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COVID-19 and Pulmonary Arterial Hypertension: Early Data and Many Questions

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Coronavirus disease (COVID-19), first described in Wuhan, China, in December 2019, is caused by a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of August 2020, the pandemic has impacted more than 21 million individuals worldwide, with those with underlying chronic health conditions, mainly hypertension and cardiovascular diseases, being at risk of developing more severe disease.

Early in the pandemic, there was speculation in the pulmonary vascular community regarding a perceived low risk for severe COVID-19 in patients with pulmonary arterial hypertension (PAH) (1). Anecdotally, PAH centers in areas hit hard by the pandemic were not observing as many patients with PAH with COVID-19 as they had anticipated. Several potential explanations were advanced. Could the disease itself or maybe PAH-specific medications be protective against COVID-19 (*see* Figure 1)? These speculations were suggested by autopsy findings of SARS-CoV-2 infecting endothelial cells with associated vascular injury, thrombosis, and inflammation (2, 3). In addition to the pathological features of endotheliitis in COVID-19, the angiotensin-converting enzyme 2 (ACE-2), key to the entry of SARS-CoV-2 into cells, is known to be downregulated in PAH (4, 5). The ACE-2 receptor, a member of the renin–angiotensin system, is essential for not only the coronavirus' entry into the cells but also its replication. In fact, ACE-2 knockout mice have lower levels of SARS-CoV and low numbers of SARS-CoV spike RNA (6). Angiotensin II, which contributes to injury and inflammation in the lungs, is converted to angiotensin (1–7) by ACE-2 (7). Angiotensin (1–7) has antiinflammatory and vasodilatory properties. Upregulation of angiotensin II and low angiotensin (1–7) levels in COVID-19 could lead to increased pulmonary vasoconstriction and dysregulation of hypoxic vasoconstrictive mechanisms. Recombinant ACE-2, pulmonary overexpression of ACE-2, and the use of small-molecule ACE-2 activators were shown to attenuate PAH through increased production of angiotensin (1–7) (5). Whether reduced ACE-2 in PAH is protective or could promote lung injury in COVID-19 disease remains unclear. Given SARS-CoV-2's tendency to infect the endothelium (2, 8) it was also proposed that the abnormal endothelium in the remodeled arteries of patients with PAH and the immune cellular landscape might limit viral replication and suppress the deleterious cytokine response induced by SARS-CoV-2. Another hypothesis advanced was that perhaps PAH-targeted therapies could have protective effects against COVID-19, through improving endothelial function and ventilation–perfusion mismatch. Studies have shown cross-talk between the endothelin system and renin–angiotensin system. In fact, endothelin-1 can downregulate ACE-2 expression in the lung epithelial cells, whereas endothelin receptor antagonists inhibit angiotensin II–induced vasoconstriction and lung injury (9, 10). Other studies showed that angiotensin (1–7) attenuates the actions of endothelin-1 on endothelial cells, mainly inflammation and growth (11). Endothelin-1 is upregulated in PAH, and endothelin receptor antagonists, frequently used to treat PAH, could be beneficial in the treatment of COVID-19 lung injury. Enhancing the nitric oxide (NO) pathway via phosphodiesterase type 5 inhibitors or soluble guanylate cyclase stimulators is another commonly used PAH-targeted therapeutic avenue. During the 2003 SARS outbreak, inhaled NO was shown to have antiviral activity against the coronavirus. Inhaled NO reversed pulmonary hypertension, improved severe hypoxia, and shortened the length of ventilatory support compared with matched control patients with SARS-CoV (12). *In vitro* studies demonstrated that NO donors increased the survival rate of

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SARS-CoV–infected eukaryotic cells, suggesting direct antiviral effects of NO (13, 14). Recently, inhaled NO using a portable delivery system was used at home to treat a patient with vasoreactive idiopathic PAH who developed COVID-19 pneumonia (15). In addition to vasodilation, inhaled NO has several other desirable properties such as bronchodilation, antiinflammatory and antithrombotic effects, and microbiocidal activity. Indeed, several clinical trials are studying inhaled NO to prevent or treat COVID-19 (16). On the other hand, patients with PAH have compromised cardiopulmonary function, which could increase their risk of death if infected with SARS-CoV-2. Expert centers are also wary of providing a false sense of security to patients with PAH in the face of this serious pandemic (17). In addition, it was recently proposed that the severe hypoxemia in COVID-19 is due to absent hypoxic pulmonary vasoconstriction, leading to severe ventilation–perfusion mismatch, in which case pulmonary vasodilators could be deleterious (18).

In light of reasonable yet opposing hypotheses of the risk of COVID-19 in patients with PAH, data are urgently needed. In this issue of *AnnalsATS*, Lee and colleagues (pp. 1576–1582) report the first study to shed some light into this (19). The authors conducted a cross-sectional survey-based study of the cumulative incidence and outcomes of COVID-19 in patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH) followed by Pulmonary Hypertension Association–accredited centers. The authors found that the cumulative incidence of recognized COVID-19 was similar to the general population. However, outcomes were worse, with a 50% rate of hospitalization and 12% mortality rate in patients with PAH and CTEPH affected by COVID-19. The fact that incidence was higher in higher prevalence states seems to validate the conclusion that the rate is probably similar to the general population. This study provides early data of COVID-19 in pulmonary vascular disease. The data are welcomed and timely and seem to refute the hypothesis that PAH and/or its targeted therapy might be protective against COVID-19. In addition, and not surprisingly, the survey showed that the pandemic caused a substantial impact on the clinical care of patients with PAH and CTEPH. There was a significant shift to telehealth, reduction in testing, and decrease in initiation of PAH-specific therapies and lung transplant referral.

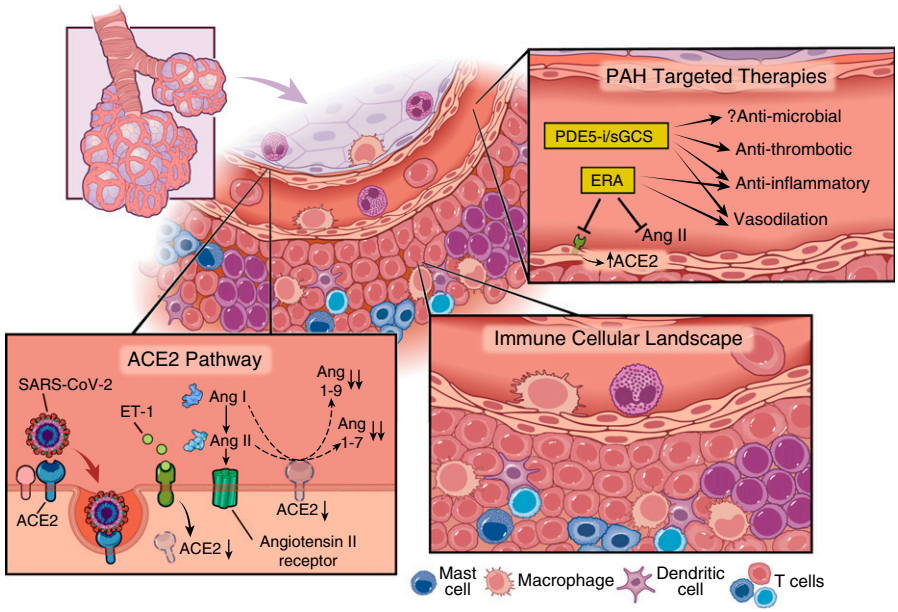

Figure 1. Schematic representation of the different mechanisms that could modify coronavirus disease (COVID-19) illness in patients with pulmonary arterial hypertension (PAH). The renin–angiotensin pathway is dysregulated in PAH with decreased angiotensin-converting enzyme 2 (ACE-2) and angiotensin (Ang) (1–7) levels. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters human cells via binding to ACE-2 receptor, which is expressed on various pulmonary cells including type II alveolar cells, macrophages, endothelial, smooth muscle cells, and perivascular pericytes. Reduced ACE-2 in PAH could impair viral entrance. However, higher angiotensin II levels could lead to worse lung injury and inflammation. The immune system plays a role in the pathogenesis of PAH with increased perivascular mast cells, macrophages, dendritic cells, and T cells and could modulate viral replication and/or the deleterious cytokine response induced by SARS-CoV-2. Another important hypothetical mechanism is the role of PAH-targeted therapies, mainly endothelin receptor antagonists (ERAs) and the nitric oxide (NO) pathway enhancers, phosphodiesterase type 5 inhibitors (PDE5-i), and soluble guanylate cyclase stimulators (sGCS). ERAs block the downregulation of ACE-2 by endothelin-1 (ET-1) and inhibit angiotensin II–induced vasoconstriction and lung injury. PAH-targeted therapies may also have antiinflammatory and antithrombotic effects. Inhaled NO has been shown to have an antimicrobial effect; however, it is unclear whether other therapies that increase signaling along the NO axis have the same effect. Lastly, PAH therapies are pulmonary vasodilators and could worsen ventilation–perfusion mismatch in COVID-19 lung injury.

The main and obvious limitations of this study are the survey-based nature of the data and that the denominator of patients at risk is simply a best estimate by the directors of the accredited centers. Furthermore, testing for COVID-19 was not systematic, and thus, this is incidence of "recognized" COVID-19 in PAH and CTEPH. In addition to 95% confidence intervals, the authors used a 30% variance in the denominator estimate, which provides some confidence that the estimates are reasonable. As is common with this pandemic, many questions persist. It remains to be seen if the effects in the delivery of care to these patients will lead to worse PAH-related outcomes. The study does not tease out changes in care for newly diagnosed versus prevalent cases or specific interventions for CTEPH such as pulmonary endarterectomy or balloon pulmonary angioplasty. Finally, the strategies used by expert centers to treat COVID-19 in PAH and CTEPH are not reported.

The authors are to be commended for quickly putting together a multicenter study of the impact of COVID-19 in PAH and CTEPH. There is considerable interest in the interactions between SARS-CoV-2 and pulmonary vascular disease. Many hypotheses have been put forward that now need to be tested in properly conducted studies. Meanwhile, practicing diligent preventive measures such as wearing a mask, social distancing, and frequent hand washing are key to prevent poor outcomes in this delicate patient population. ■

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

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Leptin as a Predictor of Incident Asthma in Offspring of Obese Mothers

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Children with asthma around the world continue to suffer from diminished quality of life and frequent hospitalizations (1). Despite extensive research, the exact environmental and genetic mechanisms that give rise to childhood asthma remain poorly described. The majority of pediatric asthma cases present roughly in the first 5 years of life, suggesting that, in addition to genetics, *in utero* environmental factors likely contribute (2). For example, accumulating evidence suggests that maternal obesity during pregnancy, excessive gestational weight gain (3), and early childhood obesity are all closely linked and associate with development of childhood asthma (4–6). An estimated 25% of new asthma cases in obese children appear to be attributable to obesity (6). However, there is a lack of a clear understanding of the obesity-mediated mechanism(s) that underlie the association of maternal obesity and incident childhood asthma.

In this issue of *AnnalsATS*, Castro-Rodriguez and colleagues (pp. 1583–1589) address this gap in knowledge through an elegant study involving participants in the Maternal Obesity and Asthma birth cohort (7). This registered study (NCT02903134)

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