Particulate Pollution and Endothelial Function
Déjà Vu All Over Again in the Air
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A growing body of epidemiological data implicates particulate matter air pollution (PM) as yet another factor in the pathogenesis of cardiovascular disease.1 PM influences susceptibility to hard events and may be particularly harmful to high-risk groups such as people with diabetes, people with hypertension, and people who smoke.2 The synergistic impact of PM in diabetes mellitus is internally consistent with previous observations, demonstrating that risk factors such as hypertension, diabetes, and smoking may potentiate atherosclerosis. Thus, if one were to predict likely pathological mechanisms, recapitulation of some the previously well-characterized pathways through which risk factors such as smoking or diabetes modulate atherosclerosis may be equally applicable to PM-mediated atherogenicity.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(Circulation. 2005;111:2869-2871.)
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Circulation is available at http://www.circulationaha.org
DOI: 10.1161/CIRCULATIONAHA.105.540872

Editorial

The synergistic impact of PM in diabetes mellitus is internally consistent with previous observations, demonstrating that risk factors such as hypertension, diabetes, and smoking may potentiate atherosclerosis. Thus, if one were to predict likely pathological mechanisms, recapitulation of some the previously well-characterized pathways through which risk factors such as smoking or diabetes modulate atherosclerosis may be equally applicable to PM-mediated atherogenicity.

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In this issue of Circulation, O’Neill and colleagues demonstrate that antecedent 6-day moving average levels of PM were negatively associated with endothelium-dependent flow-mediated dilatation and nitroglycerin-mediated dilatation in 269 subjects with diabetes mellitus (type 1, n=45; type 2, n=182) or subjects at risk for developing diabetes (n=42).

Although the results of the study represent pooled data from 4 trials, the clinical and environmental variables were merged by date to provide startling insights between variations in vasomotor tone and preceding ambient PM levels. The negative association in the type 2 diabetes population (the majority) was striking and, not surprisingly, drove the results of the study. These results are consistent with the recurring observation of impaired large-vessel endothelial function in people with type 2 diabetes.4 Another notable finding in the present study was the effect of PM on nitroglycerin-mediated dilatation. These results are similar to previous studies that noted the impact of risk factors such as diabetes on smooth muscle function and could potentially implicate abnormalities in guanylate cyclase–cyclic guanosine monophosphate signaling pathways to PM.4

Of the 4 metrics of PM measured in the study (fine particles <2.5 μm in aerodynamic diameter [PM2.5]; sulfate, black carbon, and particle number), the associations were strongest between flow-mediated dilatation and sulfates (on multivariate analysis) and between nitroglycerin-mediated dilatation and PM2.5 for the overall patient population. Black carbon (represents traffic-related sources) correlated negatively with flow-mediated dilatation in subjects with diabetes (strongest in the type 2 group), but this association weakened after the inclusion of sulfates (primarily reflects coal-burning power plants) in the model. The authors were careful to adjust for several confounding variables that may have potentially influenced the results (eg, severity of diabetes by HbA1c levels, hormone replacement therapy, alcohol use) and reassuringly demonstrate the consistency of their data even after adjusting for these variables. The results in the type 1 group showed negative but less striking trends, and this may be consistent with a greater impact of type 2 diabetes on endothelial function. Interestingly, the authors report a positive rather than a negative association among PM metrics, flow-mediated dilatation, and nitroglycerin-mediated dilatation in the “at-risk” group. Although this finding appears to contradict a “graded” effect that impaired glucose tolerance may have on endothelial function, the results may be reconciled by the limited sample size in this group that may have diminished the discriminative ability of their analysis. Another potential methodological issue that may explain some of their associations (or lack thereof) is that ambient air PM metrics (within 500 m of where subjects were examined) were used. These were presumed to reflect personal exposure and this may not necessarily be the case, especially with measures such as black carbon and particle numbers that demonstrate marked spatial variation. It is therefore important, as the authors emphasize, that lack of effect not be construed as representing “lack of evidence” for biological activity. It is conceivable that traffic-related sources and subfractions may still play an important role in modulating vessel wall responses.5

How might PM modulate endothelial function? Loss of endothelium-derived nitric oxide (NO) plays a central role in the pathogenesis of diseases such as smoking-related vascular disease, atherosclerosis, hypertension, and diabetes. The decline in NO bioavailability may be caused by multiple abnormalities in the generation of NO, including altered expression of the enzyme endothelial nitric oxide synthase, altered function of the enzyme because of the lack of its substrate l-arginine or its cofactor tetrahydrobiopterin (BH4), alterations in cellular signaling such that the enzyme is not activated, and accelerated NO destruction by superoxide.6 The latter mechanism is particularly relevant because PM is an important generator of reactive oxygen species (ROS).7–10 Although the precise locus of generation of these radicals is
hotly debated, there is reason to believe that the vasculature may be key in mediating and modulating the effects of PM. The endothelium in the lungs is the initial locus of contact for PM, and the smallest particles (PM particles <0.1 μm) have been shown to translocate from the lungs into the circulation, where they may mediate their effects. The pathological consequences of PM on the vessel wall can be summarized below, depending on the type of evidence (cellular/biochemical, animals, and human).

Cellular and Biochemical Evidence of PM Effects
Exposure of endothelial cells to diesel exhaust particles markedly reduces NO formation and may potentiate cytotoxicity. The cytotoxic effects are reversed by superoxide dismutase, catalase, and N-(2-mercaptoethyl) glycine, implicating a role for superoxide, hydrogen peroxide, and hydroxyl radicals, respectively, in these effects. In these experiments, inhibitors of nitric oxide synthase resulted in an attenuation of diesel exhaust particle–induced endothelial cell damage. Furthermore, treatment with BH4 and ebselen (a peroxynitrite scavenger) also resulted in attenuation of cell damage, suggesting that depletion of BH4 may play a role in nitric oxide synthase–mediated superoxide and peroxynitrite generation.

Data in Animal Models Supporting PM-Mediated Effects on the Vasculature
Exposure of rats to PM aerosols, even for short durations, results in marked increases in oxidative stress in the heart and lungs, as determined by in situ chemiluminescence. Increased indices of oxidant stress are associated with tissue-specific increases (in the myocardium) in antioxidant enzymes, such as superoxide dismutase and catalase consistent with adaptive responses. ROS generation in these models shows strong associations with the PM content of iron, manganese, copper, and other trace elements, consistent with the effects of transition metals in facilitating ROS. Recently, short-term exposure to PM in rats has been associated with elevations in asymmetric dimethylarginine (ADMA). Although the mechanism for this remains to be elucidated, there is strong evidence that ADMA level is determined by the enzyme dimethylarginine dimethylaminohydrolase. Oxidant stress has been shown to regulate dimethylaminohydrolase activity and thus could potentially contribute to an increase in ADMA. Another consequence of reduced NO is heightened platelet aggregation. In animal models, diesel exhaust particles accentuate in vitro measures of platelet aggregation and enhance peripheral thrombosis.

Thus, at least in cultured cells and animals, PM results in increases in oxidative stress, which may then alter bioavailable NO levels and result in endothelial dysfunction. The ROS sources activated by PM could vary, dependent on the composition, size, and eventual locus of deposition of the particles within the vessel wall.

Data in Humans Supporting PM-Mediated Effects on the Vasculature
Controlled exposures to PM result in acute responses and may explain susceptibility to cardiovascular events within a few hours of exposure to pollution. A 2-hour exposure of healthy adults to PM2.5 and ozone resulted in conduit artery (brachial) vasoconstriction, but it did not result in diminution of flow-mediated dilation of nitroglycerin dilation. Although superficially inconsistent with the O’Neill et al study, these results actually bolster the evidence that PM exposure may alter conduit vessel tone in a time- and dose-dependent manner. The study by Brook et al involved controlled exposure to PM (150 μg/m3 of ambient PM2.5 plus ozone [120 ppb]) in healthy adults. The decrease in conduit vessel diameter in this study is suggestive of a rapid direct effect of PM in diminishing basal NO levels, generation of vasostrictors such as endothelin-1, or both. In contrast, more prolonged exposure, additional abnormalities (predisposition in the form of diabetes, hypertension, and hypercholesterolemia), as was the case in the O’Neill et al study, or both may be required to induce agonist-mediated changes in endothelial function. Increases in inflammatory measures such as C-reactive protein with PM exposure have also been shown and may represent responses to endothelial dysfunction and activation of oxidant stress/cytokine pathways.

Irrespective of the mechanism, decreased bioavailable NO levels and endothelial dysfunction are likely to have other, unintended consequences such as activation of the sympathetic system, endothelin-1 pathway, and an elevation in blood pressure and this in the intermediate and long term may influence vascular morbidity and mortality. Indeed, at least 2 epidemiological studies have suggested an association between PM and an increase in blood pressure. Ibald-Mulli et al reported that total suspended particles and sulfur dioxide levels were associated with a small increase in systolic blood pressure in 2607 adults during an episode of extreme air pollution in southern Germany. In a subgroup of individuals with a high heart rate and plasma viscosity, the increase in blood pressure was most dramatic. A similar finding was reported in 66 patients during repeated visits for cardiac rehabilitation in Boston. Diastolic pressure increased in relation to the previous 2- and 5-day mean concentrations of PM2.5. Thus, it is possible that PM exposure through alterations in endothelial function, activation of the sympathetic system, endothelin-1 axis, and platelet function may predispose to hypertension and atherosclerosis (Figure).
Observational and limited cohort studies need to be confirmed by larger prospectively designed studies that test the hypothesis that PM is deleterious to vascular health. If lessons from hypercholesterolemia, hypertension, and diabetes are at all predictive, then this may be, as Yogi Berra put it, “déjà vu all over again.”

Acknowledgments
This work was supported by the following grants: R01 ES013406-01, R827351, and ES 00260 (Environmental Protection Agency and National Institute of Environmental Health Sciences center grants).

References

KEY WORDS: Editorials • endothelium • nitric oxide • free radicals • myocardial infarction
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Circulation. 2005;111:2869-2871
doi: 10.1161/CIRCULATIONAHA.105.540872
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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