Epidemiologic Evidence of Cardiovascular Effects of Particulate Air Pollution

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In the past decade researchers have developed a body of epidemiologic evidence showing increased daily cardiovascular mortality and morbidity associated with acute exposures to particulate air pollution. Associations have been found not only with cardiovascular deaths reported on death certificates but also with myocardial infarctions and ventricular fibrillation. Particulate air pollution exposure has been associated with indicators of autonomic function of the heart including increased heart rate, decreased heart rate variability, and increased cardiac arrhythmias. Several markers of increased risk for sudden cardiac death have also been associated with such exposures. These epidemiologic studies provide early guidance to possible pathways of particulate air pollution health effects, which can only be addressed fully in toxicologic and physiologic studies. *Key words*: air pollution, cardiovascular disease, epidemiology, particles. — *Environ Health Perspect* 109(suppl 4):483–486 (2001).
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Scientific and policy interests in the health effects of particulate air pollution have increased dramatically in the past decade in response to numerous epidemiologic reports of increased daily mortality associated with episodes of particulate air pollution (*1*,*2*). In a recent comprehensive analysis of daily mortality and particulate air pollution in 90 U.S. cities, Samet and colleagues (*3*–*5*) confirmed that these associations were real, robust, and not confounded by weather; furthermore, these particle effects were independent of the effects of other co-pollutants. Analyses by cause of death generally find larger relative risks for respiratory deaths. For example, in a combined analysis across six eastern U.S. cities, each 10-μg/m^3 increase in fine particle mass [particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$)] was associated with an increase in total mortality of 1.7%, compared to an increase of 3.3% in chronic obstructive pulmonary disease deaths and 4.0% in pneumonia deaths (*6*). Increased relative risks are also generally reported for cardiovascular deaths (*1*). In the combined six-city analysis, $PM_{2.5}$ was associated with a 2.1% increase in ischemic heart disease deaths. Respiratory deaths (chronic obstructive pulmonary disease, pneumonia, influenza) accounted for only 8.5% of all deaths in the United States in 1997, while cardiovascular deaths (heart, cerebrovascular, and arterial diseases) accounted for 39.5% (*7*). Thus, while the relative effects of particulate air pollution are larger for respiratory than for cardiovascular deaths, the numbers of deaths attributable to particulate air pollution are much larger for cardiovascular than for respiratory causes. Understanding the mechanisms by which these particle exposures produce sudden cardiac events is important not only scientifically but also in risk assessment and in setting public policy. Epidemiology cannot show causation, but innovative study designs do provide insights into possible causal pathways.

Several years ago several colleagues and I investigated possible mechanisms by which particles deposited in the lungs might produce an immediate, fatal cardiac event. We hypothesized that particle exposures might interfere with oxygen transport and that the resultant hypoxemia might trigger cardiac arrhythmias. To test this hypoxemia hypothesis, we recruited two panels of elderly subjects living in Utah Valley, Utah (*18*). One panel consisted of emeritus faculty from Brigham Young University and their spouses living in Orem and Provo. The other panel consisted of residents in an assisted living facility in Orem. Members of the first panel measured their oxygen saturation twice daily (on arising and before retiring) with a pulse oximeter. Pulse rate, oxygen saturation, date, and time were automatically recorded. Residents of the retirement community had the same measurements made once a day—after the evening meal.

This locale was chosen as the source of the sample population for several reasons. First, Utah Valley has frequent temperature inversions during the winter, which lead to elevated particulate air pollution episodes. Air pollution [particulate matter with a mass median aerodynamic diameter less than 10 μ (PM_{10}) and carbon monoxide] is routinely measured at multiple sights in the Valley. Second, the Valley is at a high elevation, about 1,400 m above sea level (average barometric pressure 656 mmHg). Thus, these subjects have decreased oxygen tension because of the decreased partial pressure of oxygen. Because they are on the steep side of the oxygen dissociation curve, these subjects would be expected to show more variability in their oxygen saturation than subjects at sea level. Third, the rate of smoking, a major source of reduced oxygen saturation due to carboxyhemaglobin, is very low in this community. Finally, increased cardiovascular deaths associated with PM_{10} concentrations had been convincingly demonstrated previously in the same community (*9*).

Daily oxygen saturation measurements were collected from 90 subjects for 3 months during the winter of 1995 and 1996. We found a strong positive correlation between barometric pressure and daily mean oxygen saturation of the subjects (*8*,*10*). This observation demonstrated that with the study design used, even this crude measure of hypoxemia could detect the expected physiologic link between partial pressure of oxygen in the air and oxygen saturation of the blood. Nevertheless, we found no association of oxygen saturation of the blood with PM_{10} (or carbon monoxide) concentrations (*9*). Thus, this study suggested that hypoxemia was not a factor in the mechanistic pathway between PM air pollution exposures and cardiac deaths.

In addition to oxygen saturation, the pulse oximeter also recorded pulse rate. Not wanting to waste good data (and not being averse to analyzing data outside the primary hypothesis), we analyzed the association of pulse rate and PM_{10} concentrations. To our surprise, we found a statistically significant positive association between increased pulse rate and PM_{10} (*9*). The magnitude of this effect in terms of increased beats per minute was physiologically small (0.8 beat per minute increase for 100 μg/m^3 increase in PM_{10} on the previous day). However, we also

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In this article the author describes a series of investigations over the last decade. The presentation suggests a continuous line of reasoning only apparent post hoc. Indeed, these investigations have been the result of long and intensive collaborations between researchers at the Harvard School of Public Health and colleagues from other institutions. A partial listing of researchers include J.D. Godleski, D.R. Gold, M. Mittleman, L.M. Neas, A. Peters, C.A. Pope III, M. Raizenne, F.E. Speizer, J. Schwartz, C. Shy, P.H. Stone, and R. Verrier.

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found a significant increase in a clinically relevant marker, i.e., the number of subjects whose heart rate increased by more than 5 beats and also by 10 beats per minute (increase of 29% and 95%, respectively, for an increase of 100 μg/m^3 in PM_{10} on the previous day). Thus, although we disproved our original hypothesis of particulate-induced hypoxemia, we had the suggestion of a potential autonomic link. In a long-term prospective study of myocardial risk factors in Augsburg, Germany, Peters et al. (*11*) reported increased heart rate in the participants who were examined during a major air pollution episode.

Separately, studies of dogs exposed to concentrated ambient air particles by our colleagues at the Harvard School of Public Health (*12*) showed morphologic changes in electrocardiograms (ECGs) during and after exposure to concentrated ambient particles. In collaboration with those investigators, we designed a pilot study to assess whether similar electrocardiographic changes could be observed in free-living humans. We borrowed several Holter monitors; Pope and his colleagues in Utah convinced six of the participants in the oximetry study plus one of the field technicians to wear an ambulatory ECG monitor for 24–48 hr on up to three occasions (*10*). The plan was to measure ECGs on each subject before, during, and after the PM_{10} episodes. Luckily, soon after we began the ECG monitoring, PM_{10} concentrations rose to the highest levels of the winter (maximum 147 μg/m^3). A change in air mass then cleared the Utah Valley and very low levels of PM_{10} continued for the rest of the winter. Thus, electrocardiographic data were collected over a wide range of PM_{10} exposures for each subject.

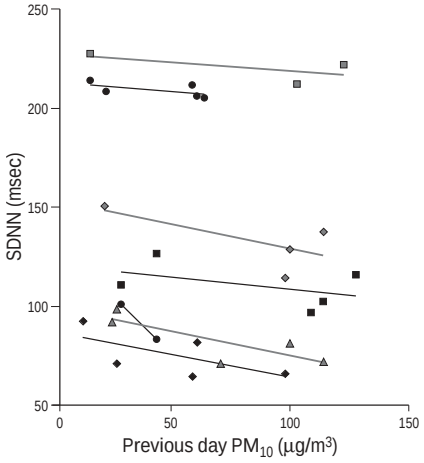

Figure 1. Twenty-four hour mean SDNN versus PM_{10} pollution levels (μg/m^3) and individual regression lines for seven individuals followed in Utah Valley. Symbols indicate different individuals (n = 7). Data from Pope et al. (*8*).

We calculated the daily average pulse rate and the standard deviation of the intervals between normal beats (SDNN). As a measure of heart rate variability, the SDNN is an indicator of autonomic tone that is a gross measure of how well the heart can respond to external stress. SDNN generally decreases with age. It is also lower during illness. Low SDNN is associated with poor cardiovascular prognosis (*13,14*). Among the seven participants in the Utah Valley ECG study, there were large differences in individual SDNN (*10*). However, for each individual, SDNN decreased with increasing PM_{10} concentrations (Figure 1). Thus, this small pilot study suggested that particulate air pollution was associated with reduced heart rate variability in these healthy, elderly subjects. We also learned that these study subjects, although highly motivated and committed to this study, found the repeated 24-hr Holter monitoring of ECGs to be very burdensome, and so an alternative data collection procedure would be required if we were to collect similar data in the future.

An alternative, more acceptable study design was to measure ECG with an ambulatory monitor repeatedly for a short period under controlled conditions. In a pilot study of 21 subjects living in a Boston, Massachusetts, residence for the elderly, ECGs were measured once a week during the summer of 1997 (*15*). ECGs were measured during a defined 30-min assessment during which the subjects engaged in 5-min periods of lying down, sitting up, standing, walking outside, sitting, and paced breathing. Analysis of the data gathered showed that fine particle concentrations in the 4 hr before ECG monitoring were associated with decreased heart rate variability. Researchers at the U.S. Environmental Protection Agency also reported particulate air pollution exposures were associated with decreased heart rate variability in panels of elderly subjects in Baltimore, Maryland (*16*).

These panel studies provide repeated snapshots of cardiac function at a specific time during the day. There is interest, however, in continuous ECG monitoring of vulnerable subjects, since most tachyarrhythmias occur at night or during the early morning. Cardiac patients with evidence of arrhythmias often have implanted devices that continuously measure their ECGs. For example, a growing number of cardiac patients have received implanted cardioverter defibrillators (ICDs). The ICD is implanted under the skin on the shoulder; an electrode is passed from the defibrillator through a vein into the right side of the heart, and attached to the ventricular wall. These devices actively monitor cardiac rhythm for abnormalities. Upon detection of a sustained ventricular tachycardia or ventricular fibrillation, the ICD can initiate a range of therapies, from pacing shocks to cardioverter shocks, to restore proper electrical function.

Patients return for clinical follow-up every 3 to 4 months, or in some cases whenever they are aware of a therapeutic discharge by the device. The dates, times, and characteristics of any detected arrhythmias and therapies are recorded automatically by the ICD and are downloaded in the clinic by radio links. Thus, these patients are passively monitored continuously for cardiac arrhythmias and the dates and times of any events are recorded as part of their routine clinical management.

We evaluated the utility of the data from the ICD as an indicator of acute cardiovascular response to air pollution in a pilot study in Boston (*17*). The dates and times of ICD discharge events were abstracted for a panel of 100 patients who live in the Boston area who were followed at the Beth Israel Deaconess Medical Center Device Clinic. The probability of a therapeutic intervention on any given day was compared to the daily measures of air pollution. We observed that an 18-μg/m^3 increase in 5-day mean $PM_{2.5}$ was associated with a 22% increase in the probability of an

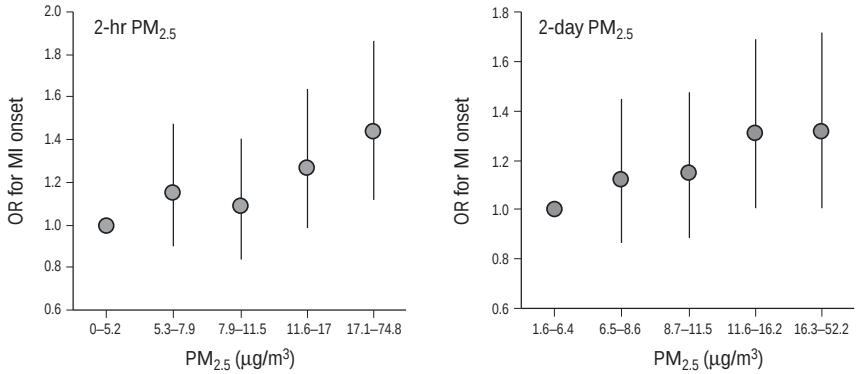

Figure 2. Odds ratio and 95% confidence interval for implanted cardioverter defibrillator discharge versus quantities of $PM_{2.5}$ exposure estimated for previous 2 hr and days simultaneously. MI, mycocardial infarction; OR, odds ratio. Data from Peters et al. (*17*).

ICD discharge. Stronger associations were found with black carbon particle mass and nitrogen dioxide exposures, all indicators of automobile and truck emissions. Thus, we had evidence that suggested that air pollution episodes could stimulate acute cardiovascular arrhythmias, which if not detected or corrected by the implanted cardioverter defibrillators, might have resulted in sudden death.

These observations led to analyses of the role of air pollution in the onset of myocardial infarctions, using data from an existing study. In that study, survivors of confirmed myocardial infarctions were interviewed in the hospital as soon as possible after admission to determine the time of onset of symptoms and their activities immediately before the onset (*18*). The risk of specific activities was estimated using a case-crossover analysis in which activities immediately before the onset of symptoms were compared to activities in matched periods. This study documented, for example, the increased risk of exercise (*19*), stress (*20*), anger (*18*), and cocaine use (*21*) on the onset of myocardial infarctions. We applied the same strategy to assess the risk of acute air pollution exposures for periods immediately before onset of myocardial infarctions with matched control periods (*22*). Data were available for 833 patients with confirmed myocardial infarction in the greater Boston area for 1995 and 1996. Hourly $PM_{2.5}$ concentrations were available for the same period from a single monitoring site in Boston. We found an increased risk of myocardial infarction for the 1–2 hr following an elevated $PM_{2.5}$ exposure and separately for the 1–2 days after an elevated 24-hour mean $PM_{2.5}$ exposure. Although $PM_{2.5}$ concentrations for these two time scales are clearly correlated, we found that these effects are separable and additive (Figure 2). This suggestion of immediate (2 hr) and delayed (2 days) response suggest that particles affect cardiovascular function by more than one mechanism.

The studies have provided further evidence that particulate air pollution exposures are associated with acute cardiovascular events. However, the studies do not identify the mechanism for these associations. Seaton et al. (*25*) suggested that particulate air pollution might act through pulmonary inflammation to trigger systemic hypercoagulability of the blood. Stone and Godleski (*24*) recently suggested that particle exposures might influence the sympathetic/parasympathetic balance, possibly through local inflammation in the lung or systemic inflammation. Is there evidence of systematic inflammation associated with particulate air pollution exposures?

Analysis of blood parameters measured in the MONICA study in Augsburg, Germany, has provided several interesting suggestions on the role of air pollution. The MONICA study was a large multinational prospective assessment of the effects of myocardial risks on survival. Subjects were assessed for cardiovascular function in 1984 and 1985 and again in 1987 and 1988. By chance a major air pollution episode affected the Augsburg study site in January 1985 during the first survey. Blood collected during this period has been compared to blood collected during other sample days in the 1984/1985 survey and to follow-up periods for the same individuals. Peters and colleagues (*25*) initially reported higher plasma viscosity of blood samples during the Augsburg air pollution episode. Recently, they reported higher average levels of C-reactive protein (CRP) during the air pollution episode (*26*), and that the odds of having a high CRP level (> 90th percentile) increased with total suspended particle levels (Figure 3). Recent studies have shown that elevated CRP concentrations, a marker of cell damage and inflammation, are associated with substantially increased risk of sudden cardiac death (*27*). These results suggest a new line of investigation in which serum markers would serve as early markers to response to particulate air pollution.

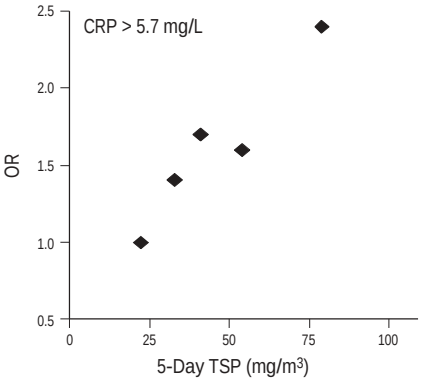

Figure 3. Odds ratio for serum CRP level greater than 5.7 mg/L (90th percentile) versus total suspended particulate (TSP) concentrations in Augsburg, Germany. Data from Peters et al. (*26*).

Table 1. Observed epidemiologic associations between short-term particulate air pollution exposures and cardiovascular effects.

Time–series studies
↑ Cardiovascular mortality
↑ Cardiovascular hospital admissions
Autonomic cardiac function in elderly
↑ Pulse rate
↓ Heart rate variability
Implanted cardiac defibrillators
↑ Cardiac arrhythmias
Case-crossover studies
↑ Onset of myocardial infarction
Serum indicators of systemic response
↑ Inflammatory markers

The earliest studies of particulate air pollution and daily mortality (*28–30*) suggested increased associations not only with respiratory deaths, but also with cardiovascular deaths. The weakness in using death certificate information to determine cause of death is well known. Therefore, the initial explanation was that these associations represented misclassification of respiratory disease as acute cardiovascular events. It is still likely that chronic (or acute) respiratory disease contributes to acute cardiovascular deaths. However, recent epidemiologic studies show that particulate air pollution exposures have a direct effect on autonomic function of the heart, as seen by changes in heart rate, heart rate variability, and cardiac arrhythmias (Table 1). Epidemiologic associations have been found not only with cardiovascular deaths identified from death certificates but also with clinically confirmed myocardial infarctions and ventricular fibrillation that required cardioverter interventions. New epidemiologic studies suggest associations with early serum markers of risk for sudden death, including coagulability and inflammation. The strong indications of increased risk for sudden cardiac events associated with particulate air pollution noted in the epidemiologic studies might have been expected based on recent observations from controlled animal exposures. On the other hand, the epidemiologic findings raise important questions that only can be fully addressed in toxicologic and physiologic studies.

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