The Air We Breathe: Respiratory Impact of Indoor Air Quality in Chronic Obstructive Pulmonary Disease

The global push for clean air has garnered much attention because of the deleterious health and environmental effects of poor air quality (1). Presently, more than 90% of the world's population lives in an area where air pollution exceeds the World Health Organization's safe limits, and according to the 2019 Global Burden of Disease (GBD) study, there were 6.7 million deaths attributable to air pollution, making it the most significant environmental threat to human health (1, 2). Air pollution also causes significant respiratory morbidity and is a modifiable risk factor for mortality for many cardiorespiratory illnesses, including chronic obstructive pulmonary disease (COPD). Many air quality interventions have focused on ambient (outdoor) pollution, but there is increasing recognition that indoor pollution, including the by-products of fuel combustion, gaseous particles such as nitrogen dioxide (NO_2), fine particulate matter, and aeroallergens, is a major contributor to respiratory morbidity, particularly in asthma, but also in COPD (3). Tobacco smoke exposure remains the most critical exposure that causes COPD; however, household air pollution is an underrecognized risk factor for the 20–25% of COPD cases that occur in never-smokers (4, 5).

In addition to indoor air pollution, household exposure to aeroallergens such as house dust mites, cockroaches, and pets constitutes a significant cause of respiratory morbidity (6–8). In contrast to inconsistent data on the role of allergen exposure in the development of sensitization and asthma, most studies that investigated the impact of exposure among sensitized patients with established asthma reported increased severity with increasing exposure (reviewed in Reference 9). Furthermore, allergens interact with viruses in sensitized patients with asthma to markedly increase the risk for hospitalization with severe acute exacerbations, among both adults (10) and children (11). Although a considerable body of evidence demonstrates the contribution of allergen exposure to the ongoing inflammatory process in asthma, this relationship has not been adequately investigated in COPD.

In this issue of the *Journal*, two reports shed light on the underappreciated impact of indoor air quality and domestic allergen exposure on the respiratory health of patients with COPD and point to novel therapeutic strategies. Putcha and colleagues (pp. 412–420) report the results of analyses examining the associations between allergen sensitization and high exposure to sensitizing allergens (cat, dog, cockroach, mouse, and dust mite) and respiratory outcomes in former smokers with COPD ($n = 183$) (12). Seventy-seven percent of patients were exposed to one or more of the tested allergens, and 17% ($n = 31$) were both sensitized and exposed to high concentrations of sensitizing allergens. Similar to previous observations in asthma (13, 14), high allergen exposures in patients with COPD with relevant sensitization were associated with adverse outcomes, including higher exacerbation risk (odds ratio, 2.31; 95% confidence interval [CI], 1.11–4.79) and significantly worse quality of life. Of note, the reported associations between COPD severity and exacerbations with the combination of sensitization and high allergen exposure was more pronounced in individuals with lower lung function.

Though intriguing, the results highlight some of the challenges of studying interactions between environmental exposures and health outcomes. First, confirmation of allergic sensitization using standard diagnostic tests does not necessarily confirm that a patient would have a biological response to exposure, and this phenotypic heterogeneity among sensitized individuals is not captured by IgE antibody positivity (15). Second, allergen concentrations in household dust samples are a relatively imprecise index of exposure and may not accurately reflect the actual personal inhaled dose (16). It is therefore possible that we may be underestimating the impact of indoor allergens, but this challenge is not unique to COPD and suggests that assessment of the sensitization and exposure interaction needs further refinement and methodological studies. Adding further complexity, in real life, patients are contemporaneously exposed to a range of other environmental agents (e.g., outdoor aeroallergens; occupational dusts, gases, and fumes; tobacco and other types of smoke), and relevant coexposures may affect the reported association. Despite these challenges, this study (12) establishes the adverse impact of aeroallergens on the respiratory health of sensitized patients with COPD and raises the important question as to whether allergen avoidance may improve outcomes among sensitized patients with COPD.

Many interventions aimed at reducing inhaled allergens and indoor air pollutants have been proposed, including the use of high-efficiency particulate air (HEPA) cleaners (17–20). Also in this issue of the *Journal*, Hansel and colleagues (pp. 421–430) report the results of the randomized Clinical Trial of Air Cleaners to Improve Indoor Air Quality and COPD Health (CLEAN AIR) (21). Given the preponderance of data on the adverse impacts of poor indoor air quality on respiratory health outcomes, the investigators assessed the effect of a 6-month intervention with air cleaners containing both HEPA and charcoal filters in the homes of patients with COPD. After baseline testing, participants with unsafe indoor air quality were either randomized (1:1) to sham treatment or had two air cleaners installed in their homes, one in their bedroom and the second in the room where they spent most of their awake time. The primary outcome was a change in St. George's Respiratory Questionnaire (SGRQ) score. Exposure assessments for particulate matter ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) or PM_{10}, NO_2, and airborne nicotine together with clinical assessments were performed before

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randomization and at 1 week, 3 months, and 6 months. Although there was no difference in SGRQ total score, at 6 months, there were marked reductions in $PM_{2.5}$, PM_{10}, and NO_2 in the air cleaner group, and these were associated with improvement in several indices of respiratory health. Treatment with air cleaners compared with sham treatment resulted in a significant reduction in SGRQ symptom subscale score (−7.67; 95% CI, −14.97 to −0.37; $P = 0.040$), marked improvement in respiratory symptoms as measured by the Breathlessness, Cough, and Sputum Scale (−0.81; 95% CI, −1.53 to −0.09; $P = 0.029$), and a lower rate of moderate exacerbations (incidence rate ratio, 0.32; 95% CI, 0.12 to 0.91; $P = 0.033$). These effects were more pronounced for individuals who spent a considerable amount of time indoors and used air cleaners more than 80% of the time.

Hansel and colleagues must be commended for designing and implementing a very well-structured and informative study that answers a clinically relevant question about the therapeutic use of indoor air cleaners for patients with COPD. A few aspects of the study warrant further discussion. First, the CLEAN AIR study missed the primary outcome of change in SGRQ score, which could be related to lower than target sample size, and this means that we must be conservative in interpreting the results. The fact that the secondary outcomes were in the direction of benefit is encouraging, however; we also do not know how long the observed benefits would persist, given that the intervention was only for 6 months. Second, HEPA filters reduce the load of indoor allergens shown to be important by Putcha and colleagues (12), as well as other particulate matter, and the air cleaners tested included both HEPA and charcoal filters (the latter resulting in NO_2 reduction), which precludes conclusions about what drove the treatment effect. Third, although we in no way advocate for the use of air cleaners to facilitate continued cigarette smoking, we do not know the impact of this intervention in current smokers. Finally, this was a single-site study, and it is unclear if the results would generalize to areas with varying indoor and outdoor environmental pollutants. That said, exposure to wildfire smoke has become a huge problem in the Mountain West of the United States as well as in many other countries. The use of HEPA air cleaners to reduce indoor exposure to wildfire $PM_{2.5}$ is an evidence-based recommendation (22).

Notwithstanding the issues we raise, the findings of these two studies demonstrate a vital interaction between respiratory health and indoor air quality in COPD. The authors show that indoor allergens worsen respiratory health and that the reduction of these allergens and other pollutants with an air cleaner with HEPA and charcoal filters may improve COPD outcomes. It is vital to recommend that patients not use air cleaners that generate ozone, which can lead to the formation of secondary pollutants harmful to respiratory health (23). The results clearly call for testing this intervention in a large, multicenter, randomized trial. Given the global failure to sufficiently control outdoor pollution, this approach could provide an opportunity to help individual patients at risk while we wait. ■

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Go with the Flow: Expanding the Definition of Acute Respiratory Distress Syndrome to Include High-Flow Nasal Oxygen

High-flow nasal oxygen (HFNO) delivers heated, humidified oxygen at very high flow rates (20–70 L/min) at concentrations up to 100% through a specialized nasal cannula. HFNO has several physiologic advantages compared with conventional oxygen delivery, including a reduction in dead space, decrease in work of breathing, and provision of low levels of end-expiratory pressure resulting in increased end-expiratory lung volume (1, 2). In addition to physiologic benefits, most patients find HFNO more comfortable than noninvasive ventilation (NIV) with a tight-fitting mask. For these reasons, over the past two decades, uptake of HFNO in the ICU setting as an alternative to conventional oxygen therapy and NIV has increased across a variety of settings, including early management of patients with acute hypoxemic respiratory failure (AHRF) due to acute lung injury. In 2015, the FLORALI (High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure) trial provided reassurance that HFNO is a safe substitute for conventional oxygen delivery or NIV in patients with AHRF and showed a mortality benefit and increase in ventilator-free days for the group treated with HFNO (3).

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The onset of the global pandemic of coronavirus disease (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in 2019 has increased the pace for the adoption of HFNO. This rapid acceleration has been driven by several unique challenges engendered by the pandemic, including *1*) massive surges in patients presenting with AHRF requiring high levels of supplemental oxygen; *2*) shortages of ICU beds, ICU staffing, and mechanical ventilators, leading more patients to be managed when possible with alternatives to invasive mechanical ventilation (IMV); *3*) the need to provide high levels of oxygen supplementation with HFNO outside of an ICU setting, which is not as feasible for NIV or IMV; and *4*) the implementation of awake proning for severe COVID-19, which is more feasible with HFNO than NIV. Despite its widespread adoption, there is currently no firm evidence in the population of patients with COVID-19 that HFNO confers benefits in terms of mortality or other clinical outcomes that have been reported in non–COVID-related AHRF, but few randomized controlled trials have been published (4, 5). Nevertheless, the entrenchment of HFNO in the ICU therapeutic armamentarium for AHRF will be one legacy of this pandemic.

As HFNO has been incorporated into the routine management of patients with AHRF, some important implications have arisen for the diagnosis of acute respiratory distress syndrome (ARDS). The Berlin definition of ARDS (6) stipulates that a patient must be receiving positive pressure ventilation with a minimum of 5 cm H_2O of continuous positive airway pressure; for moderate or severe ARDS, invasive mechanical ventilation is required. However, even before the