patients with severe acute respiratory distress syndrome (ARDS), whereas our cohort included all patients intubated for respiratory failure. If we examine comparable patients from our cohort—those with moderate to severe ARDS who were treated with prone positioning—we see similar physiologic responses. Patients in PROSEVA (Figure S2 from Reference 5) had a mean Pa_{O_2}:FI_{O_2} ratio of approximately 110 when supine, prior to first proning session, with improvement to 190 at the end of the first prone session (difference, +80). Patients in our cohort improved from a median Pa_{O_2}:FI_{O_2} ratio of 150 when supine to 232 during the first prone session (difference, +82).

Finally, we share Dr. Epelbaum's concern about the use of off-label therapies for ARDS, including statins. Preclinical and observational data published prior to COVID-19 suggested a role for statins for the treatment of viral infections, including severe acute respiratory syndrome coronavirus (SARS-CoV), 2009 influenza A (H1N1), and Middle East respiratory syndrome (6, 7). Therefore, at the time of our study, hospital guidelines recommended initiating statins for accepted secondary indications frequently present in patients with COVID-19 and not for ARDS *per se*. We agree that statin therapy has not shown benefit in unselected patients with ARDS and requires further study. We also agree that off-label therapies should ideally be used in the context of clinical trials.

Frontline experience remains critical to inform real-time patient care and shape future research. We urge the continued rigorous study of these observations to accurately inform the management of critically ill patients with COVID-19. ■

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Cigarette Smoking and COVID-19: A Complex Interaction

To the Editor:

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease (COVID-19), has expanded from Wuhan throughout China and is being exported to a growing number of countries worldwide. Despite the fact that the main complications of COVID-19 affect the lung, the prevalence of current smokers among hospitalized patients with COVID-19 has been reported consistently lower than the prevalence of smokers among the general population for that specific geographical area (1), even if one might have anticipated the opposite. Thus, the epidemiological data seem to question the role of coexisting active smoking as a risk factor for COVID-19 pneumonia.

The data from Cai and colleagues, recently published in the *Journal* (2), report upregulation of pulmonary ACE2 (angiotensin-converting enzyme 2) gene expression in ever-

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smokers compared with nonsmokers in several transcriptomic data sets of lung samples from healthy never- and ever-smokers and patients with chronic obstructive pulmonary disease. Also, they report an increase in ACE2-producing goblet cells in ever-smoker versus never-smoker lungs. These findings have putatively important implications for patients with COVID-19 because ACE2 has been shown to be the receptor used by SARS-CoV-2 to enter the host cells (3) and yet seem in contrast with the consolidated epidemiological data worldwide indicating a low prevalence of active smokers among patients with COVID-19.

Cigarette smoke induces epigenetic modifications of the bronchial epithelium, leading to mucous (goblet) cell metaplasia. As goblet cells are a major source of ACE2 in the lung, this could, in part, justify the increased levels of ACE2 found by Cai and colleagues in lungs of smokers. However, goblet cells are also the main source of mucous, which provides an essential first host barrier to inhaled pathogens that can prevent pathogen invasion and subsequent infection.

Additional factors could play a role in the interaction between active smoking and SARS-CoV-2.

First, naturally occurring structural changes in the ACE2 allelic variants can interfere with the intermolecular interactions of such variants with SARS-CoV-2 spike protein (4). It is conceivable that, upon cigarette smoke (or nicotine?) stimulation, some ACE2 allelic variants that inhibit the SARS-CoV-2 binding may undergo positive selection.

Second, nicotine interacts with many components of the RAS (renin–angiotensin system) in multiple organ systems. In the ACE/AT-II (angiotensin II)/AT_1R (angiotensin$_1$ receptor) arm, nicotine increases the expression and/or activity of renin, ACE, and AT_1R, whereas, in the compensatory ACE2/angiotensin (1–7) arm, nicotine downregulates the expression and/or activity of ACE2 and AT_2R (5). How these findings fit with the ones from Cai and colleagues is worth investigation. Interestingly, activation of nicotinic receptors can lead to enhanced protease activation that may cleave and activate the spike protein of SARS-CoV for membrane fusion (5). This effect may counterbalance the increase in ACE2 levels observed in the lungs of smokers by Cai and colleagues.

Third, ACE2 knockout mice exposed to cigarette smoke exhibit increased pulmonary inflammation with activation of metalloproteinases (6) that could, in part, contribute to the inactivation or modification of ACE2 in the lungs of the smokers.

Last, though it is possible that cigarette smoke increases the ACE2 expression by the bronchial epithelium, thus facilitating the entry of SARS-CoV-2, this does not necessarily translate into a higher risk for developing COVID-19 pneumonia.

To conclude, what is unchallengeable is that cigarette smoke is detrimental for the lungs in several ways, and further studies are needed to clarify the reasons behind the reported low prevalence of current smokers among hospitalized patients with COVID-19. The effect of current smoking on SARS-CoV-2 infection is a delicate and complex topic that should be addressed meticulously before delivering messages that could be misinterpreted. ■

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Reply to Polverino

From the Authors:

We thank our reader, Dr. Polverino, for the interest in our work and intriguing opinions. The major opinion of Dr. Polverino is that patients with coronavirus disease (COVID-19) include fewer than expected numbers of smokers. However, Dr. Polverino cites a recent study showing a 1.8-fold higher risk for death among current smokers (1). The overall lower-than-expected prevalence of smoking reported in retrospective and/or observational databases is most likely because of incomplete or incorrect information about smoking patterns. Indeed, some early reports did not include smoking demographics in patients with severe COVID-19 (2, 3), suggesting that smoking history may be overlooked in these patients. Therefore, "the

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