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STATE-OF-THE-ART PAPER

Air Pollution and Cardiovascular Injury

Epidemiology, Toxicology, and Mechanisms

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Recent epidemiologic studies show that increased levels of air pollutants are positively associated with cardiovascular morbidity and mortality. Inhalation of air pollutants affects heart rate, heart rate variability, blood pressure, vascular tone, blood coagulability, and the progression of atherosclerosis. Several categories within the general population (i.e., people with pre-existing cardiovascular disease and diabetic and elderly individuals) are considered to be more susceptible to air pollution–mediated cardiovascular effects. Major mechanisms of inhalation-mediated cardiovascular toxicity include activation of pro-inflammatory pathways and generation of reactive oxygen species. Although most studies focus on the influence of systemic effects, recent studies indicate that ultrafine particles may be translocated into the circulation and directly transported to the vasculature and heart where they can induce cardiac arrhythmias and decrease cardiac contractility and coronary flow. (J Am Coll Cardiol 2008;52:719–26) © 2008 by the American College of Cardiology Foundation

Air pollution significantly increases both morbidity and mortality in the general population (1–4). High respiratory vulnerability has been widely acknowledged as a major component of the adverse health effects of air pollution (5,6). However, during the last 15 years air pollution–induced cardiovascular toxicity has become the focus of intensive studies among cardiologists and specialists in environmental medicine (7–12). In the current review we summarize data regarding the cardiovascular toxicity of air pollution in the general population and discuss mechanisms of the effects of air pollutants on cardiac muscle and vasculature.

Historical Perspective

It was not until 1872 that Robert Angus Smith published one of the first voluminous air pollution–related studies. The book was entitled "Air and Rain. The Beginning of Chemical Climatology" (13). Smith pioneered studies of air pollutants as hazardous components of urban air and specifically analyzed their presence in "acid rains."

The 20th century was marked by several major incidents caused by acute air pollution. In December of 1930 a combination of high atmospheric pressure and mild winds pointed toward a narrow valley created a thick and almost motionless fog in the Meuse Valley in Belgium. Between December 4 and 5 a total of 60 deaths caused by the fog occurred. Most of the deaths were in the small town of Engis (Belgium). Investigation of this environmental incident revealed that the thick low fog entrapped pollutants from chimney exhausts and created a toxic cloud that resulted in these fatalities (14).

In October 1948, an environmental disaster took place in Donora, Pennsylvania. On October 26, industrial pollutants from a local smelting plant started to accumulate in the air over Donora, a small industrial town some 30 miles south of Pittsburgh. The incident caused 20 sudden deaths. An estimate indicated that from 5,000 to 7,000 people (of 14,000 residents) became ill. In addition to 20 fatalities there were 400 hospital stays (15,16).

In 1952 a major environmental incident occurred in Greater London. From December 5 to 9, a heavy fog laden by pollutants from local stoves and industrial plants almost paralyzed the entire city. There was a 48% increase in all hospital admissions and a 163% increase in respiratory disease–related admissions. During and shortly after the incident, the numbers of deaths were significantly elevated. A retrospective analysis indicated that there were almost 12,000 more deaths from December 1952 through February 1953 (17,18).

These environmental incidents triggered worldwide legislative activities that resulted in regulatory acts aimed at limiting the toxic and sometimes deadly effects of air pollutants (e.g., establishment of the Clean Air and Air Quality Acts in the U.S. in 1963 and 1967, respectively).

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Abbreviations and Acronyms

AD = aerodynamic diameter
CAP = concentrated ambient particle
HR = heart rate
HRV = heart rate variability
MI = myocardial infarction
PM = particulate matter
PM10 = coarse particle(s) (diameter ≤10 μm)
PM2.5 = fine particle(s) (diameter <2.5 μm)
ROS = reactive oxygen species
UAP = urban air particle
UFP = ultrafine particle (diameter <0.1 μm)

Size and Composition of Ambient Particles

Ambient particles include coarse particles with aerodynamic diameter (AD) 2.5 to 10 μm (PM10), fine particles (AD <2.5 μm; PM2.5), and ultrafine particles (AD <0.1 μm; UFPs). The chemical composition of particles varies greatly and depends on numerous geographical, meteorological, and source-specific variables. Generally, ambient particles include inorganic components (sulfates, nitrates, ammonium, chloride, trace metals), elemental and organic carbon, crystal materials, biological components (bacteria, spores, pollens), and adsorbed volatile and semivolatile organic compounds (19). In addition, ambient particles, when mixed with atmospheric gases (ozone, sulfur and nitric oxides, and carbon monoxide [CO]), can generate ambient aerosols.

Particulate air pollutants are derived from both human and natural activities. The PM10 particles related to human activities come from road and agricultural dust, tire wear emissions, wood combustion, construction and demolition works, and as a result of mining operations. Natural sources of PM10 include windblown dust and wildfires. Fine particles are mainly generated by gas to particle conversions and during fuel combustion and industrial activities. Major sources of PM2.5 include power plants, oil refinery and metal processing facilities, tailpipe and brake emissions from mobile sources, residential fuel combustion, and wildfires. The primary contributors to UFPs are tailpipe emissions from mobile sources (motor vehicles, aircrafts, and marine vessels).

Morbidity and Mortality Caused by Air Pollution

The relationships between air pollution and both morbidity and mortality has been thoroughly reviewed by Pope and Dockery (20). A few key studies are highlighted here to provide additional perspective.

Short-term effects. Short-term exposures to increased levels of air pollutants are directly linked to increased morbidity (as indicated by increased hospital admissions). An increase in PM10 level by 10 $\mu g/m^3$ was associated with 1.27%, 1.45%, and 2.00% increases in hospital admissions for heart disease, chronic obstructive pulmonary disease, and pneumonia, respectively (data for Chicago area hospitals for years 1988 to 1993) (21). A 9-year observation in 10 U.S. cities revealed similar increases in hospital admissions for cardiovascular disease and pneumonia for each 10-$\mu g/m^3$ increase in PM10 concentration (22). In Ontario, Canada, a 6-year period of observation revealed that a 13-$\mu g/m^3$ increase in ambient particulate sulfate resulted in statistically significant increases in hospital admissions for respiratory and cardiovascular diseases (3.7% and 2.8%, respectively) (23).

Short-term effects of air pollution on mortality are analyzed in time-series studies, which cover days and/or weeks before the death and establish association between daily deaths and daily changes in air pollution levels. Several short-term studies of mortality in communities demonstrated increases in daily death in relationship to increases in the levels of air pollution. In Coachella Valley, California, daily counts of total deaths indicated that an increase in PM10 concentration by 10 $\mu g/m^3$ was associated with a 1% increase in total mortality (24). Analysis of daily deaths in 10 U.S. cities indicated that there was a 0.67% increase in total daily death for a 10-$\mu g/m^3$ increase in PM10 concentration. The increase was more pronounced for out-of-hospital deaths and averaged 0.89% (25). A European study (APHEA2 [Air Pollution and Health: A European Approach]) demonstrated that PM10 and black smoke were predictors of daily death in studied areas. When the ambient concentrations of PM10 and black smoke were increased by 10 $\mu g/m^3$, the total number of daily deaths was increased by 0.7% and 0.5%, respectively (26). In the U.S., the National Morbidity, Mortality, and Air Pollution Study indicated a 0.41% increase in total mortality in response to a 10-$\mu g/m^3$ increase in PM10 in ambient air (27).

Long-term effects. Morbidity (as indicated by accelerated progression of atherosclerosis) is significantly increased by long-term exposure to increased levels of air pollutants (11,28).

Long-term effects of air pollution on mortality are investigated in cohort studies. These studies cover years of exposure, include large numbers of participants, and provide information on life-shortening effects of air pollution (29,30). A large-scale study based on 14- to 16-year mortality in 8,111 adults in 6 U.S. cities (HSCS [Harvard Six Cities Study]) demonstrated a close relationship between the levels of PM2.5 and lung cancer and cardiopulmonary mortality (2). Extended follow-up of the HSCS found that the increase in the relative risk of mortality averaged 16% per 10-$\mu g/m^3$ increase in the PM2.5 concentration (risk ratio 1.16) (31). One of the most comprehensive studies, known as the ACS (American Cancer Society) study (1982 through 1989), linked individual health risks for residents of approximately 150 U.S. cities with ambient air quality in those cities (risk ratio 1.17 for all-cause mortality due to the increased levels of PM2.5) (32). A subsequent follow-up of 500,000 ACS participants through December 31, 1998 indicated that there was a 4%, 6%, and 8% increased risk of all-cause, cardiopulmonary, and lung cancer mortalities, respectively, per each 10-$\mu g/m^3$ increase in PM2.5 (33).

Long-term cohort studies suggest consistently higher relative risk estimates/unit exposure than short-term stud-

ies. The most likely explanation for this is that chronic studies can capture cumulative health effects due to long-term air pollutant exposure, whereas short-term studies reflect acute effects (20). Nonetheless, both time-series and cohort studies undeniably indicate that air pollution increases morbidity and mortality in the general population.

Cardiovascular Events Triggered by Air Pollution

Analysis of daily mortality data for 20 of the largest U.S. counties for years 1987 through 1994 demonstrated that there was a 0.68% increase in cardiovascular and respiratory deaths for each 10-$\mu g/m^3$ increase in PM10 in ambient air (34). Meta-analysis of data collected during the ACS for years 1979 through 2000 indicated that long-term exposure to air pollutants was associated with an increased mortality risk in the ischemic heart disease category (risk ratio 1.18) and combined dysrhythmias, heart failure, and cardiac arrest category (risk ratio 1.13) for every 10-$\mu g/m^3$ increase in PM2.5 (9).

A 4-year study in 204 counties in the U.S. and a 10-year study in 5 major European cities indicated that hospital admissions for cardiovascular diseases are positively associated with increased levels of air pollution (35,36). When 373,566 emergency cardiovascular admissions in London hospitals from April 1, 1987 through March 31, 1994 were analyzed, positive associations were found between myocardial infarction (MI) and black smoke and atmospheric gases (nitrogen dioxide [NO_2], CO, and sulfur dioxide [SO_2]) and between angina and black smoke. The authors concluded that exposure-prevention measures could have saved at least 6,000 patients (37). The significance of air pollutants in triggering MI described in the London-based study was confirmed by Peters et al. (38) in the Determinants of Myocardial Infarction Onset Study in the greater Boston area. In addition, recent epidemiological analysis by Wellenius et al. (8) in 7 U.S. cities, including 292,918 hospital admissions for congestive heart failure (CHF), revealed that an increase in PM10 by 10 $\mu g/m^3$ resulted in a 0.72% increase in the daily admissions for CHF.

There are several categories of individuals within the general population that might be at higher risk for air pollution–mediated cardiovascular morbidity. These categories include people with pre-existing cardiovascular disease, people with diabetes, and elderly individuals (39–43). A controlled human study in 20 men with prior MI indicated that inhalation of diluted diesel exhaust particles (ambient concentration 300 $\mu g/m^3$, median AD 54 nm) resulted in greater ST-segment depression during exercise compared with exercised participants that inhaled filtered air (44).

Because the chemical composition of ambient particles varies greatly between different geographical areas, it is difficult to identify specific component(s) that elicit cardiovascular toxicity. Animal studies indicate that transition metals and carbonaceous material from particulate matter (PM) mediate some cardiotoxic effects of particulate air pollutants (45,46). Gaseous components of ambient aerosols (ozone [O_3], SO_2, NO_2, and CO) were shown to be associated with the occurrence of acute MI, increased all cardiac hospital admissions, and exacerbated exercise-related angina in stable angina patients (37,47–49). Most of these components of air pollution are derived from motor vehicles and industrial sources.

Effects of Air Pollutants on Cardiovascular Indexes in Humans

Air pollution exposure results in significant changes in many cardiovascular indexes. Some of the effects (i.e., changes in the heart rate [HR], heart rate variability [HRV], blood pressure, vascular tone, and blood coagulability) develop acutely in response to increased levels of ambient particles. At the same time the progression of atherosclerosis accelerates as a result of a more prolonged (chronic) exposure to increased concentration of particulate air pollutants.

HR and HRV. A study of residents from a Boston housing community (median age 73.3 years) demonstrated that exposure to PM2.5 (mean concentration 15.5 $\mu g/m^3$) was associated with a decreased HR (50). In contrast, an increase in ambient concentration of PM10 on a previous day by 100 $\mu g/m^3$ significantly raised the odds of an increase in HR by 5 to 10 beats/min (51). These results indicate that air pollution can dysregulate the autonomic nervous system and that the type of particles and their concentrations might affect HR in a variable fashion. Further evidence regarding the effects of air pollution on autonomic cardiac control was presented in studies investigating changes in HRV with regard to the air pollution levels. Several studies demonstrated that air pollution is associated with decreased HRV (as indicated by declines in SD of all normal RR intervals, SDNN, and in square root of the mean of the squared differences between adjacent normal RR intervals, r-MSSD) (40,43,50,52). These findings are important because according to the Framingham Heart Study, decreases in SDNN and r-MSSD are associated with increased cardiac risk (53).

Blood pressure. Data analysis from 62 ambulatory cardiac rehabilitation patients indicated that 120 h of exposure to the 10th through 90th percentile levels of PM2.5 (mean concentration 10.5 $\mu g/m^3$) was associated with increases in resting systolic and diastolic pressures by 2.7 and 2.8 mm Hg, respectively. In exercised subjects with resting HR $\geq$70 beats/min, 48-h exposure to the 10th through 90th percentile levels of PM2.5 (mean concentration 13.9 $\mu g/m^3$) resulted in a highly significant increase in diastolic blood pressure by 6.95 mm Hg and somewhat less significant ($p = 0.11$) increase in the mean arterial pressure by 4.3 mm Hg, with no effect on systolic pressure (54). The MONICA (Monitor Trends in Cardiovascular Diseases Study) trial in Germany revealed that there was a modest increase from 1.79 to 2.37 mm Hg in the systolic pressure per 90 $\mu g/m^3$ increase in total ambient air particulates. These effects of

pollutants were exacerbated in patients with underlying high blood viscosity and high HRs (55).

Vascular tone and reactivity. In the first controlled study aimed at investigating the effects of air pollutants on human vascular function, it was shown that inhalation of concentrated ambient particles (CAPs) plus ozone (approximately 150 $\mu g/m^3$ and 120 parts/billion, respectively) for 2 h by healthy volunteers caused a significant decrease in brachial artery diameter by 0.09 mm (56). Increased levels of PM2.5 and black carbon were associated with decreases in endothelium-dependent and endothelium-independent vascular reactivity in patients with type II diabetes (42).

Blood coagulability. Experimental data demonstrated that UFPs could act as prothrombotic factors in mice and hamsters (57,58). The MONICA survey indicated that plasma viscosity was increased in both men and women subjected to a 1985 air pollution episode in Augsburg, Germany (59). Analysis of levels of air pollution and changes in global coagulation parameters in 1,218 individuals from the Lombardia Region in Italy revealed that high air pollution was associated with shorter prothrombin time (60).

Atherosclerosis. In animal studies chronic inhalation of concentrated UFPs and PM2.5 or intrapharyngeal instillation of PM10 increased the severity of atherosclerotic aortic lesions in apolipoprotein E-deficient mice and Watanabe hyperlipidemic rabbits (61–63). In human studies involving 798 residents of the Los Angeles basin, Kunzli et al. (28) found a 5.9% increase in the carotid artery intima-media thickness per 10 $\mu g/m^3$ increase of PM2.5 in the ambient air. In a study investigating the role of traffic-related, long-term exposure to PM2.5 (mean concentration 22.8 $\mu g/m^3$) in 4,494 participants, a 50% reduction in the distance between the residence and a main road resulted in a 10.2% increase in coronary artery calcification (11). These studies support the concept that air pollution is causing progression of atherosclerosis.

Mechanisms of Air Pollution-Induced Toxicity

Pulmonary toxicity. The general consensus is that once deposited in the lungs, air pollutants trigger an inflammation-related cascade (64,65). Intra-tracheal instillation of ambient particles was shown to induce direct inflammatory response in rat lungs. Pre-treatment with an antioxidant (dimethylthiourea) significantly reduced inflammation in particle-treated groups (66–68).

Ghio and Devlin (69) instilled aqueous extracts of PM, collected in the Utah Valley before the closure of a local steel mill, during its closure, and after its reopening, into the lungs of healthy volunteers. The percentage of neutrophils and concentrations of fibronectin and alpha-1–antitripsin (both indicators of injury to lung tissue) in bronchoalveolar lavage fluids were increased in volunteers who received extracts from samples obtained before the closure and after the reopening of the steel mill. Pro-inflammatory effects of these extracts correlated with their abilities to generate thiobarbituric acid reactive products in vitro (index of reactive oxygen species [ROS] generation).

These results clearly indicate that pulmonary inflammation induced by ambient particles could be triggered by an ROS-dependent mechanism and that source-specific constituents can play an important role in PM toxicity.

Cardiovascular toxicity. In a dog ischemia model, inhalation exposure to CAPs significantly increased ischemic injury to the heart muscle (as evidenced by an increased ST-segment elevation) during 5-min coronary occlusion (70). Inhalation exposure of Wistar-Kyoto rats to combustion-derived PM resulted in active and chronic inflammation within the myocardium and fibrosis in the ventricles and in the interventricular septum (71). Intratracheal instillation of ambient UFPs to mice followed by 20-min coronary artery ligation and 2 h of reperfusion 24 h after the inhalational exposure to pollutants increased the amount of neutrophils in the reperfused myocardium and significantly increased the size of MI (72).

In human studies, exposure to particulate air pollutants increased circulating levels of C-reactive protein and other inflammatory markers, increased blood coagulability, caused endothelial dysfunction and acute vasoconstriction, and exacerbated myocardial ischemia (43,44,56,59,73,74). Increased concentration of C-reactive protein is a biomarker of systemic inflammation and an independent predictor of cardiovascular disease (75,76). Systemic inflammation is a well-known risk factor for developing atherosclerosis (77). Pro-thrombotic changes in blood and endothelial dysfunction and acute changes in vascular tone are important factors in triggering and/or exacerbating ischemic heart disease (78).

ROS and the cardiovascular system. In lungs, particulate air pollutants were shown to trigger pro-inflammatory signaling via an ROS-dependent mechanism (64–69). Considering the possibility that UFPs are capable of reaching the heart and other remote organs via the vasculature (79), particle-mediated toxic effects could be realized at the level of the heart and cardiac vessels. Reactive oxygen species generation in the heart muscle and/or in the endothelial cells could be one of the mechanisms responsible for the toxic effects of UFPs.

Increased amounts of ROS were shown to be closely involved in myocardial stunning, necrosis, vascular dysfunction, and apoptosis, and some of their effects were effectively blocked by free radical scavengers (80,81). In clinical settings, ROS were linked to the arrhythmias observed in patients undergoing coronary artery bypass surgery and were suggested to be involved in the pathogenesis of heart failure (82–84).

Among other pathological cardiovascular conditions triggered by or developed with the direct involvement of ROS, atherosclerosis is a noteworthy one (85).

Particulate air pollutants and ROS in the heart. Inhalation exposure to CAPs resulted in an increase in the in situ chemiluminescence (a measure of ROS generation) in rat lungs and heart (86). Intratracheal instillation of urban air particles (UAPs) or inhalation exposure to CAPs resulted

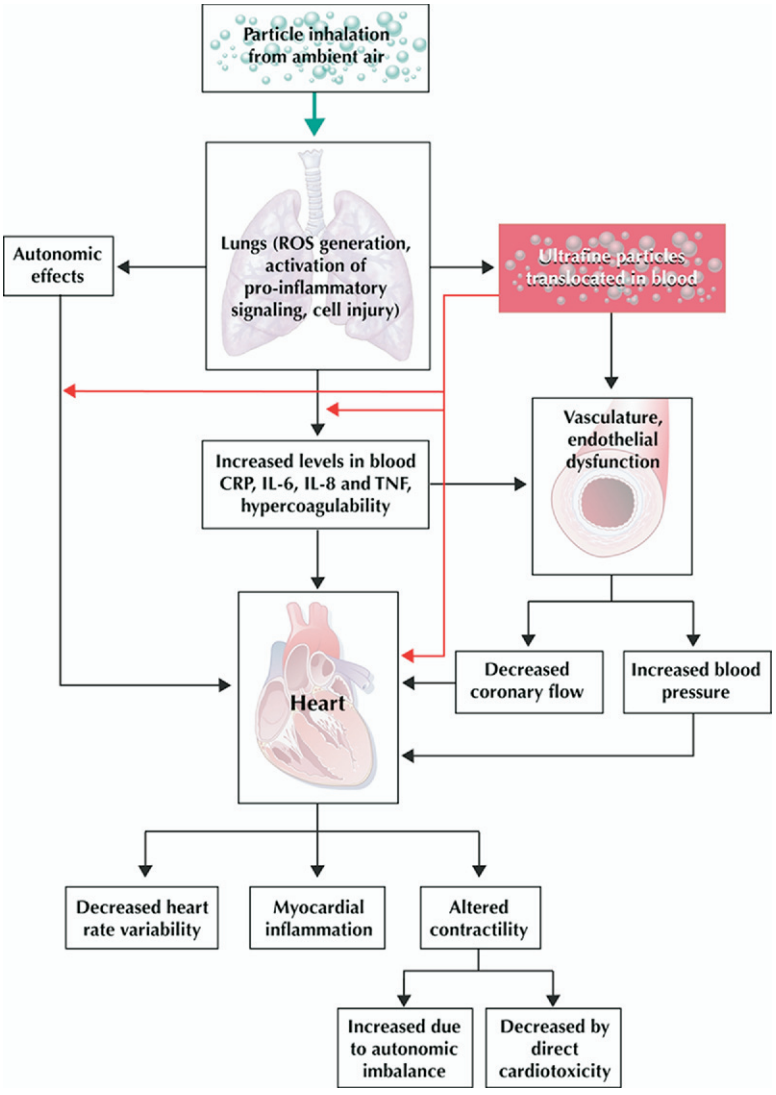

Figure 1 **Pathophysiological Mechanisms of Lung- and Circulation-Mediated Cardiovascular Toxicity of Particulate Air Pollutants**

Inhaled ambient air particles increase production of reactive oxygen species (ROS) in the airways and lung alveoli and stimulate local inflammatory reaction in the lungs. The ROS and pro-inflammatory cytokines released into the blood stream affect autonomic cardiac control (heart rate, heart rate variability, and cardiac contractility), blood pressure, vascular tone and reactivity, blood coagulability, and progression of atherosclerosis. Ultrafine particles may translocate into the circulation and induce oxidative stress and pro-inflammatory changes directly in the cardiac muscle and vasculature. Lung- and circulation-mediated and direct pathophysiological mechanisms exacerbate myocardial ischemia and increase cardiovascular mortality. CRP = C-reactive protein; IL = interleukin; TNF = tumor necrosis factor. Figure illustration by Rob Flewell.

in increased oxidative stress in the heart and was accompanied by increased HRV 30 min after the exposure. The antioxidant N-acetyl cysteine prevented both the accumulation of oxidants and changes in the HRV caused by UAPs. Both the beta-1 adrenergic antagonist (atenolol) and the muscarinic receptor antagonist (glycopyrrolate) given before the instillation of UAPs prevented oxidative stress caused by particulate pollutants. These results were also confirmed with inhalation exposure to CAPs. The authors concluded that particulate pollutants caused oxidative stress via changes in autonomic signaling, and changes in the levels of oxidants are associated with alterations in HRV (87).

Intra-tracheal instillation of diesel exhaust particles in rats abolished the protective effect of ischemic pre-conditioning against reperfusion arrhythmias. The protective effect of ischemic pre-conditioning was restored when rats were given intravenous injections of superoxide dismutase (88). These results indicated that pollutants from the diesel exhaust might affect the heart muscle via ROS-mediated mechanism. The involvement of ROS in cardiac injury was also confirmed in experiments showing that direct cardiotoxic effects of diesel

exhaust particles in neonatal rat cardiomyocytes could be attenuated by free radical scavenging systems (89).

Particulate air pollutants and ROS-mediated effects on the vasculature. Diesel exhaust particles were shown to inhibit endothelium-dependent relaxation in rat thoracic aorta via a free radical–dependent mechanism (90). The ROS-mediated effects of particles on endothelial cells might be associated with the toxic organic components present in PM. The direct cytotoxic effects of organic compounds from diesel exhaust particles on cultured human pulmonary artery endothelial cells were attenuated by free radical scavengers and antioxidants (91). Induction of oxidative stress in endothelial cells from the rat heart vasculature was also reported for organic extracts of PM2.5 (92). An ROS-related mechanism for particle-induced impairments of vascular tone and reactivity was suggested in clinical studies involving both healthy volunteers and patients with type II diabetes (42,56).

Direct and acute effects of ultrafine air pollutants. It has been suggested that after inhalation exposure ultrafine particles may translocate into the blood stream and can be found in remote organs (e.g., the heart) (79). This finding suggests that UFPs could induce direct cardiovascular toxic effects independent of their passage through the lungs. In an in vivo experiment, UFPs isolated from ambient air and injected intravenously to anesthetized rats caused an increase in the left ventricle ejection fraction without affecting the heart rate (93). This circulation-mediated effect could be attributed either to an increase in sympathetic tone or to a direct inotropic effect of ultrafine air pollutants. The observed increase in the ejection fraction has the potential to be harmful in patients with pre-existing coronary artery disease by increasing oxygen demand in the setting of impeded oxygen supply. Intravenous injection of UFPs isolated from the exhaust of a small diesel caused premature ventricular beats. When UFPs from the same source were directly instilled into the perfusion line of isolated Langendorff-perfused rat hearts, both cardiac contractility (+dP/dt) and coronary flow were dramatically decreased (by 66% and 32%, respectively) (93). The direct and acute effects of UFP most likely could be explained by their ability to generate ROS, which were shown to cause both myocardial stunning and endothelial dysfunction (80,81,90).

The comparison of the in vivo data (increased ejection fraction) versus the in vitro data (direct cardiodepressant effects) indicates that resultant cardiac effects of UFPs might depend on the combination of their circulation-mediated and direct cardiotoxic mechanisms. Figure 1 presents possible mechanisms of lung- and circulation-mediated cardiotoxicity and direct cardiac effects of ambient air pollutants.

The direct and acute effects of UFPs were confirmed in Langendorff-perfused hearts obtained from young adult and old Fisher 344/Brown Norway rats and in hearts from spontaneously hypertensive rats (SHR) and their respective control subjects (i.e., Wistar-Kyoto rats). Young and old hearts demonstrated equal functional deterioration and equal decreases in coronary flow in response to UFPs introduced directly into the cardiac vasculature via the Langendorff perfusion line, and the response to the cardiotoxic effects of UFPs was not worsened in the hearts from spontaneously hypertensive rats (94,95). In summary, these studies indicate that UFPs can directly and acutely affect cardiac contractility and coronary flow independently of lung-mediated mechanisms and that the direct cardiotoxic effects are unaffected by age or preexisting cardiovascular disease.

Conclusions

Data from numerous studies unequivocally indicate that air pollution is directly linked to the adverse cardiovascular outcomes in the general population, and effects are seen at levels at or below existing air quality standards. The major strategy in decreasing the harmful effects of air pollution is the reduction of air pollutants themselves. However, studying the epidemiology and the mechanisms of air pollution–related health effects (including cardiovascular toxicity) will possibly identify specific causal agents that can be better regulated and increase the effectiveness of our efforts to reduce the risk of developing air pollution–related health problems.

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