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Ozone and Acute Respiratory Distress Syndrome
It's in the Air We Breathe

Components of environmental air pollution have long been linked to the development of lung disease, exacerbations of lung disease, and respiratory mortality (1–3). Lower-atmospheric (tropospheric) ozone is a particularly dangerous pollutant that develops as the result of reactions between sunlight and ozone precursors primarily emitted during fossil fuel combustion (4). In animal models, acute exposure to high concentrations of ozone causes acute lung injury, and eventually death, by inducing oxidative stress, increasing permeability of the alveolar capillary barrier, and recruiting inflammatory cells to the lung (4, 5). Similarly, in human experiments, acute ozone exposure results in a transient decline in pulmonary function, the recruitment of neutrophils to the lung, release of proinflammatory cytokines, and increased epithelial permeability (6). Given these experimental findings, it is reasonable to hypothesize that ambient ozone exposure may be a risk factor for the acute respiratory distress syndrome (ARDS). Chronic ozone exposure at concentrations seen in ambient air is associated with increased mortality from respiratory causes (7, 8); however, it is unclear whether this lower-level long-term ozone exposure results in sufficient pathophysiologic changes in the lung needed to alter ARDS risk once a patient develops a predisposing condition (e.g., sepsis, trauma).

In this issue of the *Journal*, Ware and colleagues (pp. 1143–1150) present the results of a cohort study aimed at determining the association of environmental pollutant exposure and ARDS risk (9). The authors estimated daily exposure to ozone, NO_2, SO_2, fine particulate matter ($PM_{2.5}$), and coarse particulate matter (PM_{10}), using home addresses and U.S. Environmental Protection Agency air quality monitoring data in a cohort of 1,558 critically ill patients hospitalized at Vanderbilt University Medical Center in Nashville, Tennessee. Given the difficulty of extracting the ARDS diagnosis from an administrative database, the authors relied on this large, well-phenotyped cohort of patients at risk for ARDS. Extensive clinical data were collected on all enrolled subjects, and subjects were carefully reviewed for the presence of ARDS on enrollment and on the subsequent 3 days. Despite being a single-center study, enrolled subjects came from a geographically diverse area around Tennessee, including 11 neighboring states. The authors identified an independent association between long-term ozone exposure and ARDS risk, whereby the highest quartile of ozone exposure had a 14% higher ARDS risk than the lowest quartile of exposure. The authors also report an association between NO_2 exposure and ARDS, but this association was not present after adjustment for ozone. Given that NO_2 is one of several ozone precursors, it is possible that the NO_2 and ARDS relationship is mediated through NO_2's conversion to ozone. Associations between the other air pollutants, such as particulate matter, and ARDS were not identified.

The main limitation of the reported study is the assumption that the ambient ozone at a person's home address is a good surrogate for an individual's actual ozone exposure (9). Ozone is primarily an outdoor air pollutant. Individuals who spend significant time outdoors or work in a location distant from their home address may have had their chronic ozone exposure significantly under- or overestimated. Ideally, a study linking air pollution to disease risk would prospectively determine subjects' pollution exposure with a personal monitor. However, given the

likely infeasibility of such an approach to investigate critical illness, the study conducted by Ware and colleagues represents the first and strongest epidemiologic evidence for an association between components of air pollution and ARDS. The next steps are to validate their findings as well as determine whether a lower threshold of ambient ozone exists by which inhalation does not increase ARDS risk.

Although the effects of acute high-level exposure to ozone on the lung are well established, there is also a growing body of evidence that chronic ozone exposure at ambient concentrations also alters the lung, potentially priming the lung for ARDS once an individual is at risk. In a mouse model, preexposure to nonlethal concentrations of ozone was shown to prime the innate immune system, resulting in an increased Toll-like receptor-4–mediated response to subsequent stimulation with inhaled endotoxin (10). Chronic environmental ozone exposure in humans may have a similar effect, enhancing Toll-like receptor-4–mediated inflammatory signaling in the lung. This in turn may result in an increased risk of ARDS once a patient becomes critically ill.

In the study by Ware and colleagues, the association between ozone exposure and ARDS was strongest in the subgroup of patients with trauma and in patients who were active smokers (9). The authors present several hypotheses of why trauma patients may have a stronger ozone and ARDS link, including their possibly spending more time outdoors or the higher rate of smoking among the trauma population. The interaction between cigarette smoke exposure and ozone is also interesting. Cigarette smoke has recently been identified as an independent risk factor for ARDS in several at-risk populations (11–13), and is believed to have many of the same pathophysiologic effects on the lung as air pollution. It is possible that cigarette smoke and ozone have synergistic effects on the lung. In mice preexposed to cigarette smoke, subsequent exposure to ozone resulted in an exaggerated inflammatory response (14). In humans, smoking and air pollution exposure have been reported to interact, leading to an increased risk for lung cancer beyond the risk of either alone (15). The interactive effects of chronic exposure to cigarette smoke and ozone may lead to particular changes in the lung, resulting in the increased ARDS risk observed in the subgroup of smokers.

If validated in diverse geographic regions, there are several important health implications of the reported findings, particularly given worsening global air quality. First, environmental ozone, along with alcohol and cigarette smoke, joins a short list of potentially reversible risk factors for ARDS. Even at the relatively low concentrations of exposure reported, Ware and colleagues identified a significant difference in ARDS risk between those with the highest and lowest exposure, providing further evidence in support of public policies aimed at improving air quality. Second, understanding the mechanisms behind ozone and increased ARDS risk could lead to future therapeutics aimed at reversing the effects of ozone on the lung before the development of lung injury. ■

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