Air Pollution: The "Heart" of the Problem

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Air pollution exposure is associated with an increased risk of acute and chronic cardiovascular mortality. Recent observations have implicated fine particulate matter ($PM_{2.5}$) as one of the most important pollutants. Inhalation of $PM_{2.5}$ causes acute pulmonary inflammation and oxidative stress. The subsequent generation of a systemic inflammatory response could link air pollution exposure with the development of cardiovascular disease. Human experiments have demonstrated pro-arrhythmic alterations in cardiac autonomic tone, increased blood pressure, higher serum C-reactive protein levels, and alterations in blood rheology favoring coagulation following controlled pollution exposures or in relation to elevated ambient $PM_{2.5}$ levels. Recent studies have also uncovered several harmful impacts on the systemic vasculature, including the triggering of acute vasoconstriction and the enhanced development of atherosclerosis. Many questions, however, remain unanswered and future studies will be required to clarify the relevant biologic mechanisms and to identify the specific constituents responsible for mediating the adverse health impacts.

Introduction

As long ago as the early periods of the industrial revolution, mad-made emissions into the atmosphere have been thought to be harmful to health [1]. By the 1930s, observations of increased mortality following severe air pollution episodes had been documented [2] and were later epitomized by the London fog episode of 1952 [3]. In the following decades, efforts to reduce urban air pollution in the United States eventually led to the establishment of the 1970 Clean Air Act and the National Ambient Air Quality Standards (NAAQS). Air quality in most North American and European cities has subsequently improved. Despite these advances, a new generation of epidemiologic studies during the 1980s and 1990s started to uncover worrisome associations between air pollutants and adverse public health impacts, even at concentrations below the national standards.

Air Pollution

Urban air pollution is an extremely complex mixture of many compounds in gaseous, liquid, and solid phases and is ubiquitous in the industrialized world. In cities, the main source is the combustion of fossil fuels from automobiles, diesel trucks, ships, and construction equipment (mobile sources), and from heating furnaces and power plants (stationary sources). A variety of industrial processes such as steel mills and cement kilns can also significantly contribute to air pollution, while in many parts of the developing world cooking fires continue to play a role. The specific composition of this mixture is variable across locations due to differences in geography, climate, and emission sources.

In terms of the human health effects of air pollution, the particulate matter (PM) component has received the greatest attention during the past decade and will be the focus of this review. Other air pollutants of concern are ozone, nitrogen dioxide, carbon monoxide, sulfur dioxide, and volatile organic compounds. Although the gases and particles are usually regulated individually, they likely have complex additive, synergistic, or sequential biologic effects.

Particulate matter itself is a complex mixture of suspended solid and liquid particles in semi-equilibrium with surrounding gases. The particle constituents vary greatly in size, composition, and concentration, depending on origin and age. Outdoor (ambient) PM sizes range from approximately 0.001 to 100 μm in aerodynamic diameter, as shown in Figure 1. There are three main size categories for PM measured in urban air used in health effects studies and for regulation:

- Nuclei mode (smaller than 0.1 μm), often referred to as ultrafine particles (UFPs); they do not last long in the air since they deposit or rapidly form fine particles by coagulation.
- Accumulation mode (between 0.1 and approximately 1.0–2.5 μm); they account for the majority of the mass of suspended particles (Fig. 1) and deposit slowly leading to a long atmospheric lifetime of 5 to 10 days and the build-up of visible haze. These particles may readily penetrate indoor

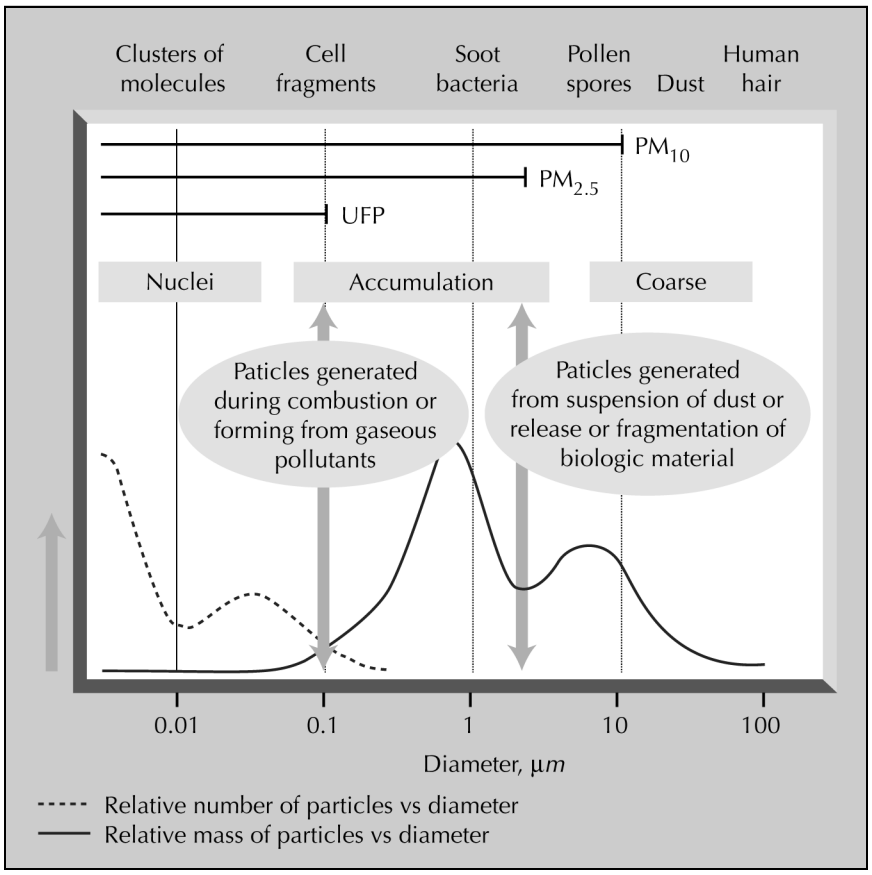

Figure 1. Characterization of particulate air pollution. The most common method to characterize particulate matter (PM) is by particle aerodynamic diameter. Current national regulations from the Environmental Protection Agency provide annual and daily limits on coarse (PM_{10}) and, as of 1997, fine ($PM_{2.5}$) particle emissions. Recent industry challenges to the $PM_{2.5}$ air quality standards of < 15 $\mu g/m^3$ (annual mean) and < 65 $\mu g/m^3$ (24-hour mean) were rejected by the US Court of Appeals in March 2002. The health effects of ultrafine PM (UFP) exposure are also being investigated.

spaces and are most strongly linked to adverse health effects.

- Coarse mode (larger than 1 μm), which extends up to 100 μm; they deposit relatively quickly with a lifetime of less than 2 days.

The size distinctions used for regulation differ slightly; $PM_{2.5}$ (fine particles) and PM_{10} refer to all particles with aerodynamic diameters smaller than 2.5 μm and 10 μm, respectively. These are measured according to the total mass of particulate matter below the specified size per cubic meter of air. UFPs are measured according to the number of particles (counts) per cubic meter of air because there are very large numbers, but small overall mass (Fig. 1). Fine particles and UFPs ($PM_{2.5}$) are formed mostly by emissions from combustion processes, while coarse particles are generated mainly by mechanical processes that break down material from a variety of noncombustion sources into small dust particles [4•].

Regulations and most of the epidemiologic study results have been based on PM measures of total mass or counts (Fig. 1). However, it has become increasingly appreciated that the specific chemical composition of the particles may actually be the more important factor with respect to impacts on health. Coarse particles consist mainly of insoluble crust-derived minerals, biologic material (such as pollen and bacteria), and sea salt. Fine particles are composed mainly of carbonaceous material (organic and elemental), inorganic compounds (*eg*, sulfate, nitrate, ammonium), and trace metal compounds (*eg*, iron, aluminum, nickel, copper, zinc, lead). There are potentially thousands of different compounds existing on fine particles that may exert harmful biologic effects. On any day or location, the PM mass concentration may be similar, yet the composition may vary greatly enough to differentially impact human health.

Evidence that fine particles impact health

Size determines where particles are likely to deposit in the respiratory tract. Particles larger than 10 μm are mainly deposited in the nose and throat and are less likely to affect health beyond the point of deposition. $PM_{2.5}$ and UFPs are able to penetrate into the airways all the way to the terminal alveoli. Smaller particles are present in larger numbers and have more total surface area and bioavailability, thus accounting for their greater biologic effects. The original reasons for increased emphasis on the $PM_{2.5}$ fraction of PM were largely based on their lung deposition, chemical composition, indoor penetration, and prolonged atmospheric lifetime [5]. Furthermore, potential health effects were found to be mediated by specific chemical compounds (*eg*, sulfate, strong acidity) known to reside in the fine fraction [6].

Until recently, there have been relatively few studies using actual $PM_{2.5}$ data in health effects studies. Those that did had unique datasets from prospective studies such as

the Harvard Six Cities Study [7], the American Cancer Society Cohort [8••], and the Children's Health Study [9]. Greater availability of coarse and fine particle measurements has led to more recent attempts to address the question of the relative effects of these two different size fractions. This research has tended to support the earlier assumptions that fine particles are more harmful, but the results have been inconsistent regarding whether coarse particles also have an effect.

Observational studies linking air pollution and cardiovascular disease

During the past 15 years there have been a tremendous number of studies on the association between variations in ambient PM levels (total suspended particles, PM_{10}, $PM_{2.5}$, UFP) and a large array of health endpoints. Presenting the results of all of these studies is beyond the intent of this paper since there are a number of reviews available to interested readers [10,11]. The update to the US Environmental Protection Agency (EPA) 1996 Criteria Document will represent the most extensive review when it is released in the near future.

The majority of the observational analyses completed have been acute effect studies using routinely available PM time series data and population-level responses in mortality or morbidity (time series or longitudinal studies). Acute effect studies examining more specific responses within a study cohort (cohort studies) in relation to temporal variations in PM have also been common. Chronic effect studies based on differences in health effect size/rate/prevalence among geographic locations in relation to geographic differences in average PM concentration (chronic or cross-sectional) have been less common. However, the chronic studies are particularly important because they have provided the only information available on the long-term effects of PM.

The common feature in the three study types mentioned above, and the reason they are considered observational, is that the PM concentrations varied naturally in time and space. In contrast, the potential health effects of those variations were assessed via a wide range of study designs to varying levels of detail. At present, the details of greatest interest relate to 1) magnitude and temporal characteristics of the acute and chronic PM effect; 2) relative toxicity of PM of different sizes, chemical composition, or origin and the potential influence of gaseous pollutants; 3) determination of the population subgroups most susceptible to PM effects; and 4) pre-existing diseases or physiologic conditions most likely to be exacerbated by exposure to PM leading to insights regarding the biologic pathways involved.

The magnitude of the PM effect is small when compared with other well-known cardiorespiratory risk factors (*eg*, active or passive smoking). It also differs somewhat among studies, probably due to the wide range of cities that have been studied and the variations in the quality, type, and amount of data available, including the amount of adjustment for confounding by gaseous air pollutants, weather, and other health determinants. The National Morbidity, Mortality, and Air Pollution Study (NMAPS) is currently considered to have yielded the most precise estimates of the magnitude of the *acute* effect because a consistent approach was used simultaneously in 90 US cities [12••]. From this analysis, Samet *et al.* [12••] reported in 2000 that across the 20 largest cities the average increase in the relative rate of death (per day) from all causes is 0.51% for each 10 $\mu g/m^3$ increase in daily average PM_{10} concentration. This value was subsequently adjusted downward to 0.2% to correct for statistical errors, but remains significant and robust [13]. The death rates were found to be associated with PM_{10} on the day of death and 1 and 2 days prior to death. Related analyses suggested that this acute effect of air pollution is actually shortening overall life expectancy by more than just a few days (not only mortality displacement).

The American Cancer Society (ACS) data compiled for the Cancer Prevention Study II provide the strongest evidence to date that *long-term* exposure to $PM_{2.5}$ is an important risk factor for cardiopulmonary mortality. The original analysis of these data [2] suggested that living in US cities with higher levels of $PM_{2.5}$ reduces life expectancy by 1.8 years compared with urban areas with low levels [10]. A recent, more detailed reanalysis of these results extended over a longer time period [8••] corroborated the earlier findings and those of Dockery *et al.* [7]. The increase in all-cause and cardiopulmonary mortality over 16 years (adjusted for potential confounders) is 6% and 9%, respectively, for a 10 $\mu g/m^3$ increase in long-term exposure to $PM_{2.5}$.

Both the ACS and NMAPS studies found that cardiopulomonary mortality risks were greater than those for all-cause mortality. This is consistent with expectations, but it was not possible to further differentiate between cardiovascular and respiratory mortality. Other studies, however, have provided evidence that persons previously diagnosed with respiratory or cardiovascular diseases are both at higher risk [6,14]. Interestingly, recent data also suggest that diabetics may be at increased risk for the adverse health effects of air pollution [14,15]. It therefore appears that although air pollution exposure impacts the entire public health, the elderly and patients with pre-existing heart, lung, or certain metabolic diseases suffer the worst consequences. Dockery [11] recently reviewed some of the evidence of cardiovascular effects of PM and pointed out that while the relative effects appear to be greater for respiratory compared with cardiovascular deaths, the potential number of PM-related deaths attributable to the latter is much larger due its greater prevalence in the population. Thus, while it is unrealistic to assume that the mechanisms by which PM impact the respiratory and cardiovascular systems are independent, it is clear that it is crucial to gain more understanding of the mechanisms associated with the cardiovascular effects.

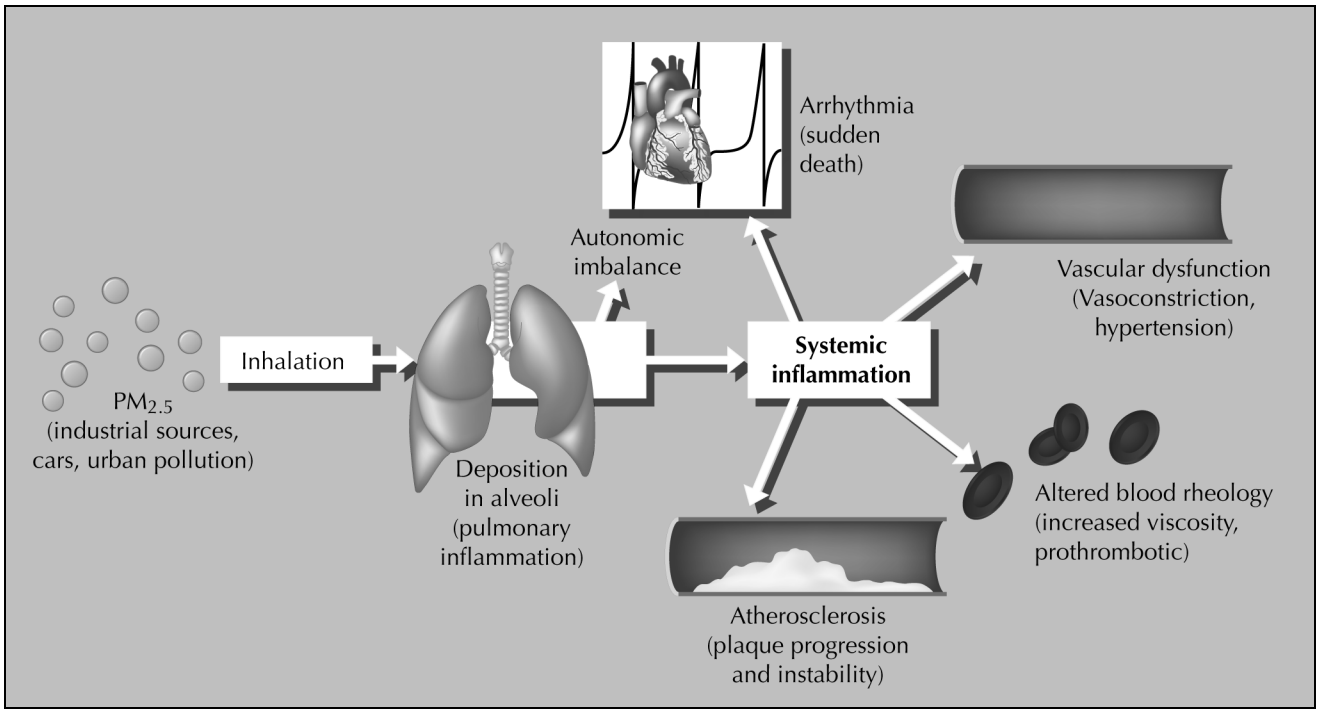

Figure 2. General mechanism of cardiovascular disease caused by particulate air pollution exposure. Inhalation of constituents of fine particulate air pollution (particulate matter [$PM_{2.5}$]) can produce pulmonary inflammation. This can directly alter autonomic balance (cardiac rhythm) and lead to a systemic-wide inflammatory response capable of triggering acute and chronic cardiovascular disease.

Mechanisms of Cardiovascular Disease

There have been relatively few experiments investigating the biologic mechanisms that link air pollution exposure with increased cardiovascular mortality. It has even been declared that the "most important" weakness of this field of science is our "inability to explain how fine particles affect health" [16]. This crucial limitation has served to help fuel legal attacks on the 1997 EPA air quality standards for $PM_{2.5}$ by a coalition of industry and business groups [17]. In response, the scientific research effort to overcome this shortcoming has grown considerably during the past few years. The result has been a substantially improved understanding of the mechanisms whereby air pollution impacts cardiovascular health [18]. However, due to the heterogeneous nature of airborne pollutants and the huge variation in the characteristics of individuals exposed, it is not surprising that some disparity in the observed biologic responses and the risks associated with air pollution exposure has been reported.

Generalized schemata

The principal present-day hypothesis was initially proposed by Seaton and MacNee [19]. When inhaled at environmentally relevant concentrations, fine particulates small enough to reach the terminal alveoli (generally < 2.5 µm in diameter) can provoke a pulmonary inflammatory reaction with the subsequent release of blood-borne mediators into the circulation. In turn, these are capable of triggering a wide array of harmful physiologic responses in susceptible individuals. The sum of these deleterious impacts has both short- and long-term adverse consequences. The risks for acute coronary events and sudden death, as well as the potential for the chronic development of atherosclerosis and cardiovascular disease, are both enhanced (Fig. 2).

One alternate hypothesis suggests that exposure to UFPs may also produce adverse health consequences, or be partly responsible for the $PM_{2.5}$ effects. Recent experiments have shown that inhaled ultrafine carbon particles rapidly translocate unimpeded into the systemic circulation of humans and can thereby have a direct impact on the cardiovascular system [20]. However, UFPs have thus far received less attention due to limited available data and their short atmospheric lifetime [10,11]. Not discounting a potential additive effect, the wealth of the current evidence implicates $PM_{2.5}$ as the primary mediator of the cardiovascular mortality related to air pollution.

Inflammatory responses and atherosclerosis

An assortment of studies have now confirmed the presence of an inflammatory reaction following $PM_{2.5}$ inhalation in the lungs [21–24] and systemic circulation [23–28], including the coronary vascular bed [23]. An important instigating event appears to be the generation of increased oxidative stress within the pulmonary tissue [21,29–33]. Constituents of $PM_{2.5}$ [29], in particular several transitional metals found in various concentrations of different

industrial emissions [30,31,33], can stimulate the production of reactive oxygen species. Activation of pulmonary macrophages by the direct uptake of particulate matter can also initiate free-radical generation [21,33]. The activated macrophages can subsequently release proinflammatory cytokines into the circulation through a process dependent on the induction of nuclear factor κB by intracellular oxidative stress [21,31]. Indeed, incubation of human alveolar macrophages with atmospheric particles causes a dose-dependent production of a number of cytokines, including tumor necrosis factor-α [26].

Evidence for an inflammatory response that is transmitted beyond the lungs comes from several experiments. Raised C-reactive protein (CRP) levels have been associated with high ambient particulate air pollution concentrations in British adults [25]. During a severe air pollution episode in Germany, serum CRP [28] and plasma viscosity [34] were increased in healthy men. An elevated neutrophil count was found after a controlled exposure to diesel exhaust in healthy volunteers [24]. Higher circulating band neutrophil counts [27] and proinflammatory cytokine levels (interleukin-1β and interleukin-6) [26] occurred in military recruits following an air pollution event caused by forest fires in Southeast Asia. These findings strongly support a direct biologic linkage between air pollution and cardiovascular disease, as many plasma markers of inflammation are known to independently predict an increased risk for future cardiac events [35].

Systemic inflammation could link short-term $PM_{2.5}$ exposure to acute cardiac events by triggering instability of coronary arterial plaques [35] and by promoting procoagulant alterations in blood rheology such as elevations in blood fibrinogen [36]. However, the chronic exposure to air pollution may be of even greater health consequence. The long-term potential for the development of coronary artery disease itself may be enhanced, as atherosclerosis is now established as an inflammatory disease of the arterial vasculature [35]. Recent experimental evidence confirms this concept. Just 4 weeks of particulate air pollution exposure to rabbits directly induced atherosclerotic plaque formation and lesion progression to a more vulnerable phenotype [37••]. Supporting a direct linkage between pollution inhalation and atherosclerosis, atheroma formation was significantly correlated to the number of alveolar macrophages that phagocytosed fine particles.

Autonomic tone and cardiac arrhythmia

Short-term particulate air pollution exposure could also trigger acute cardiac events by disrupting autonomic nervous system balance and cardiac rhythm. Time series studies have reported significant reductions in overall heart rate variability in association with higher ambient air pollution levels in elderly subjects [38,39] and with occupational exposure concentrations in healthy young adults [40]. Decreased heart rate variability reflects a disturbance of cardiac autonomic function and predicts an increased risk for sudden death and overall mortality. As would be expected from epidemiologic studies, elderly patients and subjects with pre-existing vascular health problems were more strongly affected [40].

Analyses of the frequency domain in heart rate variability have demonstrated both impaired [38] and increased [39] cardiac vagal autonomic tone related to increased air pollution levels. These discordant findings are most likely a result of differences in environmental exposure characteristics and subject populations between studies. Nevertheless, they suggest that short-term exposure to ambient levels of air pollution has the potential to promote both brady- and tachyarrhythmias in susceptible individuals [41]. In support of this concept, high ambient particulate levels have been associated with an increased frequency of implanted defibrillator discharges [42].

Fine particle exposure could be linked to alterations in autonomic balance and cardiac rhythm by several mechanisms [41]. Inhalation of $PM_{2.5}$ can cause a systemic sympathetic stress response promoting a faster heart rate, reduced heart rate variability, and thus trigger tachyarrhythmias. It can stimulate pulmonary irritant receptors leading to increased parasympathetic tone via stimulation of vagal afferents and consequently promote brady-arrhythmias. On a long-term basis, $PM_{2.5}$-induced systemic inflammation and elevated circulating cytokine levels have the capability to impair cardiac myocyte and electrophysiologic function [41]. Although the underlying mechanism is not completely understood, fatal cardiac arrhythmia is a primary candidate for the origin of sudden cardiovascular events related to air pollution.

Vascular function

All known cardiovascular risk factors are associated with impaired vascular endothelial function [35,43]. Endothelial dysfunction plays a pivotal role in the genesis of atherosclerosis and independently conveys a poor long-term prognosis [35,43,44]. Inhalation of environmental tobacco smoke (similar in characteristics to $PM_{2.5}$) causes rapid vasoconstriction [45], increases plasma endothelin levels [46], and triggers endothelial dysfunction [47]. Consequently, the impact of particulate air pollution on vascular function has been the subject of recent investigations.

Diesel exhaust particles are cytotoxic to pulmonary endothelial cells and impair endothelial-dependent vasodilatation due to increased oxidative stress [33,48]. Rats exposed to urban particulate matter were found to have increased circulating plasma levels of endothelin-1 [49], a marker for increased cardiovascular mortality. With these findings in mind, we investigated the effect of short-term $PM_{2.5}$ and ozone inhalation on vascular reactivity in healthy adults [50••]. Study subjects were exposed for 2-hour periods to concentrated ambient fine particles plus ozone at high environmental levels (150 $\mu g/m^3$ and 120 parts per billion, respectively) versus filtered air in a randomized, double-blind, cross-over fash-

ion. Brachial artery tone and reactivity, which are known to parallel coronary vasomotion [36], were determined by high-resolution vascular ultrasonography. Although endothelial-dependent vasodilatation was not immediately impaired by these exposure conditions, a significant 0.09-mm brachial artery vasoconstriction (mean reduction in basal diameter of approximately 3%) was observed. This was the first demonstration that the inhalation of common urban air pollutants actually has an impact on the vasculature of humans.

The vasoconstriction could be a result of air pollution–mediated sympathetic nervous system activation [38,51]. It could also occur in reaction to systemic oxidative stress and inflammation by instigating an imbalance in arterial tissue vasoactive mediators (Fig. 3) [35]. Further studies will be required to determine the specific air pollution component responsible and the underlying biologic mechanism of vasoconstriction. Regardless, in susceptible individuals with pre-existing obstructive coronary lesions, this degree of sudden vasoconstriction could promote cardiac ischemia and/or trigger myocardial infarctions by disrupting plaque stability. In support of this concept, a recent European study has reported an independent association with increased ambient particulate air pollution levels (ultrafine and $PM_{2.5}$) and the risk of developing myocardial ischemia during repeated exercise stress testing in patients with coronary artery disease [52]. Subjects not on β-blocker therapy had an odds ratio of 8.40 (1.76–40.21) for significant ST-segment depression > 0.1 mV with every 10 $\mu g/m^3$ increase in environmental $PM_{2.5}$ concentration. These results corroborate that the short-term cardiovascular mortality and increased risk for acute myocardial infarction [53] associated with particulate air pollution is at least partially mediated by enhanced susceptibility for myocardial ischemia.

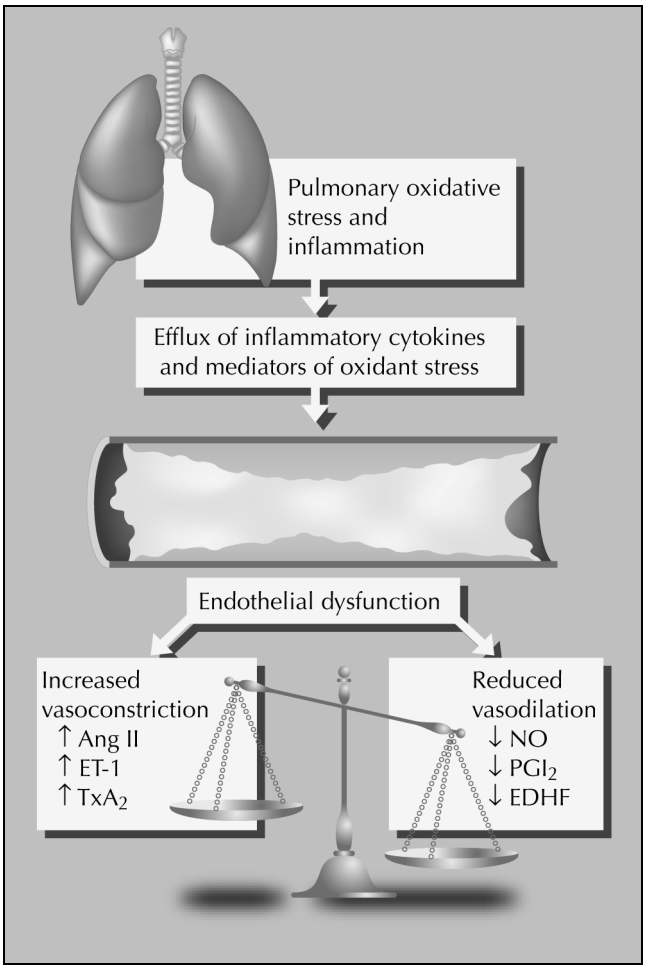

Figure 3. Potential mechanism of vascular dysfunction due to particulate air pollution inhalation. Endothelial dysfunction and acute arterial vasoconstriction could occur after air pollution inhalation as a result of an imbalance in local tissue endogenous vasoactive mediators due to systemic inflammation and oxidative stress adversely impacting vascular function. Ang II—angiotensin II; EDHF—endothelial-derived hyperpolarizing factor; ET-1—endothelin-1; NO—nitric oxide; PGI_2—prostacyclin; TxA_2—thromboxane.

Implications for essential hypertension

Arterial blood pressure has been demonstrated to increase following environmental fine particle exposure to rats [54]. In a similar fashion, a modest elevation in systemic blood pressure occurred in healthy adults shortly following an air pollution episode in Germany [55]. In a subgroup of individuals with higher heart rates, systolic pressure increased by as much as 7.8 mm Hg. The vasopressor response was directly associated with environmental fine particle concentrations. These findings suggest that the vasoconstriction observed in the brachial artery [50] occurs in the resistance microvasculature as well, perhaps due to enhanced endothelin expression [49] and sympathetic nervous system activity [38]. We therefore speculate that chronic exposure to fine particulate air pollution, at the levels encountered in present-day industrialized nations, may be a previously unappreciated risk factor for developing essential hypertension. Future studies are required to confirm this hypothesis.

Conclusions

Particulate air pollution is associated with increased short-term cardiovascular events. People at highest risk tend to be those with pre-existing vascular disease, diabetes mellitus, and the elderly. Perhaps even more importantly, chronic air pollution exposure significantly elevates the long-term risk for premature cardiopulmonary death throughout the entire population. Fine particle inhalation triggers a systemic inflammatory response that can lead to cardiac arrhythmias, arterial dysfunction, myocardial ischemia, procoagulant alterations in blood rheology, and can promote the genesis of atherosclerosis. The risk for developing chronic arterial hypertension may also be increased. Further studies are required to clarify the biologic importance of the observed cardiovascular responses in the induction of the adverse health effects that occur at ambient pollution levels. It is also important to identify

and better characterize the pertinent toxic components in the complex mixture of urban air pollution. Due to the vast number of individuals exposed worldwide to burgeoning urban and industrial emissions, answering these remaining questions will greatly aid in the effort to reduce the substantial global public health burden of air pollution.

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