receptor-α that blocks both IL-4 and IL-13 signaling and is of particular interest given what we now know about the signaling mechanism of mucus production (11).

In conclusion, intraluminal mucus or plugs are an important feature of asthma pathophysiology. Tang and colleagues advance this understanding by establishing plugs as a stable asthma phenotype and contributor to airflow obstruction (9), collectively framing intraluminal plugs as a therapeutic target. We share the authors' enthusiasm and call for novel interventions to eliminate intraluminal plugs but also question if old tricks, including the normalization of sputum eosinophils, expectorants, mucoregulators, or mucolytics, may be effective strategies for most people with asthma. The impaction of mucus might also be determined by the anatomy of the airways. Although old mucolytic therapies and expectorants may be partially effective to dislodge impacted mucus, they may not prevent the formation of new mucus. New therapies such as anti-IL4R monoclonal antibodies, directly targeting MUC5 (by aerosolized or other routes), or targeting consequences of mucin crosslinking facilitated by the interaction of thiocyanate and peroxidase (12) might be more effective. It would appear that mucus clearance might be just as important, if not more important, than luminal eosinophil clearing in some patients with severe asthma, and even in milder asthma for symptoms such as cough. The CT mucus score will likely be leveraged as an outcome measure or for participant selection in forthcoming intervention studies. Although CT is a promising tool to assess intraluminal mucus, its limitations must be recognized, and there is a need for optimization, automation, validation, and standardization before integration into daily clinical practice. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Getting to the How and Why: Are Individuals with Chronic Obstructive Pulmonary Disease More Susceptible to the Health Effects of Air Pollution Exposure?

It's practically public health dogma: individuals with chronic obstructive pulmonary disease (COPD) are at increased risk of adverse health effects related to pollution exposure. This assertion is based on a large number of epidemiologic studies demonstrating that short-term exposure to pollutants is a trigger for acute COPD exacerbations, as determined by increased respiratory symptoms, medication usage, urgent care visits, and hospitalizations (1, 2). Long-term pollution exposure has also been linked with increased COPD incidence, severity, and progression (3–6). According to one analysis in the Global Burden of Diseases study, ambient air pollution is the second most common cause of death and disability owing to COPD (7).

Originally Published in Press as DOI: 10.1164/rccm.202202-0293ED on March 10, 2022

The biological underpinnings for these adverse effects are thought to be related to pollutant-induced inflammation, oxidative stress, and immune dysregulation in the lung. Yet few toxicologic studies have focused specifically on COPD and air pollution, particularly because animal models of COPD are expensive, time consuming, and technologically challenging (8). Historically, human controlled exposure studies have played an important role in providing mechanistic evidence for the health effects of pollutant exposure. Owing to ethical considerations, the endpoints of these studies have focused on temporary, reversible health effects. However, when subclinical findings are in the pathway for development of disease, they provide compelling evidence for causal associations (9).

It is within this context that, in this issue of the *Journal*, Ryu and colleagues (pp. 1046–1052) report findings from a controlled human crossover study of the short-term effects of diesel exhaust exposure in older adults with and without COPD (10). The study enrolled 20 healthy participants (9 ex-smokers and 11 never-smokers) and 10 ex-smokers with mild to moderate COPD and used diesel exhaust (DE) as a model for traffic-related air pollution—the major source of ambient pollutants worldwide—at concentrations typically encountered during heavy traffic. Each participant underwent two exposure sessions, randomized to order, to both filtered air and DE at 300 $\mu g/m^3$ for 2 hours. Twenty-four-hour postexposure peripheral blood samples and bronchoscopies were performed for measurement of inflammation markers, proteases, and antiproteases.

As hypothesized, the authors found that the individuals with COPD exhibited more effects of DE exposure relative to the other participants. Although DE exposure caused an increase in circulating lymphocytes in all participants, only the participants with COPD had significant changes to BAL markers. Specifically, there was an increase in BAL SAA (serum amyloid-A) and MMP-10 (matrix metalloproteinase 10) with a borderline increase (did not maintain statistical significance after multiple comparison testing) in CRP (C-reactive protein) and VCAM-1 (vascular cell adhesion protein-1). There were no observed changes in airway cellularity or spirometry in any participants.

The observed rise in BAL concentrations of SAA, CRP, and VCAM-1 is indicative of acute oxidative stress, inflammation, and promotion of neutrophilic infiltration in the airways after DE exposure. These findings provide support for the current understanding of pollutant-mediated pulmonary injury and parallel observations of earlier studies. Prior studies of DE exposure in healthy participants have reported increased expression of mRNA proinflammatory mediators and proteins, such as IL-8 and myeloperoxidase; as well as variable increases in cellular infiltrates in sputum, BAL, and bronchial mucosal biopsies (11, 12). Although many specific proinflammatory mediators previously reported were not elevated in the current study findings, the authors point out that these molecular markers are acute-phase reactants and may have already returned to normal by 24-hour postexposure bronchoscopy.

A more novel finding in the study was the increase in MMP-10 after DE exposure in participants with COPD. Although the functions of specific MMPs have not been fully delineated, MMP-10 is believed to have an important regulatory role in the induction of extracellular matrix degradation and the pathogenesis of COPD. MMP-10 expression is induced by macrophages in response to injury and infection and is increased in more severe forms of emphysema in human smokers (13). Murine studies also support a critical role for MMP-10 in emphysema pathogenesis (14). Although the observed change in MMP may not have clinical implications and needs to be replicated, the findings may help advance a mechanistic model that establishes biologic plausibility for the association between air pollution and new-onset COPD.

It is interesting that only the subgroup of participants with COPD exhibited DE-induced changes in pulmonary markers. Although this provides additional evidence of enhanced susceptibility for individuals with COPD, it perhaps raises more questions than answers. Are the health effects related to increased particle deposition from obstructive airway disease and thus indicative of an increased internalized dose of pollutants? Or is the differential response to environmental contaminants in comparison with ex-smokers representative of an underlying genetic predisposition to develop disease? Or perhaps, are the observed adverse effects a consequence of COPD-induced changes in macrophage function and immune dysregulation? Although provocative, these findings need to be interpreted with caution, particularly because other controlled exposure studies including subjects with obstructive airway disease have had mixed results, with some paradoxically finding less adverse health effects in relationship to healthy subjects (15).

Studies to evaluate COPD-specific susceptibility to air pollution in terms of inflammatory and protease changes in the lower respiratory tract are lacking, and this study attempts to fill this knowledge gap. Limitations of this study include a time-point that may have missed the peak of inflammatory changes, and the small sample size, reducing power to detect meaningful differences, especially when accounting for multiple comparisons. However, this study is meant to be exploratory, and future studies will need to validate these markers and explore etiologies for these changes to provide mechanistic insight.

Overall, this study highlights the importance of rigorous clinical trials in air pollution research in uncovering mechanisms of disease susceptibility. Understanding the how and why pollution affects sensitive populations can help identify novel interventions to limit toxicity and motivate regulatory action to reduce emissions. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Should We Wean Patients off Vasopressors before Weaning Them off Ventilation?

Failed extubation and subsequent reintubation are independently associated with mortality and morbidity of patients under mechanical ventilation (1). This is the reason why, before starting the weaning process, one carefully waits until the patient has reached a sufficient degree of autonomy (2). Among the criteria used to ensure autonomy, it must be admitted that the absence of vasopressor infusion is one of the least solid. Although it is obvious that the patient must be sufficiently awake and positive end-expiratory pressure and $F_{I_{O_2}}$ must be low, testifying to a minimal respiratory autonomy, the need to be rid of vasopressor support before weaning from mechanical ventilation is less evident.

In many cases, the persistence of vasopressor support is accompanied by persistent dependence on the ventilator or other remaining failures, and the question of extubating the patient under vasopressors does not arise. Also, if there is ongoing myocardial ischemia or major circulatory failure, with obvious signs of tissue hypoxia, and if the doses of vasopressors are increasing, it is obvious that extubation must be avoided. The increase in oxygen consumption owing to the reactivation of the respiratory muscles would aggravate tissue hypoxia, and extubation is clearly unreasonable in this context.

But in other cases, when the infusion of a low dose of a vasopressor is the only obstacle that remains, what justifies refraining from extubating the patient? The answer to this question is still pending.

The risk is not that extubation under vasopressors would expose the patient to weaning-induced cardiac dysfunction, even if it is a frequent cause of weaning failure (3). Indeed, this acute cardiac failure, and the frequently associated pulmonary edema, are mainly owing to unfavorable changes in the loading conditions of both ventricles during the transition to spontaneous breathing. The increase in cardiac preload owing to the inspiratory fall in intrathoracic pressure, the increase in right ventricular afterload owing to high-volume ventilation, and the increase in left ventricular afterload owing to hypertension are the main mechanisms involved (4). Then, there is no reason why the persistence of low arterial tone and the administration of a vasopressor should contribute to it. In fact, the reason one refrains from extubating a patient on a low dose of a vasopressor is simply the fear that the underlying disease that led to the intubation did not completely resolve, if there is no other clear hemodynamic reason why the patient should worsen.

In this issue of the *Journal*, Zarrabian and colleagues (pp. 1053–1063) retrospectively reviewed 6,140 adult patients in Calgary

Originally Published in Press as DOI: 10.1164/rccm.202201-0175ED on March 8, 2022