Editorial

Air Quality and Cardiovascular Health

Smoke and Pollution Matter

Annette Peters, PhD

Ambient particulate matter has been associated consistently with an increased risk for mortality largely due to cardiovascular diseases.[1] Although the relative risk estimates from epidemiological studies are small, they apply to almost the entire population of the United States. Consequently, exposure to ambient particles produces considerable burden of disease, and its mitigation offers the benefit of improving life expectancy.[2]

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Can Cigarette Smoke and Ambient Particulate Matter Be Compared?

Over the past decade, research has substantiated the understanding of the pathophysiological mechanisms linking ambient particles to the cardiovascular system[3,4] once it was noted that ambient air pollution elicits systemic inflammatory responses in the general population.[5] An update of the American Heart Association statement on air pollution and cardiovascular disease[3] is under way. Mechanisms considered for active and secondhand smoke as well as ambient air pollution are strikingly similar.[4,6,7] They include progression of atherosclerotic plaques to vulnerable forms, prothrombotic states, endothelial dysfunction, and altered autonomic nervous system control (Figure). Increased systemic oxidative stress is considered the key mechanism responsible for most of these pathophysiological changes. Increased risks for cardiovascular disease in general and coronary artery disease in particular have been documented for active and secondhand smoke as well as ambient particulate matter. Deep venous thrombosis has been added to this list recently.[8]

Nevertheless, the public health relevance of particulate matter in the light of the smoking literature remains hotly debated. Smokers are exposed to considerably higher cumulative doses of particulate matter than the general nonsmoking population. Mortality due to low doses of ambient particles may be considered counterintuitive compared with doses of particles tolerated by smoking individuals. A systematic assessment of the exposure-response function ranging from low doses of inhaled particles due to ambient air pollution to smoking of tens of pack-years of cigarettes with respect to cardiovascular disease morbidity and mortality has been missing. The article by Pope and colleagues[9] in this issue addresses this concern by estimating the cumulative dose of different degrees of smoking and the associated risk for cardiovascular disease mortality based on >1 million participants from the American Cancer Society Study II. They find that light smokers have only a small risk reduction compared with heavy smokers, indicating a flattening exposure-response function. Light smokers, who smoke ≤3 cigarettes per day, have a relative risk of 1.63 for ischemic heart disease mortality (95% confidence interval, 1.36 to 1.96), whereas smokers smoking ≥23 cigarettes have a relative risk of 1.97 (95% confidence interval, 1.86 to 2.10). However, heavy smokers are estimated to have 18-fold higher doses of fine particles, measured as particulate matter <2.5 μm ($PM_{2.5}$). Light smokers have 50- to 100-fold higher doses than daily exposure with 10 $\mu g/m^3$ $PM_{2.5}$ would exhibit. The relative risks for ischemic heart disease mortality based on the estimated cumulative doses calculated for ambient air pollution, secondhand smoke, and active smoke exposure fall on a straight line when a logarithmic scale for the exposure is applied. The resulting exposure-response function indicates a flattening curve. This observation raises the question of why smokers seem to be less susceptible. A flattening of the exposure-response function has also been observed for acute effects of particulate matter on all-cause mortality in locations with historically very high concentrations of ambient particles such as London, United Kingdom,[9] or the coal basin of the Czech Republic.[10] The consistently emerging shape of the exposure-response functions observed in studies of short-term and long-term exposures of particulate matter from various sources is puzzling and not well understood. It seems likely that we face a complex interplay of defense and tolerance mechanisms activated in response to particulate matter. In addition, one may hypothesize that smoking is only sustained by individuals who have a sufficient degree of defenses against the massive smoke exposure.

Pope and colleagues need to be highly complimented for this daring endeavor to find a scale on which these different estimates of particulate matter exposure can be integrated. Recent abatement of smoking in public places in Europe has had significant effects on hospital admissions for cardiovascular disease and in particular for coronary artery disease.[11,12] The benefit was present both in smokers and nonsmokers.[12] When this recent evidence is considered, it calls for sustained

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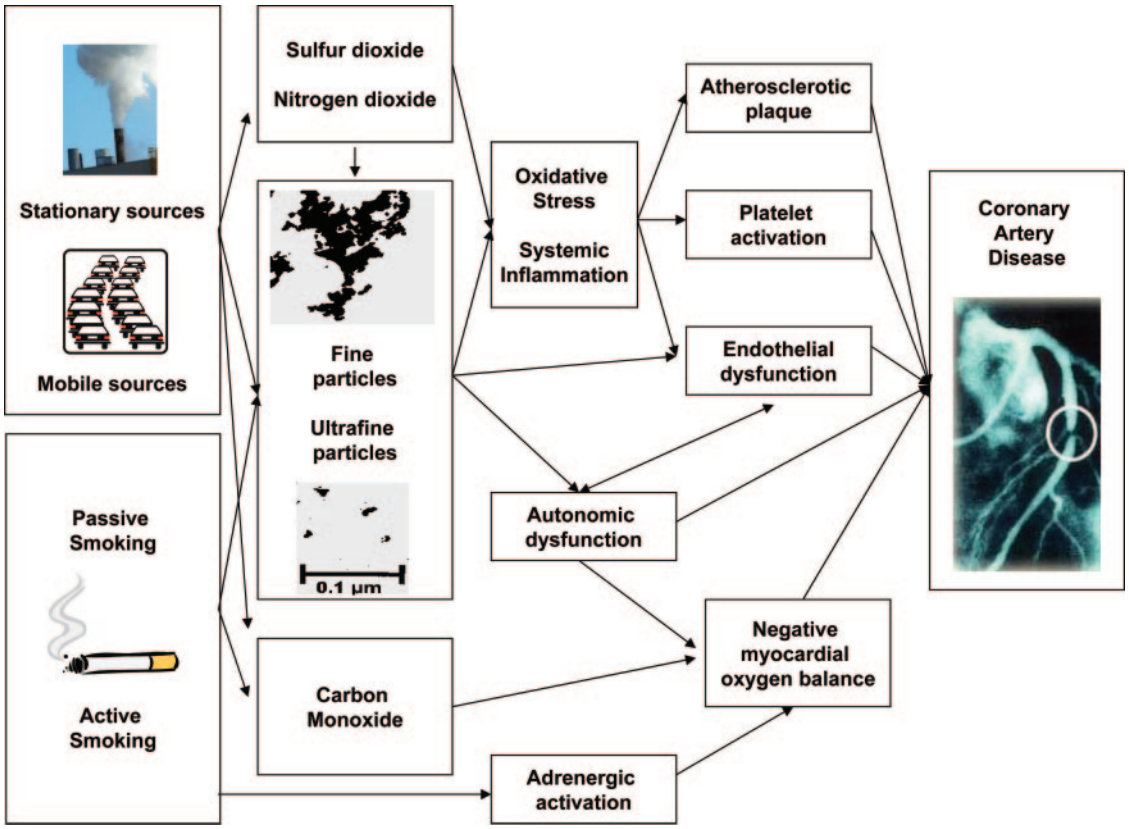

Figure. Overview on pathomechanism linking ambient air pollution,[4] secondhand smoke,[7] and active smoking to acute coronary syndromes.

efforts to reduce the exposure to particulate matter indoors and outdoors.

Aerosols: Studying Mixtures of Gaseous and Particulate Matter Pollutants

Outdoors as well as indoors, air quality is determined by the aerosol form, which is considered the particulate and the gaseous phase of air. Although recent research has focused on better understanding the widespread health effects of particles, the US Environmental Protection Agency regulates the gaseous pollutants carbon monoxide (CO), nitrogen dioxide (NO_2), ozone, and sulfur dioxide (http://www.epa.gov/air/criteria.html). These pollutants are considered to be adverse to human health (Figure) and, in addition, the standards enable to control air pollution from various sources of combustion.[13]

Ambient particulate matter has been associated consistently with hospitalization for cardiovascular disease on the basis of Medicare data for nearly the entire United States.[14] Emergency department visits provide the best timed data using administrative databases because time of admission is recorded and relatively close to the onset of the disease. The first publication on ambient air pollution and hospital admission by Schwartz and Morris[15] in 1995 assessed the impact of various pollutants, including CO, on hospital admissions.

The article by Bell and colleagues[16] published in this issue demonstrates an association between elevated CO concentrations and same-day hospital emergency department visits in 126 US counties. The authors accumulated a large database over a recent 6-year period (1999–2005) with a median number of nearly 75 000 daily emergency department visits across the entire United States. Although the daily minimum levels for 1-hour maximum CO concentrations were comparable between counties, high levels varied considerably. The risk for hospital admission increased 0.96% (95% posterior interval, 0.79% to 1.12%) when CO was considered alone in the model. Adjustments for NO_2 halved the estimated risk and reduced it to 0.55% (95% posterior interval, 0.36% to 0.74%), whereas the NO_2 concentrations themselves remained as well associated with the emergency department visits at 1.34% (95% posterior interval, 1.06% to 1.62%). The association between CO and emergency department visits remained positive and robust even after adjustments for $PM_{2.5}$ and elemental carbon. The extensive statistical analyses indicate that for consideration of pollutant mixtures, CO is an important component.

Air Quality Standards for Carbon Monoxide: An Overlooked Component of the Mixture?

Current air quality standards in the United States adopt the World Health Organization guidelines of 2000,[13] indicating limit values at 9 ppm daily 8-hour maximum CO concentrations but enforcing 35 ppm as 1-hour maximum CO concentrations instead of 26 ppm (http://www.epa.gov/air/criteria.html).

Although these limit values are well attained within nearly all US counties, they are clearly above the levels at which Bell and colleagues describe an association with emergency

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department visits due to cardiovascular diseases. The association between CO and emergency department visits does not seem to have a threshold at low concentrations, and the exposure response function seems to be linear at the lower end of the distribution.

The World Health Organization guideline values "are based on the Coburn-Foster-Kane exponential equation, which takes into account all the known physiological variables affecting carbon monoxide uptake. The . . . guideline values . . . have been determined in such a way that the COHb level of 2.5% is not exceeded, even when a normal subject engages in light or moderate exercise."[13] The nationwide analyses now provided in this issue, however, suggest that emergency department visits for ischemic heart disease, arrhythmia, heart failure, and cerebrovascular disease are more frequent on days with high CO concentrations. As has been suggested earlier for particulate matter and traffic-related exposures, acute adverse health effects of ambient air pollution seem to occur in vulnerable subpopulations.[17] In particular, these associations have been observed in persons with underlying atherothrombotic disease or with an increased risk of arrhythmia. Therefore, it might be very plausible that guidelines set to protect healthy normal individuals may not be adequate for vulnerable subpopulations.

The question arises of whether we already know that tighter regulation of CO is mandated or whether CO is a surrogate marker for its source. CO is mainly emitted by on-road and non-road combustion of gasoline (http://www.epa.gov/oms/invntory/overview/pollutants/carbonmon.htm). The statistical analyses conducted by Bell and colleagues suggest that the observed effects for CO are independent of NO_2, elemental carbon concentrations, and $PM_{2.5}$.[16] However, the fact that the gaseous pollutants NO_2 and CO are exhibiting the strongest and most consistent associations with emergency department visits in the article by Bell and colleagues is likely to be attributed to the availability of daily data for gaseous but not particulate matter ($PM_{2.5}$ or elemental carbon).

The Role of Ultrafine Particles?

With the recent focus on establishing the associations between particulate matter and cardiovascular disease exacerbation, effect estimates for other gaseous pollutants have been reported rarely. Forastiere and colleagues[18] have assessed coronary artery disease hospital admissions and ambient air pollution including CO, NO_2, PM, and ultrafine particles. They found the strongest associations for CO and ultrafine particle concentrations for fatal and nonfatal hospitalization for acute myocardial infarction in Rome, Italy. These findings are very much in agreement with the reports by Bell and colleagues in this issue. Similarly, during a follow-up of incident myocardial infarction survivors in 5 European cities, all pollutants, including CO, NO_2, PM, and ultrafine particles, were associated with hospital readmissions.[19] This European multicenter study suggested that the mixture of pollutants was responsible for this association, although the pollutants were only moderately correlated and to a different degree in the different study locations.

In addition, there seemed to be a correlation between ambient CO and personal $PM_{2.5}$ in Baltimore, Md, during the winter,[20] so that there is room for speculation that CO might be an independent indicator for health-relevant properties of our air pollution mixture in urban areas. There seems to be a need to further follow up these findings both with respect to the regular evaluation of air quality guidelines as well as with respect to research geared to address the concerns raised by work of Bell and colleagues.

Overall, the 2 articles published in this issue of *Circulation*[9,16] make important contributions to the assessment of the role of the environment for cardiovascular health. First, they are highlights of the consistently emerging evidence that both indoor and outdoor air quality is a modifiable risk factor for cardiovascular disease. Second, smoking literature and air pollution literature provide consistent evidence for health effects of particulate matter. Third, health effects of low-dose smoking, secondhand smoke, and air pollution are probably still underestimated by decision makers around the world. Fourth, regulation of air quality needs sustained reassessment of emerging and existing air quality measures in addition to a standard for $PM_{2.5}$.

Disclosures

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