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PERSPECTIVE

Smoking and COVID-19: The Real Deal

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The coronavirus disease (COVID-19) pandemic has had a devastating impact globally with millions of individuals infected and a rising death toll that now surpasses one million (1). It is therefore critical to identify risk factors for worse outcomes related to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. The use of tobacco products is such a potential risk factor, given its adverse effects on health and the high prevalence of use. Both electronic and combustible tobacco products have been shown to cause damage to the lungs (2, 3) and to alter the immune system response leading to increased susceptibility to most respiratory viruses. Although research is ongoing, there are several proposed mechanisms by which SARS-CoV-2 may increase susceptibility to infection or lead to worse clinical outcomes.

Overall, the epidemiological data are mixed on whether tobacco use increases the risk of COVID-19 infection. However, there is clear evidence that tobacco use is associated with worse clinical outcomes, including the risk of mortality, with current smokers having a greater risk of in-hospital death (9.4% compared with 5.6% for nonsmokers) (4–6). The OpenSAFELY study linked electronic health records with in-hospital deaths in the United Kingdom, for approximately 17 million individuals in the United Kingdom. Accounting only for age and sex, smokers and former smokers had a 25% and 80%, respectively, higher risk of mortality compared with nonsmokers (7). With regard to incident infection, meta-analyses have shown that current smokers are at a reduced risk of SARS-CoV-2 infection (8). However, the literature is generally flawed by significant heterogeneity on how smoking status was determined, leading to missing data, inability to separate current, former, and never-smokers, reliance on self-report or electronic medical records, and lack of data on frequency and duration of use of tobacco products. Furthermore, in many of these studies, there is a high representation of healthcare workers who are less likely to smoke than the general population but are at greater risk of exposure to SARS-CoV-2. Conversely, emerging evidence suggests that the use of electronic cigarette products is linked to a fivefold greater likelihood of testing positive for COVID-19 (9). This study, however, relied on an Internet panel and self-report. These data suggest a smoking paradox for COVID-19, with current smokers being at a lower risk for infection but at a significantly greater risk for worse outcomes.

What are the possible mechanisms by which smoking could affect SARS-CoV-2 infection and the outcome of COVID-19? The smoking-related comorbidities (cardiovascular disease, chronic obstructive pulmonary disease [COPD]) provide the most coherent connection between smoking and COVID-19 severity. However, several disease mechanisms, anchored in smoking-associated lung injury, altered host defenses, and the unique aspects of SARS-CoV-2 infectivity, are also relevant.

Airway and Airspace Injury (Direct Toxic Effects)

Smoking delivers myriad tissue toxicants to the lung that can culminate in geographic injury to both airway and airspace compartments. Although the pathologic effects of tobacco smoke on the oropharynx are well known and underscore the risk of malignancy, the involvement of the nasal epithelium, the recognized portal of entry for SARS-CoV-2, is less well described. Limited surveys of chronic smokers and animal models of smoke exposure do show nasal epithelial pathology that approximates changes in the proximal airway with epithelial cell loss and expansion of mucosecretory cells (10–12). Nasal and smell dysfunction, signature presenting symptoms in COVID-19, are frequent in chronic smokers implicating common injury mechanisms. As of this writing, no studies of viral abundance in smokers versus nonsmokers with COVID-19 have been published.

Lower airway pathology featuring epithelial metaplasia, dysfunctional ciliated cells, goblet cell hyperplasia, and secretory gland expansion are known consequences of chronic smoke exposure (13–15). This battery of effects certainly impairs viral clearance given the compromise of the mucociliary apparatus (16). The smoke-induced production of damaging oxidants compromises tissue repair and confers enhanced susceptibility to infection (17). Whether the altered airway epithelial composition enhances viral infectivity is unknown, but answers to that question will be informed by advanced

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preclinical and *in vitro* models of smoking plus SARS-CoV-2 infection.

Inflammation Profile That Supports Viral Pathogenesis

An important consideration is whether smoking compromises antiviral inflammatory cascades or contributes to the inability to regulate such responses. COVID-19 is a staged disorder punctuated by early viral replication and dispersal in the airway and lungs followed by either resolution (appropriate antiviral response) or progressive tissue pathology (persistent antiviral response or direct tissue injury). Smoking is a known risk factor for influenza infection, potentially reflecting a broad susceptibility across respiratory viruses (18–20). Airway epithelial cells exposed to whole smoke or isolated from smokers display attenuated interferon signaling with poly I:C treatment or viral infections (21–23). Nicotine also suppresses interferon-mediated antiviral responses in cell systems (24). Taken together, active smoking creates a proviral milieu that is potentially exploited by many respiratory viruses.

Alteration in Angiotensin-Converting Enzyme 2 Abundance

Successful SARS-CoV-2 infection of airway epithelial cells involves a coordinated series of molecular events. The initial trigger is the SARS-CoV-2 spike protein engagement with angiotensin-converting enzyme 2 receptors, followed by a protease-mediated activation of membrane fusion and then use of the endocytic machinery to facilitate viral replication and eventual release from the dying cell. Does smoking impact any of these critical events? Many consider measurable or elevated lung angiotensin-converting enzyme 2 expression as a risk factor for SARS-CoV-2 infection and the effect of smoking on the expression of lung angiotensin-converting enzyme 2 has been examined by scores of investigators. As angiotensin-converting enzyme 2 harbors known lung-protective effects, largely exerted by enhancing counterregulatory renin–angiotensin signaling, the increased expression could either facilitate viral engagement or serve to reinforce host defenses or both. Among published studies, there is an overrepresentation of analyses of RNA datasets from lungs of smokers compared with nonsmokers or from resident lung cells. Findings from these studies have been variable with most showing persuasive evidence of angiotensin-converting enzyme 2 induction among smokers, whereas others show no significant difference (25–31). Furthermore, the few studies that measured angiotensin-converting enzyme 2 protein in the lungs or in the resident cells of smokers versus nonsmokers show a modest increase in angiotensin-converting enzyme 2 expression with active smoking (32). A strenuous exploration of how and whether tobacco smoke or nicotine exposure affects coronavirus 2 infectivity or viral titers is needed to provide context to the angiotensin-converting enzyme 2 expression data.

Disturbances in RAS Signaling

Alterations in renin–angiotensin system (RAS) signaling plausibly underscore selective manifestations of COVID-19 because the virus receptor is an angiotensin processing enzyme that seems to be downregulated on acute lung injury and/or coronavirus infection (33–36). The loss of critical angiotensin-converting enzyme 2 functions such as the *1*) degradation of proinflammatory angiotensin II (AngII), *2*) complex tissue-protective effects, and, in its soluble form, *3*) possible antiviral decoy interactions may serve to enable virulence, infectivity, and overall morbidity (37–39). The tissue-protective effects of angiotensin-converting enzyme 2 are believed to reside in the coupled hydrolysis of AngII and production of Ang1–7. Blood AngII concentration are elevated in patients with COVID-19 and associated with the degree of hypoxia (40). Despite evidence that antagonism of conventional RAS signaling resulting in reduced AngII production protects against cigarette smoke–induced lung injury in experimental COPD and is associated with improved COPD outcomes, whether such approaches might improve COVID-19 morbidity in smokers is unknown (41–43). Clearly, measurements of the activity of RAS processing enzymes and the resultant product peptides in smoking and nonsmoking patients with COVID-19 would provide some guidance for pilot therapeutic studies.

Nicotine Signaling and SARS-CoV-2 Infection

There is an argument that nicotine exposure and signaling could paradoxically reduce SARS-CoV-2 infection and morbidity (44). Nicotine has well-established antiinflammatory effects that reside in its interaction with the α7 subtype of nicotinic receptors, but it has varied effects on interferon-mediated antiviral cascades (45–48). Nicotine also induces angiotensin-converting enzyme 2 expression in primary airway epithelial cells in a dose-dependent manner (49). A transcriptomic survey of airway epithelial cells shows a significant positive correlation between angiotensin-converting enzyme 2 expression and the α7 nicotinic receptor expression (50). Delivery and context may also contribute to nicotine-specific effects on COVID-19. Low-level exposures to nicotine containing e-cigarette vapor increase lung inflammation and angiotensin-converting enzyme 2 expression in an α7 nicotinic receptor–dependent fashion (51). The preponderance of data does not currently support a therapeutic role for nicotine in COVID-19, but further studies elucidating the specific effects of nicotine in a variety of delivery contexts are needed. Furthermore, given the public health consequences of nicotine dependence, caution is the most prudent posture.

Summary and Perspective

Given the adverse impact of nicotine product use on COVID-19 outcomes, it is critical to continue to promote treatments for nicotine dependence as a public health goal. The possible opposing effects of nicotine on the SARS-CoV-2 infection/morbidity axis create a strong incentive to dissect this complex relationship of smoking and COVID-19 pathogenesis. Future research efforts must disentangle this association. Objectives include *1*) more expansive epidemiological population health data that includes clear metrics for assessing smoking status; *2*) preclinical research that models relevant aspects of cigarette smoke exposure and SARS-CoV-2 infection to reveal the critical mechanisms that contribute to disease development and morbidity; and *3*) mechanistic parsing of lung nicotine delivery to delineate important paracrine and autocrine interactions between nicotine signaling and

virus: angiotensin-converting enzyme 2 engagement and processing. The inclusion of smoking/vaping status in vaccine trials could yield enlightening data on infectivity rates by tobacco product exposure. By combining careful cohort phenotyping for tobacco product exposures and disease expression with informative preclinical studies, the complex relationship between smoking and COVID-19 can be better elucidated and ultimately serve public health objectives. ■

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

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