Chronic Air Pollution Exposure and Endothelial Dysfunction

What You Can’t See—Can Harm You*

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Fine particulate matter air pollution <2.5 μm in diameter (PM2.5), a pervasive and often “invisible” component of modern-day atmospheres, has been linked to numerous adverse outcomes, including increased cardiovascular (CV) morbidity and mortality. Indeed, an American Heart Association scientific statement recently concluded that the overall evidence is consistent with PM2.5 being causally related to CV diseases (1). There remains little doubt that higher ambient PM2.5 levels over a few days can promote acute CV events (1,2). Although the short-term risks for a single individual are small, due to the vast number of individuals affected worldwide, the public health burden of air pollution is enormous. It has been estimated that up to 4.8% of acute myocardial infarctions are potentially attributable to recent exposures (2). Although alarming, these figures (limited to the acute impact of pollution) in actuality represent an underestimation of the totality of PM2.5-related CV health effects.

Accumulating evidence supports the reasoning that the CV risks posed by PM2.5 mirror those of other classical risk factors (1). The health risks posed by brief perturbations in any factor (e.g., an acute elevation in blood pressure) are markedly outweighed by those induced by the cumulative actions of pervasive long-term abnormalities (e.g., chronic hypertension). Hence, not only the magnitude but also the duration of exposure to a risk factor is important when considering the sum totality of ensuing health risks. In the context of air pollution, prospective cohort studies generally report an order of magnitude greater increase in CV risk induced by several years of PM2.5 exposure compared with that associated with inhaling similar levels over only a few days (1,3). One hypothesis put forth to explain these observations has been that repetitive exposures have cumulative and pernicious effects on the CV system, both amplifying the adverse effects of other CV risk factors and increasing the detrimental impact of later PM2.5 exposures (i.e., increasing future susceptibility) (1,4). Emerging data also support a role for chronic air pollution exposures in promoting the genesis of overt disease states, such as atherosclerosis, hypertension, and diabetes mellitus (1,5).

Using data from the MESA (Multi-Ethnic Study of Atherosclerosis) cohort, the study by Krishnan et al. (6) in this issue of the Journal provides new insights into the adverse CV actions of long-term air pollution exposure. Leveraging off of the numerous inherent strengths of the MESA, the authors performed the first assessment of the chronic effects of long-term PM2.5 exposure on vascular endothelial function as assessed by using flow-mediated dilation (FMD) of the brachial artery. FMD is a marker of nitric oxide–dependent vasodilation and is a validated metric of overall vascular endothelial health as well as an independent predictor of CV prognosis (7). However, a limitation of the MESA study design was that nitroglycerin–mediated vasodilation was not evaluated; hence, the differential impact of air pollution on the endothelium versus smooth muscle function could not be deciphered (6,7).

The principal finding of this current MESA Air report was that a 3 μg/m3 higher annual average PM2.5 exposure was associated with a significant 0.3% reduction in FMD (6). This magnitude of vascular dysfunction, although seemingly small, was analogous to the adverse effects of smoking or 5 years of aging. This finding suggests that individuals living in regions affected by even modestly higher air pollution levels are at risk for experiencing a clinically pertinent chronic impairment in vascular function. This novel observation should re-awaken us to the fact that even “invisible” elements, such as chronic exposure to low levels of air pollution commonly encountered in the United States, can have significant adverse effects on CV health.

Several strengths of the current study (6) merit highlighting. It is among the largest investigations linking air pollution exposure with CV imaging endpoints (1). Although not involving the entire MESA cohort, 3,040 patients is an enviable sample size for an FMD-based study. This size is likely why the authors were able to find significant adverse vascular effects despite the small interquartile range (3 μg/m3) in PM2.5 exposure levels. The richness of the acquired covariates and patient-related information also allowed for numerous explorations of effect modification and sensitivity analyses. In this regard, their findings support previous suppositions that women might be more susceptible (1) and provide new insights into other potential at-risk groups. The quality and standardization of ultrasound methods, critically important for FMD protocols, were also previously well established for this study. Finally, enormous efforts were paid to developing and validating estimates of “chronic” residence-level PM2.5 exposures using advanced spatiotemporal models. This exper-
mement strength likely reduced the occurrence of significant exposure misclassifications capable of obfuscating true air pollution–mediated health effects.

How do the current findings of Krishnan et al. (6) compare with previous studies? A number of controlled experiments and panel studies have evaluated the effects of air pollutants on vascular function; however, these studies were conducted only after short-term periods of exposure (1). Previous findings have been mixed, with some reports demonstrating reduced endothelial-dependent vasodilation (with or without concomitant blunted nitroglycerin-mediated dilation), whereas others have observed acute arterial vasoconstriction. How does one reconcile this variability and place it into context given these new study findings? Differences in populations, patient susceptibilities, underlying CV diseases, and risk factors, as well as the known intrinsic variability of endothelial function testing as an outcome (e.g., biological aspects and technical limitations) (7), are undoubtedly contributing explanations. It is moreover possible that the air pollutants evaluated across the published studies may also be partially to blame. PM$_{2.5}$ is not a homogeneous entity but is composed of numerous chemical compounds (1). Differing pollution sources, characteristics, and mixtures could in theory elicit discordant vascular responses. Unfortunately, because only PM$_{2.5}$ mass was evaluated in the current MESA Air report (6), the specific components (e.g., metals, organic carbon) and pollution sources (e.g., traffic, regional) most responsible for perturbing vascular function continue to be obscure. In this regard, it is interesting to note that the reported FMD responses differed somewhat among the 5 cities. Perhaps future analyses of this cohort will provide much-needed insights into the responsible or most harmful airborne compounds as well as the impact of multiple co-pollutants together (e.g., ozone, nitrogen oxides).

The most novel aspect of the current study (6) was the exploration of the effects of “long-term” PM$_{2.5}$ exposure on vascular function. However, deciphering the temporal associations between exposures and health outcomes is a complicated issue that cannot be completely elucidated by any single experiment. It is important to note that the current results cannot rule out the possibility that only “subacute” periods of PM$_{2.5}$ exposure (e.g., a few weeks) are all that is biologically required to cause most (or all of the PM$_{2.5}$-induced vascular dysfunction attributed to their year-long exposure metric (4). There is a large missing time window between 3 days and 1 year (the acute versus chronic exposure metrics in their study [6]). This possibility is supported by a previous publication from MESA (8). Although blood pressure was not found to be associated with PM$_{2.5}$ levels during the previous 1 to 7 days, it was significantly elevated in relation to the levels during the previous 30 to 60 days. A significant relation would have been missed if the health effect was evaluated solely in regard to the preceding few days’ concentrations. In the current MESA Air report, although trends toward reductions in brachial artery diam-

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