Focused Perspectives

Relative Effects of Air Pollution on Lungs and Heart
Robert L. Johnson, Jr, MD

It has been assumed that damage from exposure to tobacco smoke and other particulate air pollutants is imposed primarily on the lungs and is associated with increased morbidity and mortality rates in patients with preexisting lung disease. This is supported by a considerable amount of previous data, such as the mortality data from the December 1952 London smog disaster, which may have caused as many as 12,000 deaths, almost all in patients with preexisting lung disease. Total suspended particulate matter (PM) was as high as 3000 μg/m³. Similar patterns of elevated morbidity and mortality rates, primarily in patients with preexisting lung disease, have been documented in other acute episodes of air pollution in the past. However, evidence from the past 10 years shows that sudden increases in ambient air pollution can also rapidly raise morbidity and mortality rates in patients with existing cardiovascular disease, as much or more than the rise associated with lung disease. In the present issue of Circulation, Pope and associates report interesting new data on the effects on mortality rates, primarily in patients with preexisting lung disease, have been documented in other acute episodes of air pollution in the past. However, evidence from the past 10 years shows that sudden increases in ambient air pollution can also rapidly raise morbidity and mortality rates in patients with existing cardiovascular disease, as much or more than the rise associated with lung disease. In the present issue of Circulation, Pope and associates report interesting new data on the effects on mortality rate of long-term differences, as opposed to sudden transient increases, in levels of air pollution. Data were derived from a large, comprehensive study initiated by the American Cancer Society and linked to cancer prevention. The study involved a large population of subjects enrolled in 1982 from metropolitan centers in all 50 states and Puerto Rico. Vital status of participants was collected every 2 years for the subsequent 16 years, and a cause of death was identified for 98% of the known fatalities. Metropolitan area of residence was known for each participant, and particle counts of fine particulates were averaged over quarterly intervals throughout the year for each included metropolitan area. A questionnaire provided additional data, allowing for differences in mortality rate in response to pollution to be controlled for potentially confounding differences in age, sex, race, smoking, education, marital status, body mass, alcohol use, occupational exposures, and diet.

Unexpected Risk Ratios for Mortality
Cox proportional hazard regressions were derived to estimate risk ratios for mortality from identified causes of death relative to differences in regional levels of air pollution. Risk of death from cardiovascular disease (myocardial infarction, heart failure, and fatal arrhythmias) in response to chronically high levels of air pollution was much greater than that from lung disease. This observation is surprising on the basis of traditional views that the lungs are most affected by air pollution, even though awareness of air pollution as an important cause of death from cardiovascular disease has been increasing. Even more surprising is the finding that the risk ratio for death from chronic obstructive pulmonary disease (COPD) in “never” smokers tended to be <1.0 (ie, 0.83; 95% confidence intervals, 0.77 to 0.93), as if pollution by particulates conferred some protection against death from COPD. These new findings require some thought as to why causes of death from air pollution are apparently shifting from lung disease to cardiovascular disease. Some factors that can affect the outcome of a pollution study involving high levels of PM are listed below:

1. Differences in particle size, density, and shape.
2. Levels of tobacco use in the population at risk.
3. Differences between short-term and long-term study design.

Effect of Differently Sized Particulates on Deposition and Retention
Inhaled particulates usually are described in terms of aerodynamic size as ≤PM10 or ≤PM2.5 (Table 1). PM stands for particulate matter and the subscript for aerodynamic diameter (da) in micrometers. Aerodynamic behavior of particles (ie, rates of sedimentation and diffusion) depends not only on mean anatomic diameter (da) but also on particle density and shape. For a particle of a given da, shape, and density, da is the adjusted diameter required to maintain the same aerodynamic properties if specific density were 1.0 and shape were spherical. da is estimated as follows:

\[ da = d_a \left( \frac{6\pi}{k}\right) \left( \frac{\text{specific density}}{k} \right) \]

where k is an empirical shape factor. Particulates with the same da have approximately the same sedimentation rate and diffusion coefficient in the lung and penetrate to the same depth during a breath before deposition (Table 1). Particles >PM10 seldom reach the lung acinus; they are filtered out during inspiration by wall impact due to inertial forces at sites of turbulence in the nose or larynx or at branch points of conducting airways and ultimately are removed by ciliary action. Particles with da ≤2.5 μm and >0.1 μm are called fine particulates and are sedimented out in the gas exchange region of the lung (lung acinus), where air movement is slow. These particles tend to be retained in respiratory bronchioles within the central part of the acinus. Their removal from respiratory bronchioles is inefficient for lack of cilia and lack of an appropriate surface for efficient removal by macrophages. Thus, chronic particle retention and tissue remodel-
TABLE 1. Standard Description of Inhaled Pollutants

<table>
<thead>
<tr>
<th>Particle</th>
<th>Symbol</th>
<th>(d_a) (\mu m^*)</th>
<th>Deposition by</th>
<th>Site of Deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarse PM (_{10})</td>
<td>&gt;10</td>
<td>Wall impact</td>
<td>Conducting airways</td>
<td></td>
</tr>
<tr>
<td>Fine PM (_{2.5})</td>
<td>(\leq10,&gt;2.5)</td>
<td>Combination†</td>
<td>Combination†</td>
<td></td>
</tr>
<tr>
<td>Ultrafine PM (_{0.1})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.1</td>
<td>Diffusion</td>
<td>Alveoli</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Aerodynamic diameter takes into account particle density and deviation of shape from a simple sphere. A high-density particle has a \(d_a\) that is higher than its \(d_m\).

†Combined deposition by wall impact and sedimentation in conducting airways and respiratory bronchioles, respectively.

...ing is common in the central acinus, where centriacinar (or centrilobular) emphysema develops in smokers. Particles \(\leq0.1\ \mu m\) diameter are referred to as ultrafine and aerodynamically are too small to sediment out during normal breathing; however, they are deposited on alveolar walls by diffusion or are breathed back out again without deposition. They are rapidly removed by a combination of phagocytosis, lymphatic flow toward hilar nodes, and capillary blood flow, and they appear to not be retained in large numbers in the peripheral blood within 10 to 20 minutes. Similar transport into blood is reported after tracheal instillation of ultrafine, radioactively labeled colloidal albumin in hamsters.

Ultrafine particles probably are capable of causing much greater tissue damage than larger particles when deposited and may be the greatest source of elevated risk for death from ischemic heart disease or fatal arrhythmia. The lungs seem to provide rapid transport of these potentially damaging particles from inspired air to circulating blood. This is consistent with the significant increase in risk of triggering a myocardial infarction within 1 to 3 hours of a sudden increase in fine particulate pollution (\(d_a<2.5\ \mu m\)), and the increased risk may persist several days after the exposure. Increases in concentration of PM\(_{2.5}\) particulates also have been noted to cause mean heart rate to increase and to depress heart rate variability, suggesting altered autonomic control, which may be associated with higher risk of cardiac arrhythmias.

Diesel exhaust fumes are made up largely of fine and ultrafine carbonaceous particulates generated by incomplete combustion. Experimental intratracheal instillation of these particles in hamsters caused platelet activation in blood perfusing the lung and enhanced peripheral thrombosis in an experimental arterial and venous thrombosis model.

Pollutant particulates have been collected from the Los Angeles basin and separated into coarse, fine, and ultrafine particulates to compare their independent in vitro effects on macrophages. Ultrafine particles caused significantly greater oxidative stress and mitochondrial damage per microgram of particles—probably because of their smaller size, larger surface-to-volume ratio, and ability to penetrate into the cell interior and localize near mitochondria. Even small air microbubbles infused into the circulation will activate platelets and leukocytes at the air–plasma surface interface created and will induce pulmonary capillary leaks and edema.

Effects of a High Incidence of Smoking in the Population at Risk

In the study reported in this issue of Circulation by Pope et al, risk of death from different causes in response to increased pollution has been separated into that collected from “never,” “past,” and current smokers (see Tables 4 and 5 in Pope et al). Data from these tables summarize the most important and interesting observations from the article. Relative risk of death from cardiovascular and lung disease becomes reversed in magnitude between never smokers and current smokers. The difference is very large; risk of death from lung disease in current smokers increases by an order of magnitude compared with never smokers. In Table 2 of the present editorial, these data from Pope et al are compared with the mortality data from the 1952 London smog disaster summarized by Schwartz. Results from the 1952 London smog were not adjusted for smoking. Smoking undoubtedly was more prevalent in 1952 than in the 1980s, when the data reported by Pope et al were collected. Elevated risk ratios for death from COPD in current smokers from Table 4 of Pope et al are very similar to the fold increase in death from COPD in the London smog of 1952. When adjustment is made for current or past smoking, risk of death from lung disease falls to nothing or reverses. In patients with COPD, a risk ratio significantly less than 1.0 for death from COPD does not mean that air pollution is protective; more likely, it means that more of these patients are dying from pneumonia or from cardiovascular complications.

Short-Term Versus Long-Term Studies

In short-term studies of mortality from sudden increases in air pollution, recorded causes of death may represent premature triggering of an event that was about to happen anyway in patients with preexisting lung or cardiovascular disease. These short-term increases in mortality rate in response to transient increases in air pollution do not provide clear information on the role of air pollution on the natural progression of the disease, such as would be provided by a chronic elevation of blood cholesterol or a chronic smoking history. The study reported by Pope et al is a long-term study, comparing effects of differences in average quarterly pollution levels among metropolitan regions on causes of mortalities.
death from lung and cardiovascular disease. Such observations may provide evidence for or against an active role of long-term increases in air pollution on disease progression. It is here that the study provides the most interesting new information. By the elimination of the confounding issue of current and past smoking on mortality rate in Tables 4 and 5 of Pope et al, the overriding effect of smoking in the population at risk on mortality from air pollution becomes very clear. Eliminating smoking as a risk factor greatly reduces risk of death from both lung and cardiovascular disease, but this reduction is seen to a much greater extent in death from lung disease. The data also suggest that that a high incidence of smoking in the population at risk must have had a similar overriding effect on mortality from lung disease in many of the early short-term studies of air pollution disasters such as the London smog of 1952.

Conclusions

1. Chronically high levels of air pollution with fine and ultrafine suspended particulates constitute an important risk factor for progression of and death from cardiovascular disease in current smokers, past smokers, and never smokers.

2. Chronically high levels of air pollution appear not to be an important cause for increased risk of death from lung disease in never smokers, although this conclusion by Pope and his associates requires some reservations.

3. If the population at risk for high levels of chronic air pollution is made up of smokers, risk of death from lung disease is an order of magnitude greater than in a population of never smokers, whereas risk of death from cardiovascular disease is only about 50% to 70% higher. Thus, in a population of smokers, risk of death from lung disease becomes about 5 times higher than that from cardiovascular disease.

4. This explains why in much earlier studies of mortality from air pollution when incidence of smoking was very high, such as during the London smog of 1952, the risk of death from lung disease was very high (Table 2), but that from heart disease appeared insignificant.

5. These new findings should not be misinterpreted to indicate that high levels of air pollution have little or no effect on the lungs of never smokers. In never smokers, there is clear evidence that high levels of air pollution cause structural damage in the lung periphery and accelerate decline in lung function. Non-smokers exposed to high levels of air pollution will probably not die of COPD, but they may develop a higher-than-normal risk of death from pneumonia or influenza consistent with the present data.

References


Key Words: Focused Perspectives ▪ mortality ▪ smoking ▪ respiration ▪ air pollution
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Circulation. 2004;109:5-7
doi: 10.1161/01.CIR.0000110643.19575.79
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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