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Air Pollution and Mortality: Are We Closer to Understanding the How?

Exposure to ambient air pollution is associated with the occurrence of cardiovascular events (especially fatal events) in many epidemiological studies, and the effects are observed with short-term increases in exposure as well as long-term average exposures (1, 2). How inhalation of relatively low concentrations of pollutants might cause this effect is a question that has proved challenging to researchers in the laboratory and in the field. A number of potential mechanistic pathways have been proposed, but few have been eliminated, and there is a lack of a coherent biological mechanism. While understanding the precise mechanism is not necessary to reducing overall pollution levels and gaining public benefit, understanding the pathways involved will permit the most targeted means of reducing pollution-related health consequences. Once a mechanism is confirmed, the relative toxicity of specific pollutant components can be tested, efforts can be focused on reducing exposure to the most dangerous, and better guidance given to clinicians and the exposed populations.

Many investigators have reasonably proposed that inhalation of fine particles (or gaseous agents that are fellow travelers with the particles) initiates an inflammatory cascade that ultimately results in vascular effects (3). But is the initial insult in the lung or do the pollutants pass into circulation and exert toxic effects directly in the vascular bed? Regrettably, studies have not yet clarified this, and even observations of systemic inflammation from air pollution are inconsistent (4–7).

The concept of oxidative stress has been invoked by some investigators as the key underpinning phenomenon for pollution related cardiovascular events (8), though the discussion has sometimes been imprecise. If target tissue-level oxidative stress occurs, is it actually due to inherent chemical redox activity of the inhaled pollutants or to the activation of specific host defense (and detoxification) pathways that generate reactive oxygen species?

Investigators have also proposed that the autonomic nervous system is a major player in the response to air pollution, largely bolstered by observational studies showing (though not consistently) decreases in heart rate variability which might reflect a tipping of autonomic balance in favor of sympathetic activation (9, 10). But if this really occurs, is it an important phenomenon reflecting direct neurogenic response in the lung with resulting enhanced susceptibility to arrhythmic events, or again a downstream indication of a larger inflammatory phenomenon?

Still other investigators have focused on prothrombotic effects of pollutants, with evidence of impaired fibrinolysis and thrombosis (11, 12). But again, questions remain about whether this is an early or downstream part of the response, resulting from particulate activation of the coagulation cascade or an occurrence secondary to pulmonary inflammation or endothelial activation. The proposed mechanisms are clearly not mutually

exclusive, and there may be important and interwoven truth to many if not all of these potential explanations, especially if the vascular endothelium serves a central role in modulating these effects.

Two studies in this issue of the *Journal* represent different approaches in young healthy human subjects in attempts to elucidate mechanisms underlying the epidemiological observations. Törnqvist and colleagues (pp. 395–400) report on a human experimental design using freshly diluted diesel exhaust inhalation, while Chuang and colleagues (pp. 370–376) used a panel design to associate short-term fluctuations in particulate exposure to changes in a number of physiological parameters (13, 14).

Building on a prior observation from their group, in which forearm plethysmographic perturbations consistent with endothelial dysfunction were seen immediately after diesel exhaust exposure (11), Törnqvist and coworkers report here that the effects are extended to 24 hours—with diesel exhaust inducing a reduced forearm blood flow response to acetylcholine and bradykinin, but not endothelium-independent agents (13). However, at the 24-hour time point, endothelial tissue plasminogen activator (tPA) release was not impaired as it was at 6 to 8 hours after exposure. They further note not only systemic evidence of inflammation (circulating interleukin-6 and tumor necrosis factor- α) and endothelial activation (p-selectin), but also decreased total antioxidant capacity of plasma [by reduction of 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radicals]. Their results support the role of oxidative stress in the physiologic response to pollutants by an assessment of electron spin resonance of collected and resuspended particles from their system—showing attenuation of the diesel exhaust particulate spin resonance with superoxide dismutase comparable to the attenuation of the pyrogallol signal. These results provide confirmation of early studies, and some insight into how pollutant exposures can result in effects for subsequent periods measured in days.

Chuang and colleagues describe a panel study in Taipei, in which blood and electrocardiographic markers were repeatedly collected over 3 months to examine multiple potential mechanistic pathways (14). They had the benefit of fairly large daily fluctuations in exposure, presumably dictated by meteorological conditions. While their inflammatory, oxidative stress, fibrinolysis, and coagulation health markers did not change consistently as hypothesized with fine particles, they did detect associations with some PM components and credited these to traffic-related air pollution—though such components (i.e., sulfate) are not typically associated with traffic sources. Their measure of “oxidative stress” (urinary 8-hydroxy-2'-deoxyguanosine, assessing oxidative DNA damage) was not associated with pollution exposures. Heart rate variability metrics, on the other hand,

consistently demonstrated negative associations with all air pollutants examined, in a manner that appeared to be independent of inflammation. Their stated intent was to determine whether the various pathways were activated “simultaneously,” but the study relied on exposure averaging periods that were too imprecise to hope to determine the time course of physiologic events or determine which pathways are the most important. This simply may be too much to ask of this study design, especially when daily exposure concentrations are highly correlated with preceding days.

The findings in both of these papers are mostly consistent with previous studies and together do not preclude any of the proposed pathways discussed above. They advance the field somewhat by this consistency, but provide modest additional guidance on the initiation or development of the cascade of events that result in clinical cardiovascular events. The interplay of different pathways clearly requires further exploration, which also necessitates a better understanding of the timing of each proposed biological pathway.

It is useful to integrate epidemiologic and toxicologic approaches to elucidate the mechanism of the effects of air pollution on health. Many questions remain to be answered. While these questions should by no means slow the important efforts to reduce exposures and benefit global public health (15), we must continue with careful investigations into the details of the biological mechanisms of air pollution's effects. However, the time has come for more tightly focused and hypothesis-driven approaches to understanding the initiating events, necessary pathways, and key effectors of the cardiovascular effects of air pollutants.

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