause cardiovascular dysfunction is the subject of current laboratory and epidemiological work. The association between levels of air pollution exposure and cardiovascular disease has been investigated in conjunction with increasing body mass index (BMI) or presence of obesity/overweight. Examining the long-term effects of air pollution on cardiovascular events, a stronger association was found as BMI and waist-to-hip ratio increased (158). Another study in a multi-ethnic cohort found that atherosclerotic effects were higher with obese subjects (100).

Examining the interactions using a three-year concentration of air pollutants, it was found that air pollution was associated with cardiovascular disease and stroke that was increased with overweight subjects, and further increased with obesity (200). An additional long-term study found that obesity and air pollution together had no change in all-cause deaths but were positively associated with coronary-related deaths (198), indicating the effect on deaths from obesity may be specific to cardiovascular disease. In one study, there was no interaction between PM_{2.5} and BMI (256), which furthers the need for a larger study including obese populations. Concerning diabetes, long-term exposure to higher PM was associated with prevalence of diabetes after adjustment for BMI (92). Further examination of the biological mechanisms behind obesity and diabetes are necessary to place claims concerning their synergistic ability to cause cardiovascular dysfunction and disease.

Physical activity behavior

The average adult may breathe up to 20,000 L of air per day, providing a perfect entry point for particles and pollutants to enter the body. This opportunity for particle deposition into the lung is enhanced during exercise owing to characteristic high ventilation rates and a shift from nasal to oral breathing, the latter occurring around 30 to 40 L min⁻¹ (170). In support,

controlled studies have demonstrated a 3 to 4.5 and 6- to 10-fold increase in particle deposition into the lung during the transition from rest to light- and high-intensity exercise, respectively (47,74). As a result, the adverse health effects associated with exercise in a polluted environment are increasingly recognized (71, 106). In addition, Rundell et al. recently reviewed in *Comprehensive Physiology* the role of air quality and temperature on exercise-induced symptoms calling to question physical activity in polluted environments (216).

Tobacco smoke

First-, second- and perhaps third-hand exposure to tobacco smoke is an important contributor to indoor as well as outdoor pollution. Poorly ventilated areas, such as the interior of a building, are particularly concerning as Americans, Canadians and Germans are estimated to spend approximately 15.6 to 15.8 h per day indoors (34). Over 45 years ago, Repace and Lowrey demonstrated that levels of respirable suspended particulates from tobacco smoke overpower the effects of mechanical ventilation and is a major public health concern (204). Importantly, this concern is also relevant to non-smokers with passive exposure. In fact, even just passive exposure to one cigarette per day has been shown to promote an inflammatory response and atherosclerosis (185). According to the WHO's 2012 report 21% of the global population above the age of 15 smoked tobacco, with the highest rates observed amongst men and individuals residing in the Western Pacific Region. Countries such as China have exceedingly high-rates of smoking (>50% in men) that contribute to high levels of indoor air pollution that are worse than their oft-publicized outdoor air pollution (148). In light of similar health effects, some have suggested similar patho-physiological mechanisms for PM and smoke exposure.

Though challenging to identify the independent and combined effects of PM and smoke exposure, using data from the American Cancer Society cohort, examined relative risks of cardiovascular and respiratory mortality stratified by smoking status and observed considerably elevated risks for smokers (190). In fact, the risk of death for lung disease increases by an order of magnitude in current versus never smokers. However, the positive association between PM_{2.5} and cardiovascular disease and events remains significant and robust after adjustment for smoking. Elevated risks among smokers for cardiovascular mortality induced by exposure to PM_{2.5} have also been reported in the Women's Health Initiative study (157), but not in the Nurses' Health Study where smoking attenuated the risk estimates for all-cause mortality (198). Although the effect modification of smoking is not entirely clear, Puett et al. suggested that smoking might mask the health effects and impact of air pollution exposure.

Developmental Exposure to Air Pollution

The fetal environment is critical not only in the determination of birth outcomes, but the resulting adult cardiovascular phenotype. Conditions such as maternal malnutrition, obesity, or smoking during gestation have not only been shown to result in significantly lower weight or other adverse outcomes at birth, but also have been shown to result in poor cardiovascular outcomes in adulthood, such as ischemic heart disease (13,14). Observations such as these

shape the developmental origins of adult disease (Barker) hypothesis, which postulates that adverse fetal conditions result in negative alterations of organogenesis that only become evident in adulthood, and is reviewed elsewhere (10, 44). This is best demonstrated concerning maternal obesity, where the fetal environment is affected in a number of ways including decreased utero-placental blood flow, inflammation, and increased lipid levels (208). The link between this adverse fetal environment and development of cardiovascular disease has been shown in offspring from obese mothers (118, 159, 205, 271), demonstrating that not only undernutrition but other conditions adversely affecting the fetal environment can result in adulthood cardiovascular disease.

Due to the longevity that would be necessary for studies to examine the effects of pollutant exposure during development on adult cardiovascular outcomes, and because monitoring air pollution levels is a relatively recent practice, clinical evidence for intrauterine air pollutant exposure causing adulthood disease is lacking, though the evidence that air pollution affects birth outcomes is emerging. The strongest evidence for this exists with significant negative correlations between pollutant levels and birth weight. PM_{10} and $PM_{2.5}$ exposure levels have been negatively associated with term birth weight in a multinational study (73). To examine the relationship between the composition of $PM_{2.5}$ and birth weight, a source apportionment study was conducted using sample filters, where lower birth weight was positively associated with the road dust, combustion, and motor vehicle components (28). Other studies have separated the exposure by trimester, and negative associations were found for all trimesters and total pregnancy between $PM_{2.5}$ or NO_2 and birth weight (220). Low birth weight, though not intrauterine growth restriction were found to be associated with increased levels of total suspended particles (TSPs) and SO_2 , an association that was stronger when only exposure during the first trimester was considered (32).

Research has also been conducted to assess pollutant levels and additional birth outcomes. In one study using data from 22 countries, $PM_{2.5}$ was associated with low birth weight, and at higher levels, preterm birth (94). Preterm birth has been found to be associated with TSP, PM_{10} , CO, and SO_2 (32,207), though results have not been consistent. A minimal association between $PM_{2.5}$ or CO and preterm birth at specific time points near implantation and birth has been found (202,214). Recently, stillborn risk has been found to be positively associated with $PM_{2.5}$ levels (76). These studies indicate that $PM_{2.5}$ and other environmental contaminants are able to diminish birth outcomes, and are viable targets to investigate their effects on the fetal environment and subsequent adult cardiovascular condition.

A few studies using the controlled exposure of animals during development have been conducted with adulthood end-points. In one study, mice were exposed to high levels of diesel exhaust (DE, $300 \mu g/m^3$) during gestation (257). The dams exposed to DE had placental abnormalities and the resulting offspring had reduced blood pressure but no change in cardiac function in adulthood, though cardiac remodeling in response to trans-aortic constriction was exaggerated (257). Recent work in our lab has shown that mice exposed perinatally to ambient $PM_{2.5}$ ($\sim 52 \mu g/m^3$) had significantly reduced cardiovascular dysfunction at adulthood, evidenced by echocardiography and pressure-volume loops, and further shown by reduction in the contractility of isolated cardiac myocytes (109). These mice also had alterations in calcium-handling proteins and prolonged action-potential

duration, providing further evidence that PM exposure during the critical window of development can lead to an incipient heart-failure phenotype evidenced at the molecular, cellular, and organ level (109).

Future research utilizing these models and clinical case-control studies should be focused to address several concerns. First, it would be important to understand if prenatal exposure to air pollution causes a higher propensity for cardiovascular disease, especially in the setting of other risk factors, including obesity and diabetes. For clinical guidelines, it would also be important to understand if there is a critical window in which air pollution exerts its effects on the fetus. Though organogenesis occurs during the first trimester, the current lines of evidence linking air pollution to birth outcomes are conflicting and further research is needed that separates exposures into trimesters, or even smaller time points. It is also important to know the dosage of air pollution that causes alterations in the fetal environment to alter and justify changes in clinical recommendations and environmental policy.

Conclusion

It has been known for years that air pollution exposure, particularly at very high levels, has a negative effect on cardiovascular health. However, until recently the mechanisms for these effects have remained unknown. We also have provided evidence of several other key environmental contributors to altered cardiovascular health, which can synergize with air pollution exposure to exacerbate preexisting conditions. Continued public health efforts are required to further define the ill effects of air pollution exposure on heart and vascular health, as well as determine preventative strategies to lessen the clinical consequences of exposure. To prevent further exacerbation of health effects related to environmental modulators, it is imperative to understand the mechanisms of action of these effects, as well as if they can be treated/prevented by controlling the levels of PM.

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Didactic Synopsis

Major teaching points

1. Cardiovascular disease is a leading cause of death in the world, and is associated with both increased morbidity and mortality.
2. Many causes of cardiovascular diseases are known, including genetic, dietary, and environmental in origin.
3. Air pollution exposure is a known trigger of increased cardiovascular disease, both during adulthood and the developmental periods.
4. Many other external triggers of cardiovascular disease exist, including stress, temperature, and noise pollution.
5. Preexisting conditions can exacerbate the effect of external triggers on cardiovascular disease.

Figure 1.
Overall schematic of proposed environmental modulators of cardiovascular health.