A Road Forward to Improve Public Health

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Air quality has improved in many countries, including the United States, during the past few decades.\(^1,2\) Importantly, these gains have translated into observable health benefits. Reductions in fine particulate matter (PM) have significantly contributed to the increase in life expectancy in the United States since the 1980s.\(^2\) However, the burden of adverse health effects caused by high levels of air pollution continues to grow throughout many regions of the world. Outdoor air pollution ranks as the 8th-leading risk factor for death among high-income countries.\(^3\) Estimates are that anthropogenic fine PM contributes to \(\sim 3.5\) million cardiopulmonary deaths globally per year.\(^4\) Perhaps not well appreciated is the reality that cardiovascular (CV) deaths likely constitute the largest portion of this mortality.\(^1\)

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Despite improvements in vehicular emissions, many factors related to urbanization (eg, increased commuting, traffic congestion, denser road networks) conspire to make traffic-related sources a major cause of air pollution exposures worldwide.\(^5\) Compounding this problem in modern-day societies, mounting evidence implicates traffic as a specific pollution source associated with CV morbidity and mortality.\(^5\) Therefore, a better understanding of the CV effects posed by vehicular emissions, as well as feasible means to mitigate them, is of growing public health importance. In many regions, diesel engines are a major contributor to this pollution (eg, \(\sim 50\%\) of cars in Europe, areas of commercial goods movement, and ports).\(^5\) Most of the standard diesel vehicles and equipment in use today produce particle emissions that are many times greater than those produced by gasoline engines, and thus they warrant ongoing attention.\(^5\)

In the present issue of *Circulation*, Lucking et al report the results of a study investigating a host of CV responses after short-term diesel exhaust exposure.\(^6\) Their protocol used well validated methods, pertinent CV outcomes, and relevant exposures. Nineteen healthy subjects completed 3 blinded, randomized, hour-long exposures to filtered air, whole dilute diesel exhaust, and exhaust after passing through a continuously regenerating particle trap. Lucking et al’s findings corroborate the detrimental vascular and prothrombotic effects previously reported by them\(^1,7\) and others.\(^1,8\) Brief exposure to the full dilute diesel exhaust impaired microvascular endothelial-dependent as well as verapamil-induced smooth muscle–mediated vasodilatation while promoting ex vivo thrombus formation. There were some recognized, albeit not fully understood, differences compared with previous reports of similar subjects and engine-running conditions\(^1,7\) including blunted verapamil-induced vasodilatation, lack of reduction in arterial compliance, and a nonsignificant trend for impaired sodium nitroprusside–mediated vasodilatation and tissue plasminogen activator release. It is unclear if these represent true variations of biological importance not mechanistically elucidated, or chance differences among studies with relatively few subjects. Nonetheless, the principal study finding indicating impaired arteriole endothelial-dependent (acetylcholine- and bradykinin-mediated) vasodilatation notably occurred in a consistent manner. Together with the observed prothrombotic alterations, these responses corroborate the plausibility that high but relevant concentrations of diesel pollution are capable of triggering acute CV events among susceptible individuals.

However, what was distinctive about the current protocol was the effort to address an important and timely question: By reducing PM emissions, can the particle trap used prevent ensuing adverse responses? The study also indirectly addressed some aspects of whether the exhaust constituents within the particle or gas phases (or both) are principally responsible. Though diesel particles can impair nitric oxide bioavailability via oxidative stress pathways when in contact with the vasculature,\(^1\) this phenomenon likely has little relevance to real-life exposures. Whether PM or associated constituents reach the systemic vasculature of humans, let alone whether they do so in harmful concentrations, remains controversial.\(^3\) In addition, diesel exhaust is a highly complex mixture consisting of particles (ranging from tens of nanometers to a \(\mu\)m in diameter) and gases, with some of them readily transitioning between states (ie, semivolatile organic compounds), and all of them reacting among each other while being influenced by atmospheric conditions.\(^1\) This presents a complicated web of potentialities to consider (Figure). Many of the gaseous pollutants covary with traffic-related PM (eg, nitrogen oxides [NO\(_x\)] and hydrocarbons), and their individual or confounding effects are difficult to untangle. Other constituents (eg, combustion-generated ultrafine particles) are short lived and confined to domains close to points of emission. Some pollutants linked to health effects may only be serving as source markers and not be toxic per se, whereas exposures to others may be a true concern, yet are difficult to accurately characterize (eg, ultrafine particles). In addition, atmospheric chemistry fosters reactions among pollutants and on particle surfaces that can alter their toxicity preceding...
Overlapping and/or complimentary systemic biological pathways may be triggered by each component on inhalation. In theory, the combined actions of a mixture could thereafter cause antagonistic, additive, or even synergistic adverse CV responses compared with a pollutant encountered in isolation. Hence, the responsible sources and constituents are difficult to conclusively identify by epidemiological studies alone. Exposure protocols such as the one performed by Lucking et al that experimentally control for these numerous factors while eliminating other confounders (eg, roadway noise) can not only help reveal biological mechanisms, but more directly test the relative toxicity of pollution components.

During the study, the use of a continuously regenerating particle trap was able to substantially reduce the particle mass and concentration during exposures (PM$_{10}$ = 7.2 μg/m$^3$; particle number = 30 to 300/cm$^3$) compared with the whole unfiltered diesel exhaust (PM$_{10}$ = 320 μg/m$^3$; particle number = 150 000 to 200 000/cm$^3$). The major new finding was that this reduction in PM exposure mitigated the impairment in microvascular endothelial function and prothrombotic alterations that were induced by the whole dilute diesel engine exhaust containing high mass and number concentrations of ultrafine/fine particles. These benefits occurred despite the measured total gaseous hydrocarbons being less altered and nitrogen oxides being similar between the 2 exposures, although the NO$_2$:NO$_x$ ratio was altered. These findings by Lucking et al provide persuasive evidence that it is the inhalation of diesel particles that plays a primary role in acutely instigating these specific CV responses. There was no evidence for the speculated generation of more harmful particles or vapors, at least in relation to the outcomes tested and at the greatly reduced PM concentrations. Given the paucity of human data, these new findings carry substantial weight, particularly since they accord with their previous study showing that nitrogen dioxide alone does not acutely impair vasomotor or fibrinolytic function. Similarly, we demonstrated that ozone (another common gaseous copollutant), alone or in combination with fine PM, did not promote or worsen any of several adverse CV responses induced by concentrated ambient particles.

Although these findings add support to the contention that it is traffic-related particles that are responsible for causing the vascular and prothrombotic abnormalities, at least by an hour-long exposure, a few animal studies contrarily suggest that nonparticulate pollutants are important. Campen et al have shown that gaseous volatile organics can acutely impair vasomotor responses, whereas longer exposures to monoxide gases alter transcriptional expression of vascular molecules (eg, endothelin and matrix metalloproteinases). In separate experiments, ozone exposure for 8 weeks has been shown to promote vascular dysfunction via oxidative stress. Differences in methods, doses, and durations of exposures, the specific CV outcomes investigated, or the susceptibilities of the animal models may explain these discordances compared
with the current study. The findings by Lucking et al do not, however, eliminate the possibility that in certain scenarios (eg, longer durations and/or among susceptible patients) nonparticulate components may pose a threat to the CV system. Gaseous pollutants may also affect other CV outcomes not investigated (eg, autonomic tone, atherosclerosis, plaque stability), not to mention their established adverse effect on pulmonary health. Because no single study can answer every question, further investigations of the adverse CV effects of combined pollutant exposures are still warranted. Indeed, the health effects of exposures considered in a multipollutant context is currently a prime focus of research coordinated by the US Environmental Protection Agency, and is an important priority raised by the National Research Council.

The study by Lucking et al has provided an important piece to the puzzle of how air pollutants can affect human CV health. Nevertheless, additional tasks remain, including elucidation of finer mechanistic details (eg, systemic pathways coupling PM inhalation to reduced endogenous vasodilator function within the vasculature). Given that airborne PM is also a complex amalgam, the responsible components (eg, metals, organic carbon species) or mixtures thereof remain to be identified. In this context, it is still technically probable that the gaseous pollutants are important for affecting health even if the particle trap used abrogated adverse CV responses. The particle trap used can reduce some gaseous pollutants not fully characterized in the study (eg, CO, benzene, 1,3 butadiene, and carbonyls). Furthermore, gas–particle partitioning of semivolatile organic compounds, which occurs postcombustion and during normal dilution (Figure), may have been altered during the exposures, complicating accurate differentiation of the pollutant phases (as is also the case during atmospheric measurement). Exposure to >95% pure elemental carbon ultrafine particles, generated differently from diesel combustion and in the absence of gaseous copollutants, produces a less conspicuous impairment in vascular function. This suggests that particle composition plays a role in causing adverse CV responses. Not only are primary diesel particles likely more toxic, but reactions with combustion gases/vapors in the exhaust further alters their chemistry to potentially make them more harmful to the CV system on inhalation.

What is clear is that the inhalation of combustion-related particles is capable of posing an immediate threat to the CV system, and that the overall evidence is robust enough to infer a causal relationship. Although many finer scientific details require elucidation, this should not distract from presently focusing more efforts on the ultimate goal: reducing pollution to enhance human health. Beyond government regulation, evidence exists that individual-level actions can lower exposures in a manner that translates into CV health benefits. For example, household particle filtration devices have been shown in at least 2 studies to improve microvascular endothelial function within only a few days. The fact that a commercially available particle trap not only dramatically lowered PM emissions, as has been shown previously, but had demonstrable cardioprotective benefits, adds justification to US 2007 emission standards for heavy-duty trucks and buses, which largely necessitate use of similar control technologies. These new findings support ongoing efforts to reduce particle pollution through programs targeting diesel emissions, such as the Diesel Emission Reduction Act and the National Clean Diesel Campaign. Retrofitting older diesel vehicles with particle trap technologies is cost-effective and potentially capable of yielding large public health and economic benefits. The important study by Lucking et al provides new mechanistic evidence that bolsters support for these projected health benefits. Altogether, the wealth of existing data demonstrates that the time is ripe for coordinated efforts to reduce PM exposures globally in order to improve cardiopulmonary health and, in going down this road, diesel emissions are an important source to consider.

Disclosures
None.

References


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