

Aruni Bhatnagar

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Cardiovascular pathophysiology of environmental pollutants

Aruni Bhatnagar

Division of Cardiology, Department of Medicine, University of Louisville, Louisville, Kentucky 40202

CARDIOVASCULAR DISEASE (CVD) is the leading cause of mortality in the industrialized world. In the United States alone, it kills 1 million people per year; accounting for over 40% of all deaths (50). Despite significant medical advances, the decline in CVD mortality in the United States that began in the 1960s has leveled off, and recent estimates suggest that it may be even beginning to rise again (33). More alarmingly, CVD is rapidly becoming a major cause of death worldwide, and current projections indicate that between 1990 and 2020, the proportion of worldwide deaths from CVD will increase from 28.9% to 36.3% (58). With the ominous increase in the incidence of diabetes and obesity, both of which profoundly affect cardiovascular health (6), the total burden of CVD in the future may be even greater. Although intensively studied, the reasons underlying the high incidence of CVD remain unclear. Several “risk factors” have been associated with the development of CVD, but it is sobering to consider that many patients suffering from heart disease have no established risk (32), suggesting that quantitatively important determinants of CVD are currently unknown (33).

The development of CVD is a result of a chronic and complex interplay between genetic and environmental factors. Whereas genetic makeup is a critical determinant (related to a set of nonmodifiable risk factors such as age, sex, family history, height, and postmenopausal status in women), large changes in the incidence of CVD over the last century indicate that environmental influences are also as important. Multiple studies show that nongenetic factors such as diet, smoking, physical activity, and alcohol intake significantly modify CVD risk (50). In addition, it has been reported that migration of genetically similar populations to new environments alters CVD risk (33), indicating that heart disease is not an inevitable fate of an aging population, but that its development is profoundly modified by the environment. Other contributors of risk, e.g., elevated low-density lipoprotein (LDL) cholesterol, hypertension, diabetes, obesity, reduced high-density lipoprotein (HDL), lipoprotein a, fibrinogen, homocysteine, plasminogen activator inhibitor, and left ventricular hypertrophy are a combination of environmental and genetic factors. Indeed, the term “risk factor” was coined by the Framingham group investigating the epidemiology of CVD (50). Since then there have been extensive and ongoing efforts to establish that environmental factors contribute to the induction, progression, and severity of CVD; although a clear role of environmental pollutants in affecting heart disease is only now beginning to emerge.

There are multiple reasons for the delayed appreciation of cardiovascular toxicity as a significant outcome of pollutant exposure. Whereas some of these reasons relate to historical chance or bias, others may be related to the difficulty in

demonstrating small changes in CVD risk over the high background levels of the disease. Added to this is the experimental difficulty in demonstrating the effects of pollutants on CVD because only the severity and progression, rather than induction, of the disease are likely to be affected. Such demonstrations require well-established animal models of ongoing CVD, some of which have become available only in the last few years [e.g., the apolipoprotein E-knockout (apoE)- or the LDL-receptor null mice] or are still under development (such as those for studying the cardiovascular complications of effect of Type 2 diabetes on CVD). Finally, because the heart and blood vessels are neither the site of primary exposure (as lung, gut, or skin) nor of metabolism and detoxification (e.g., kidney or liver), it has been tacitly assumed that cardiovascular tissues suffer less from exposure to environmental toxins. This assumption is, however, not supported by extensive data demonstrating robust cardiovascular effects of environmental pollutants. The most dramatic example of these is provided by the studies on the cardiovascular effects from smoking, which have consistently demonstrated over the past 30 years that smoking dramatically exacerbates CVD (50). More than 400,000 deaths in the United States per year are due to tobacco smoke-related illness, roughly half of which could be attributed to cardiovascular causes (3). The untoward cardiovascular effects of tobacco smoke and its constituents such as butadiene are graded and appear on exposure to concentrations that are much lower than those that lead to cancer (50, 65). In animal models, exposure to cigarette smoke has been directly shown to increase atherogenesis (25) and myocardial infarct size (99). Moreover, exposure to second-hand cigarette smoke exacerbates atherosclerotic lesion formation and mitochondrial DNA damage in the aorta of apoE-null mice (42), indicating that passive smoking could affect CVD progression synergistically with hypercholesterolemia.

The high vulnerability of cardiovascular tissues to environmental pollutants is dramatically underscored by a recent report showing that the hearts of rats exposed to environmental tobacco smoke accumulate as many DNA adducts as the lung (36). When the exposure was stopped, the number of DNA lesions in lung and the tracheal epithelium was diminished, but no significant DNA repair was observed in the myocardium, indicating a relatively high vulnerability of the heart to chronic and cumulative injury caused by environmental toxins (36). In addition to tobacco smoke, other pollutants have also been reported to affect cardiovascular tissues (*vide infra*). However, the most persuasive data to emerge from such studies relate to the effects of ambient particulate matter on heart disease and CVD mortality. These data point toward a link between the levels of air particulates and CVD and lend support to the notion that pollutants can adversely affect cardiovascular health.

Address for reprint requests and other correspondence: A. Bhatnagar, Division of Cardiology, Dept. of Medicine, Room 421, Delia Baxter Bldg., 580 S. Preston St., Louisville, KY 40202 (E-mail: aruni@louisville.edu).

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LINK BETWEEN AIR POLLUTION AND HEART DISEASE

Extensive epidemiological studies suggest a link between particulate air pollution and daily mortality rates as well as between overall mortality and long-term exposure. Consistent associations have been demonstrated (21, 46, 69, 76) with both respirable particles ($<10\ \mu\text{m}$ in diameter; PM_{10}) and fine particles that reach the deep lung ($<2.5\ \mu\text{m}$; $\text{PM}_{2.5}$). Depending on the method of analysis and the specific urban populations examined, it has been estimated that each $10\ \mu\text{g}/\text{m}^3$ elevation in the PM_{10} level increases the relative rate of death from all causes by 0.4–1% (21,46,69,76) and each $10\ \mu\text{g}/\text{m}^3$ increase in long-term average $\text{PM}_{2.5}$ is associated with a 4% increased risk of all cause mortality and a 6% increased risk of cardiopulmonary mortality (11).

A potential link between air particulates and CVD in particular is suggested by several time series studies showing that elevated PM_{10} and $\text{PM}_{2.5}$ levels are associated with an increase in cardiovascular hospital admissions (20, 68, 78, 79). Stratification by diagnosis suggests specific associations with ischemic heart disease and congestive heart failure (35). Heart failure deaths, which make up 10% of all cardiovascular deaths, accounted for 30% of cardiovascular deaths related to PM (35). Elevated $\text{PM}_{2.5}$ concentrations have also been associated with a transient risk of acute myocardial infarction within a few hours and 1 day after exposure (66).

Although the relationship between PM exposure and cardiopulmonary mortality appears causal, specific mechanisms by which exposure to air particulates affects cardiovascular health remain unclear (82, 90). Both PM_{10} and $\text{PM}_{2.5}$ can penetrate the airways and alveoli of the lung, and the ultrafine particles ($<0.1\ \mu\text{m}$ in diameter) have been shown to also pass into systemic circulation (59, 60) and cause extrapulmonary toxicity. The observations that air pollution accelerates heart rate, diminishes heart rate variability (HRV), and increases the incidence of arrhythmias suggest primary effects on myocardial excitability or autonomic regulation of the heart or both (82, 90). In a small and heterogeneous cohort of elderly subjects, a negative association between HRV and mean heart rate and PM_{10} levels has been reported (70), suggesting perturbations in the cardiac autonomic function. A similar association was found in two other cohort studies (28, 51) as well as in a linear study on an occupational cohort that was continuously monitored for $\text{PM}_{2.5}$ exposures (52). Both long-acting and short-acting components were reported, indicating acute as well as cumulative effects that could be related to changes in sympathetic tone and cytokines. Most recently, decreased HRV has been demonstrated in elderly people exposed to concentrated ambient particles (19).

Autonomic changes have also been observed in animal studies. Dogs exposed to concentrated ambient particles show increasing sympathetic influences with increasing cumulative exposure dose (27). Normal rats exposed to residual oil fly ash (ROFA) or its metal constituents display bradycardia and arrhythmia (12), whereas rats with myocardial infarction and preexisting premature ventricular complexes exposed to ROFA show increased arrhythmia frequency (95). Nonetheless, specific mediators of PM-induced changes in autonomic regulation, sinus rhythm, conduction disturbances, and susceptibility to arrhythmia remain unidentified. Whereas PM exposure has been shown to increase systemic (87) and local cytokine

release in the lung and lung cells (14, 22, 38) and to stimulate irritant receptors (89), it remains unclear to what extent these changes contribute to its cardiovascular toxicity, although direct irritant disturbance of cardiovascular function during PM inhalation has been demonstrated in spontaneously hypertensive rats (44).

Increases in markers of vascular inflammation such as endothelins and C-reactive protein have been reported in rats or humans exposed to particulates (67, 86), but no unifying concepts have emerged. The observations that PM exposures lead to an elevation of blood pressure and endothelins in the absence of lung injury and without changing blood oxygenation levels (91) does however suggest that hypoxia is unlikely to be a significant cause of cardiovascular changes caused by PM exposure. The hypoxemia hypothesis is also inconsistent with the lack of correlation between blood oxygen saturation and PM_{10} levels in high-altitude dwellers (20). Therefore, a likely scenario may be a cumulative multifactorial effect on hemostatic, vasoconstrictive, and autonomic factors leading to increased electrical instability and triggering myocardial infarction in a susceptible population. The recent observations that concentrated ambient particle exposures enhance ischemia in a dog model of acute coronary occlusion (94) and increase conduit artery vasoconstriction in healthy adults (9) provide one plausible mechanism by which PM exposure could precipitate sudden coronary vasoconstriction in flow-limited occlusive arteries or rupture unstable plaques, but the underlying cellular and molecular mechanisms remain unclear.

In addition to precipitous events, PM exposure could also induce chronic and pervasive cardiovascular injury. Such effects are suggested by studies on rats showing PM-induced increases in cardiac chemiluminescence after acute exposures (31), increases in fibrinogen and blood viscosity after 7 days of exposure (86), and low-grade inflammatory injury to the myocardium (45) as well as coronary and renal arteries in mice (57) after chronic exposures. In addition, a 4-wk exposure to PM_{10} has also been shown to accelerate atherosclerotic lesion progression in Watanabe heritable hyperlipidemic rabbits (83). This increase in atherosclerotic lesions was correlated with the number of alveolar macrophages, suggesting that PM exposure increases vulnerability to plaque rupture. Hence, further studies are clearly warranted to determine how chronic exposures to low levels of PM affect atherogenesis and the formation of arterial lesions. Moreover, because lipid peroxidation and oxidative stress are key elements in arterial accumulation of cholesterol and plaque progression (26), vascular deposition of redox active PM particles (particularly their metal constituents) could exacerbate cholesterol oxidation and the formation of lipid-laden cells. These effects of PM are likely to depend critically on the nature of the airborne particulates, their size, composition, reactivity, and their ability to penetrate cardiovascular tissues and elicit detrimental responses.

PM COMPOSITION AND METAL TOXICITY

The composition of air particulates is highly heterogeneous and varies with geographic location and local climate, season, industry, and traffic. The particulates are made up of combustible products, resuspended crustal and biological materials (pollen, bacteria, viruses, and endotoxins), metals (e.g., Fe, V, Ni, Cu, Zn, Pb, Mn), inorganic compounds (oxides, nitrates,

and sulfates), polyaromatic hydrocarbons, ethers, amines, and nitriles as well as carboxylic acids and aldehydes (56, 98). With such a heterogeneous composition, systemic identification of toxicity due to individual components is a daunting task and represents a major challenge to the field. However, several reports suggest that much of PM toxicity is related to the transition metal content of the particles. For instance, in rats subjected to intratracheal PM instillation, the lung dose of bioavailable transition metals, but not instilled PM mass, was the primary determinant of the acute inflammatory response (18). In agreement, some investigators studying the direct effects of PM on cells in culture have reported that PM-generated oxidants and toxicity are prevented by removing metals or by metal-chelating agents (29, 39, 41, 71). Collectively, these studies are consistent with the view that PM exposures result in the delivery of metals to multiple extrapulmonary sites where they form reactive centers that continually catalyze the generation of reactive oxygen species and induce oxidative stress.

Whereas PM-associated metals in general may be toxic, the role of specific metals is less well understood. Several PM-associated metals have been tested for their contribution to toxicity. Universally high toxicity has been attributed to vanadium, although the Ni, Cu, Fe, and Zn content of PM has also been linked to selective measures of toxicity in a tissue-specific manner (1, 14, 43). For cardiovascular exposures in particular, Ni has been linked to the cardiodepressant effects of ROFA exposure (72, 96), and changes in HRV have been correlated with V and Pb content in broiler workers (53). Clearly, further work is warranted, not only to elucidate the role of metals in PM toxicity, but also to study the effects of environmental transition metals on CVD in general. To date little is known in regard to mechanisms by which nonparticulate exposure to environmental metals affects cardiovascular health. Basics of metal delivery and deposition in cardiovascular tissues remain largely unknown, although studies with Ni (62), Cr (24), Hg (13), and Cd (40) show that environmental exposure to these metals results in their deposition in the heart and blood vessels, and that the cardiovascular tissues are significant targets of metal toxicity. Moreover, the cardiotoxicity of transition metals, heavy metals, and metalloids is well known. Long-term arsenic exposure is associated with peripheral vascular disease and with an increase in the incidence of ischemic heart disease (93). Exposures to cadmium are associated with arterial hypertension in men (77) and young monkeys (2) and increases aortic resistance in rabbits (85). Interestingly, large increases in myocardial trace element concentration have been observed in cases of idiopathic dilated cardiomyopathy (24). Furthermore, an increase in the incidence of heart failure in Japanese inhabitants of an area polluted by cadmium has been reported (61). These observations underscore the relevance of metal pollutants (in air particulates or drinking water) to CVD risk while at the same time point toward a greater need for understanding the metabolism of exogenous as well as endogenous trace metals (particularly Fe and Cu) and how they affect CVD.

GASEOUS POLLUTANTS

In addition to metals, the effects of PM could be mediated or modified by other gaseous pollutants. Atmospheric CO and NO₂ levels have been shown to be associated with hospital

admissions for ischemic heart disease (48) and with an increased risk of ST-segment depression during repeated exercise tests performed by patients with stable coronary artery disease (63). Increased risk of cardiovascular morbidity and mortality on CO exposure has been documented by several epidemiological studies (10, 54, 97). Ozone is an additional copollutant, which is very effective in inducing pulmonary inflammation and edema (15), and animal studies demonstrate a direct bradycardiac effect of ozone exposure (5). Moreover, chronic (1 parts/million for 2 wk) exposure to ozone has been reported to increase total blood cholesterol levels in guinea pigs and rats (88), but the observations were not followed up by more mechanistic studies. Even though human ozone exposures have been associated with a decrease in heart rate variability (28), no firm data have emerged linking environmental ozone exposure to increased cardiovascular morbidity and mortality. In general, the effects of gaseous pollutants on CVD have not been systematically examined, and the mechanisms by which they could affect CV health remain speculative.

ENVIRONMENTAL ALDEHYDES

Because aldehydes increase in the air in parallel with PM, and several aldehydes such as crotonaldehyde, glyoxal, glycoaldehyde, and hydroxybenzaldehyde are important constituents of PM_{2.5} (56, 74), it appears likely that they could mediate, at least in part, the cardiotoxic effects of PM exposure. Moreover, several volatile aldehydes may be PM copollutants. Aldehydes are present in high concentrations in automobile exhaust and smog and are generated during combustion of organic material in any form (coal, wood, paper, or cotton). They constitute 1 to 2% of the volatiles generated from automobile exhaust and the burning of fossil fuels (23). Cigarette smoke contains 50–70 parts/million acrolein, and 0.04–2.2 parts/million acrolein has been detected near petrochemical plants (23). In addition, acrolein and related aldehydes are also present in high abundance in several food substances, and their concentration is particularly high in fried foods and reheated oils (17, 23). With the exception of metals, aldehydes are the major toxicants in drinking water. Over 36 different aldehydes are found in drinking water, of which acrolein and endrin have been classified as the two highest priority pollutants (23).

Extensive epidemiological and experimental data suggest that aldehydes affect cardiovascular health. Direct exposure to high concentrations of unsaturated aldehydes is cardiotoxic. They induce contractile arrest of the perfused heart (80) and arrhythmogenic changes in the myocyte excitability (7). Even the less reactive saturated aldehydes, when delivered intravenously, cause prolongation of the Q-T interval, arrhythmogenesis, and ventricular fibrillation in dogs (37). Low doses of acrolein and formaldehyde (0.05–0.1 mg/kg iv) elicit vasopressor effects (23), suggesting that increased systolic blood pressure may be one of the main symptoms of acute aldehyde exposure. Chronic changes in cardiovascular tissues on aldehyde exposure have also been documented. Repeated exposure to α -ethylacrolein for 13 wk has been found to cause cardiac hypertrophy (4). Additionally, exposure to low concentrations of acrolein leads to an increased deposition of the aldehyde in the aorta in cockerels (64) and increases hypercholesterolemia and plaque formation in the atherosclerosis-prone apoE-null

mice (8). Occupational exposure to aldehydes could also induce cardiovascular changes. The increased risk of atherosclerotic heart disease in plant workers producing formaldehyde (81) and the higher incidence of heart disease in undertakers (49), embalmers (92), and perfumery workers (30) has been linked to aldehyde exposure. Finally, the high concentration of aldehydes in cigarette smoke (17) raises the possibility that some of the adverse cardiovascular effects of smoking are related to aldehyde toxicity.

In addition to direct exposure to aldehydes, exposure to industrial pollutants that generate aldehydes has also been linked to an increased risk of cardiovascular disease. Exposure to 1,3-butadiene (which is metabolized to crotonaldehyde, 75) is associated with an increased incidence of atherosclerosis, particularly in African-American workers exposed to butadiene in styrene-butadiene rubber polymer manufacturing plants (55). The atherogenic potential of butadiene has also been substantiated in studies on experimental animals. Exposure to 20 parts/million butadiene has been shown to accelerate atherogenesis in cockerels (65), supporting the idea that butadiene exposure is a significant risk factor for atherosclerosis. This is particularly significant given that butadiene is a ubiquitous pollutant abundant in urban air (34). Similar increases in CVD risk have been suggested for workers exposed to vinyl chloride, which is metabolized via cytochrome P_{450} to its active constituent, chloroaldehyde (84). The increased incidence of cardiovascular disease in vinyl chloride-exposed populations is evinced by a 7-year study of 1,100 workers exposed to vinyl chloride monomer (47). This study showed a significant increase in cardiovascular diseases, including hypertension, myocardial infarction, and other circulatory disorders in vinyl chloride-exposed workers.

POLLUTION MAY BE A NEW RISK FACTOR FOR HEART DISEASE

The totality of evidence discussed above strongly supports the view that exposure to environmental toxins significantly increases CVD risk, which contributes to the overall health burden of air pollution. The World Health Organization (WHO) has ranked air pollution as one of the top ten contributors to preventable deaths (16). In 1995, the WHO estimated that 460,000 avoidable deaths occur annually as a result of outdoor urban exposures, and in 1997, it was estimated that annually nearly 700,000 deaths are related to air pollution and that about 8 million avoidable deaths will occur per annum worldwide by 2020 (16). In a recent European assessment (46), outdoor air pollution (PM_{10}) was found to be responsible for 6% of total mortality, half of which was attributed to automobile emissions. Because excess mortality associated with PM is largely related to cardiopulmonary deaths, the contribution of CVD to the overall health burden of pollution is likely to be numerically significant. For instance, there are approximately 350,000 sudden cardiac deaths each year in the United States alone, of which as many as 60,000 deaths could be related to particulate air pollution (82).

Additional, less readily quantifiable, cardiovascular burden of pollution may be related to pervasive changes such as hypertension or dyslipidemia that have been shown to be caused by exposure to aldehydes, particulates, insecticides, and metals. Collectively, these data raise the possibility of an

etiologic relationship between chronic pollutant exposure and hypertension or hypercholesterolemia and could partially account for the endemism of CVD in the industrialized world. Not only could pollutants exacerbate and accelerate CVD, risk factors associated with CVD could predispose and sensitize for pollutant toxicity. Thus preexisting CVD in itself could be a risk factor of environmental toxicity. Chronic hypercholesterolemia, for instance, could significantly affect xenobiotic metabolism and disposition by either altering the expression of detoxification enzymes in liver and peripheral tissues or by providing additional circulating nucleophilic binding sites (e.g., lysine residues of apolipoprotein and ethanolamine phospholipids). Moreover, interaction with lipoprotein nucleophiles could decrease xenobiotic clearance and deliver xenobiotics to otherwise inaccessible vascular sites, prevent receptor-mediated lipoprotein clearance, and dysregulate lipoprotein metabolism. Binding to reactive electrophiles could also in turn activate the lipoprotein, facilitating the formation of the prothrombinase complex leading to increased blood coagulability (cf, 100). Such interactions have the potential of setting up positive feedback cycles in which environmental pollutants could prevent lipoprotein clearance and increase their thrombogenicity, which in turn would diminish xenobiotic clearance and metabolism and facilitate xenobiotic delivery to sites not accessible to detoxification enzymes (e.g., the vascular intima). Additionally, xenobiotic-induced dysregulation of redox-activated *trans*-acting factors could initiate chemical atherogenesis (73). Such scenarios are currently speculative, however, that they are likely and supported indirectly by multiple lines of evidence points to an urgent need for further study.

Realizing the need for studying the cardiotoxicity as a significant consequence of exposure to environmental pollutants, the National Institute of Environmental Health Sciences, the National Heart, Lung, and Blood Institute, and the Environmental Protection Agency collaboratively organized a workshop on the "Role of Environmental Agents in Cardiovascular Disease." This workshop stressed the need for systematic elucidation of environmental causes of cardiovascular toxicity and for more extensive epidemiological and screening strategies for identifying cardiotoxin pollutants ("heart disease-causing" akin to "cancer-causing" chemicals). It was recommended that such identifications be followed by elucidation of toxin-specific metabolism and of the molecular, cellular, and systemic mechanisms that mediate the cardiotoxic effects of common environmental pollutants. Finally, because not all exposed individuals are likely to be equally sensitive, identification of specific susceptibility factors (old-age, diabetes, hypercholesterolemia) was suggested. It was expected that together these studies will lead to the identification of environmental pollutants as heretofore unrecognized CVD risk factors and spur the development of the new discipline of "Environmental Cardiology."

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