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COVID-19 Lung Injury and "Typical" Acute Respiratory Distress Syndrome: The Danger of Presumed Equivalency

To the Editor:

I have read the article entitled "COVID-19 Lung Injury and High Altitude Pulmonary Edema: A False Equation with Dangerous Implications" by Luks and Swenson published April 24, 2020 (1).

Although the authors' knowledge about high-altitude pulmonary edema (HAPE) is beyond reproach, contained in this article are unproven assumptions with regard to the pathophysiology underlying coronavirus disease 2019 (COVID-19) lung disease. The authors posit that the natural evolution of COVID-19 involves "alveolar flooding, atelectasis, severely diminished lung compliance, ventilation–perfusion mismatch and right-to-left shunt." This has not been scientifically confirmed and is based on a presumption of equivalency between COVID-19 lung and known alveolar disorders leading to acute respiratory distress syndrome. I find this presumed equivalency to be the most dangerous of possible false equations.

In the face of a pandemic in which so many practicing physicians admit to honest bewilderment, at some point, we must be allowed to fall back on scientific principles that are governed by natural law. The equation of motion of the respiratory system is one such principle. Relying on that natural truth, it seems highly unlikely that a disease that causes such a severe level of hypoxemia due to alveolar collapse/filling, which is to say hypoxemia defined by loss of functional lung volume, could present with normal or near-normal pulmonary compliance.

Presuming to know what is unknown is more detrimental to medical advancement than voicing the notion that COVID-19 lung disease *may* involve pathophysiologic mechanisms similar to those that are believed to underlie HAPE. In light of a most striking and unusual similarity, progressive hypocapnic hypoxemia manifesting clinically as hypoxemia out of proportion to dyspnea, it seems reasonable to initiate a debate about whether what is used to treat one might be effective in treating the other.

I do appreciate the authors' concern and their imparted wisdom. If COVID-19 is a problem of impaired rather than exaggerated pulmonary vasoconstriction, the treatment of COVID-19 with medications used to treat HAPE may cause harm. We should heed their caution. However, we should not retreat from a study of the similarities between high-altitude hypoxemia and COVID-19

hypoxemia. A comparison of the two may yet yield answers to questions of great clinical import. For example, in COVID-19 lung disease, a hypoxemic condition that progresses over several days in which many patients do not appear to be in distress, what is more injurious: accepting a lower oxygen saturation as measured by pulse oximetry or initiating invasive mechanical ventilation?

With great respect for the authors' well-meaning concern to avoid patient harm, let me be clear about mine: I am concerned that the alveolar filling/collapse, low-compliance pulmonary disease being seen in the intensive care unit is predominantly due to ventilator-induced lung injury rather than to the natural evolution of COVID-19 disease. That is not to say that this iatrogenic lung injury, if confirmed by further data, is avoidable. We are tasked with preserving life, and it is highly likely that to maintain oxygenation at viable levels for life, we must injure lungs along the way and then do our best to heal them, as we are.

I suspect that in the coming months, new research will show that COVID-19 mortality is caused by vascular endothelial rather than alveolar epithelial dysfunction. This will likely lead to intense debate over alterations to currently adopted ventilation strategies that have historically been used to treat alveolar filling/collapse disease. To safely ventilate COVID-19 lungs, our oxygenation and ventilation targets may need to change. Given their experience in treating a condition of well-tolerated hypoxemia leading to pulmonary vascular dysfunction, these authors are precisely the experts we will need to help redefine those targets. I look forward to once again hearing and heeding their concerns.

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

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Reply: COVID-19 Lung Injury and "Typical" Acute Respiratory Distress Syndrome: The Danger of Presumed Equivalency

From the Authors:

We appreciate the opportunity to respond to Dr. Kyle-Sidell's letter regarding our article on coronavirus disease (COVID-19) lung injury and high-altitude pulmonary edema (HAPE) (1). Although we agree it is necessary to identify the best means for treating respiratory failure due to COVID-19, we believe it is important to highlight some important misconceptions and address broader concerns raised within the letter.

With regard to misconceptions, the author writes that our claims about the natural evolution of lung injury in COVID-19 have not been confirmed and are erroneously based on a presumption of equivalence between COVID-19 and other causes of acute respiratory distress syndrome (ARDS). This statement overlooks the fact that the majority of patients in published series meet the Berlin definition of ARDS (2, 3) and that published autopsy results (4, 5), early autopsy results in preprint form, and autopsy studies from related coronavirus infections—severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus—document the presence of hyaline membranes and other findings consistent with diffuse alveolar damage, the histopathological correlate of the pathophysiology we cite and the hallmark of ARDS. Vascular lesions, including microthrombi, have been noted, but these findings are entirely consistent with prior reports on non-COVID ARDS (6).

The author also refers to hypocapnic hypoxemia manifesting as hypoxemia out of proportion to dyspnea as a "most striking and unusual similarity" between HAPE and COVID-19. In fact, the absence of dyspnea is uncommon in HAPE, and hypocapnia is a highly common finding in many causes of both acute and chronic hypoxemic respiratory failure. Hypoxemia stimulates peripheral chemoreceptor output, which in turn increases minute ventilation. Together with stimulation to ventilation from other factors, including fear, fever, sympathetic nervous system activation, and lung inflammation, this augments CO_2 elimination from uninvolved areas of the lung and causes hypocapnia. The presence of hypocapnic hypoxemia is nonspecific, and its presence in HAPE and COVID-19 in no way implies a shared pathophysiology.

Finally, the author states, without supporting evidence, that patients with COVID-19 have "normal or near-normal pulmonary compliance." To date, only three published reports have documented static compliance in COVID-19, and in two of them (2, 3) the average static compliance was low (<35 ml/cm H_2O) and consistent with that seen in prior studies of ARDS. Although the recent letter from Gattinoni and colleagues (7) reports a higher average of 50 m/cm H_2O, it is apparent from the letter's accompanying figure that some patients had markedly decreased compliance. Furthermore, compliance values of 50 ml/cm H_2O, which are about half those seen in healthy, spontaneously breathing individuals (100 cm/H_2O) and, therefore, not normal, have actually been seen in patients in prior large ARDS cohorts (8).

On a broader level, the author seems to imply that all of the severe pathology in COVID-19 lung injury is related to ventilator-induced lung injury (VILI) rather than evolution of the disease. There are no published data to support this assertion. The compliance data from the two reports noted above (2, 3) were obtained on the first day of mechanical ventilation, which would indicate that severe injury was present in many of these patients at the time of intubation. Furthermore, the fact that the majority of patients with other