Air Pollution
An Insidious and Pervasive Component of Cardiac Risk
Richard L. Verrier, PhD; Murray A. Mittleman, MD, DrPH; Peter H. Stone, MD

It has long been appreciated that fine particulate air pollution contributes to the pathology of respiratory disease and cancer.1,2 The more elusive link to cardiovascular disease, however, has been recognized only in the last decade. Epidemiological1–5 and experimental laboratory6 evidence has been mounting that supports the postulate that elevated concentrations of particulate air pollution contribute to cardiovascular morbidity, hospitalization, and mortality.

A major challenge to systematic study in this field is the complexity of the particulate components of air pollution. Ambient air particulate matter (PM) consists of a mixture of combustive byproducts and resuspended crustal materials, as well as biological materials such as pollen, endotoxins, bacteria, and viruses. Regulated airborne particulates are generally classified by aerodynamic diameter, as coarse (PM10, 2.5 to 10 μm), fine (PM2.5, <2.5 μm), or ultrafine (PM0.1, <0.1 μm). Ultrafine particles come directly out of smokestacks and tailpipes and grow rapidly into the fine size range. Thus, fine particles result primarily from combustion sources, whereas coarse particles result primarily from mechanical crushing, grinding, or abrasion of surfaces. Particles <10 μm in diameter1 and, especially, finer particles <2.5 μm in diameter1–2.5 have been most commonly associated with cardiovascular risk.

Every geographic region has a unique blend of particulate air pollution. Health risks due to ambient air particles have been documented not only in cities that are considered among the most heavily polluted, such as Los Angeles, Houston, and Steubenville, Ohio,1,4 but also in cities that are considered to have relatively clean air, including Boston,1,5 Seattle, and Minneapolis.4 Current data from the Environmental Protection Agency project that, nationwide, as many as 60 000 deaths annually are related to particulate air pollution.7 Pope and colleagues2 concluded from mortality data on 500 000 deaths throughout the United States between 1979 and 2000 that for every 10-μg/m3 increase in fine particles (PM2.5), all-cause mortality increased by 6% annually and cardiopulmonary mortality by 9%. A lesser increase in all-cause mortality (by 0.51%) and in cardiorespiratory mortality (by 0.68%) has been observed4 for every 10-μg/m3 increase in coarser particles (measuring up to 10 μm in diameter).

It has recently been demonstrated that inhaled fine particles can be detected within minutes of exposure in the systemic circulation, where they can persist for hours, providing a route of entry into all organ systems.8 This observation points to a plausible pathway for health effects of inhaled particles. Several important cardiovascular effects have been documented, including disruption of autonomic nervous system activity by decreased heart rate variability,9,10 arterial vasoconstriction,11 cardiac arrhythmias in patients with implantable defibrillators,12 cardiac events including myocardial infarction5 that required hospitalization,3 and exacerbation of ST-segment changes in experimental models of myocardial infarction.6 A significant role has been suggested for increases in inflammatory mediators, as evidenced by C-reactive protein, increased white cell counts, and plasma viscosity,13--16 arising as a result of cytokine production linked to deposition of particulate matter in the airways and alveoli. The potential involvement of inflammatory mediators is central to the concept of plaque vulnerability in the occurrence of acute cardiovascular events.17 In addition to these acute events, chronic effects after exposure to high levels of air particulates have been reported. Suwa and colleagues18 recently observed in rabbits that exposure to high levels of air pollution particulate matter is associated with progression of atherosclerotic lesions with greater volume, increased plaque cell turnover and extracellular lipid pools in coronary and aortic lesions, and greater total lipid content in aortic lesions. These factors may all contribute to increased plaque vulnerability.

In the present issue of Circulation, Pekkanen and colleagues19 present the results of the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. In this investigation, the authors followed a cohort of patients with established coronary heart disease with biweekly submaximal exercise tests over a 6-month period. They observed among subjects in Helsinki that the risk of developing ischemia during exercise was significantly elevated at 2 days after exposure to increased environmental levels of fine particulate air pollution, with the strongest effects for PM1.1 and PM2.5. The importance of this observation is that it highlights myocardial ischemia as a significant potential mechanism responsible for the adverse cardiac outcomes associated with poor air quality. It remains unclear whether ischemia contributes to the adverse cardiac outcomes observed in epidemiological studies through a mechanism...
related to plaque rupture leading to an acute coronary syndrome and/or to precipitation of life-threatening arrhythmias.

It is noteworthy that the myocardial ischemia provoked by exercise in the setting of poor air quality occurred only with substantial increases in heart rate. At the Helsinki site, the mean heart rate rose from 61 to 90 bpm, an increase to 53% of maximum predicted heart rate for age. Forty-seven percent of the patients never developed ST-segment depression during any of their exercise sessions, and it is not noted whether those patients who developed ST-segment depression were the same individuals whose heart rates increased most with exercise. Only 1 ECG lead, V5, was monitored for ischemic ST-segment depression during exercise, and it is possible that additional ischemic episodes in other patients would have been identified if more leads had been analyzed. In the other two ULTRA sites, the staff members were reluctant to challenge their patients physically and there were considerably smaller increases in heart rate. Consequently, ST-segment depression did not occur frequently in these patients.

In the patients who developed ST-segment depression with exercise, it would be valuable to know if the “ischemic threshold” (heart rate × blood pressure at the onset of ST-segment depression) varied with the severity of air pollution. Unfortunately, the roles of blood pressure and the rate-pressure product were not systematically studied. Because ischemia during outpatient daily activities occurs at lower heart rates than during a supervised exercise test, it would also be important to know whether episodes of myocardial ischemia were recorded with ambulatory ECG (Holter) monitors during routine daily activities in these patients. It may be possible that the cardiac risk identified by Pekkanen et al19 during the exercise tests represents only a small amount of the actual ischemic risk that these patients encounter throughout the day. Variations of the ischemic threshold at different times would imply that air pollution is adversely affecting the coronary endothelium and leading to different degrees of vasoconstriction. Furthermore, other factors may play a role in pollution-induced changes in oxygen supply and myocardial perfusion. The candidate mechanisms include changes in plasma viscosity,15 hematocrit factors,13,14 and alterations in endothelial function,11,18 which could occur as a result of oxidant stress19 or disruption due to inflammatory consequences of air pollutants.

Whereas this study by Pekkanen and colleagues19 indicated an important association between particulate air pollution and exercise-induced myocardial ischemia, it has left unanswered several questions. Although the original protocol was designed to evaluate patients in 3 cities, the final report included data from 45 subjects evaluated in a single city over a 6-month time frame. The 22 subjects who had either no episodes of ischemia or episodes at every visit did not provide information about the relationship between air pollution and myocardial ischemia. Thus, all of the inferences are based on 23 patients, a relatively small sample size, leaving open the question of robustness of the results and generalizability of the findings and requiring further verification in larger populations in a variety of cities with differing mixtures of particulate air pollution.

As is the case for any novel investigation, the study by Pekkanen and coworkers19 raises more questions than it answers. Foremost among the questions to be addressed is the identification of the specific particles responsible, including their size, composition, and origin, as differential effects based on these characteristics would be anticipated. Further investigations to provide additional verification and a mechanistic framework must be explored on multiple levels, including epidemiological studies with detailed individual level data, clinical studies to evaluate further the physiological and pathophysiological responses in various populations, studies of exposure assessments in experimental models to evaluate potential effects of specific toxins, and studies at cellular and subcellular levels to evaluate effects on oxidation products and plaque vulnerability. Promising targets of investigation would also include effects on the autonomic nervous system and on the endothelium, coronary vascular resistance, and reactivity. The present study is focused on patients with known cardiac disease. It is unclear whether the risk is present only in those coronary artery disease patients with provokable ischemia during exercise testing. It will also be important to determine whether other patient populations are also susceptible, such as those with diabetes20 or pulmonary disease. The current investigation also suggests that patients with a history of myocardial infarction may have higher risk and those taking β-receptor blocking agents a lower risk; however, the relatively small sample size leads to wide confidence intervals and imprecise estimates of effects in these subgroups, making the subgroup analyses intriguing but inconclusive. Given the key feature that air pollutants can induce inflammation in the lung and potentially in the vascular endothelium, antiinflammatory agents and antioxidants are worth of evaluation.

The problem of particulate air pollution is pervasive and growing. An even greater concomitant toll on public health from this insidious contributor to cardiac disease can be anticipated. The American Heart Association, National Institutes of Health, and regulatory agencies have an important opportunity through education, funding, and regulation of clean air standards to exert a major impact on cardiovascular health.

Acknowledgment

Supported by National Institutes of Health National Institute of Environmental Health Sciences grants P01 ES 09825 and P01 ES 08129 (Bethesda, Md).

References


**Key Words:** Editorials cardiovascular diseases ischemia risk factors air pollution
Air Pollution: An Insidious and Pervasive Component of Cardiac Risk
Richard L. Verrier, Murray A. Mittleman and Peter H. Stone

Circulation. 2002;106:890-892
doi: 10.1161/01.CIR.0000027434.34445.23
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/106/8/890

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/