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 cardiovascular deaths. For example, in a combined analysis across six eastern U.S. cities, each 10-µg/m³ increase in fine particle mass (particulate matter with aerodynamic diameter less than 2.5 µm (PM₁₀)) 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, PM₁₀ 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 µm (PM₁₀) 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 mm Hg). 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 carboxyhemoglobin, is very low in this community. Finally, increased cardiovascular deaths associated with PM₁₀ 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 PM₁₀ (or carbon monoxide) concentrations (9). Thus, this study suggested that hypoxemia was not a factor in the mechanistic pathway between PM₁₀ 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 PM₁₀ concentrations. To our surprise, we found a statistically significant positive association between increased pulse rate and PM₁₀ (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/m³ increase in PM₁₀ on the previous day). However, we also...
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/m² in PM₁₀ 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 these 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 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 PM₁₀ episodes. Luckily, soon after we began the ECG monitoring, PM₁₀ concentrations rose to the highest levels of the winter (maximum 147 µg/m²). A change in air mass then cleared the Utah Valley and very low levels of PM₁₀ continued for the rest of the winter. Thus, electrocardiographic data were collected over a wide range of PM₁₀ exposures for each subject.

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 PM₁₀ 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).

![Figure 1](image1.png)

**Figure 1.** Twenty-four hour mean SDNN versus PM₁₀ pollution levels (µg/m³) and individual regression lines for seven individuals followed in Utah Valley. Symbols indicate different individuals (n = 7). Data from Pope et al. (8).

![Figure 2](image2.png)

**Figure 2.** Odds ratio and 95% confidence interval for implanted cardioverter defibrillator discharge versus quantities of PM₂.₅ exposure estimated for previous 2 hr and days simultaneously. MI, myocardial infarction; OR, odds ratio. Data from Peters et al. (17).
Cardiovascular effects of particulate air pollution

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 recognized. 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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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 |
|--------------------|--------------------------|-----------------------------------|-------------------------------------|------------|-----------------------|-----------------------------------|---------------------|
| Short-term studies | Onset of myocardial infarction | Serum indicators of systemic response | Inflammatory markers |

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).
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